Vol. 13 · Issues 1-3 · Jan-Mar 2008
www.eurosurveillance.org

Eurosurveillance

In this issue

- Special focus on tuberculosis: Featuring an article with the latest Europe-wide data which shows the progress made and the remaining challenges

Also

- A European survey on public health policies for managing cases of meningococcal disease and their contacts
- High rates of metallo-beta-lactamase-producing Klebsiella pneumoniae in Greece: A review of the current evidence

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Vol. 13 · Issues 1–3 · Jan–Mar 2008

Peer-reviewed European information on communicable disease surveillance and control

Eurosurveillance

Editorial Team
Based at the European Centre for Disease Prevention and Control (ECDC), 171 83 Stockholm | Sweden

Telephone Number:
+46 (0)8 586 01138 or +46 (0)8 586 01136

Fax number:
+46 (0)8 586 01294

E-mail:
Eurosurveillance@ecdc.europa.eu

Editor-in-Chief
Karl Ekdahl

Managing Editor
Ines Steffens

Assistant Editors
Jeremy Duns
Kathrin Hagmaier
Renata Mikolajczyk

Associate Editors
Andrea Ammon, ECDC, Stockholm, Sweden
Mike Catchpole, Health Protection Agency, London, United Kingdom
Denis Coulombier, ECDC, Stockholm, Sweden
Christian Drosten, Universitätsklinikum Bonn, Bonn, Germany
Johan Giesecke, ECDC, Stockholm, Sweden
Herman Goossens, Universiteit Antwerpen, Antwerp, Belgium
David Heymann, World Health Organisation, Geneva, Switzerland
Karl Kristinsson, Landspitali University Hospital, Reykjavik, Iceland
Irena Klavs, National Institute of Public Health, Ljubljana, Slovenia
Daniel Lévy-Bruhl, Institut de Veille Sanitaire, Paris, France
Richard Pebody, Health Protection Agency, London, United Kingdom
Panayotis T. Tassios, University of Athens, Athens, Greece
Hélène Therre, Institut de Veille Sanitaire, Paris, France
Henriette de Valk, Institut de Veille Sanitaire, Paris, France
Sylvie van der Werf, Institut Pasteur, Paris, France

Editorial Board
See inner back cover

Layout and webmaster
ECDC/HCU webteam

www.eurosurveillance.org

Contents

Editorials

Special topic tuberculosis

Surveillance and outbreak reports

Research articles

Euroroundups

Review articles

Perspectives

Rapid communications

Letters

Articles published in Eurosurveillance are indexed in PubMed/MEDLINE

The Eurosurveillance print edition is a compilation of weekly and monthly electronic releases published on the Eurosurveillance website. Only a representative selection of Eurosurveillance's weekly release articles from each three month period are printed here, and the full listing of all Eurosurveillance articles can be found in the Archives section of the website.

Editorials

EUROSURVEILLANCE MOVES ON...

K Ekdahl (karl.ekdahl)[1], I Steffens[1]
1. Eurosurveillance, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

From this issue of *Eurosurveillance*, the two previous electronic releases (weekly and monthly) of the journal have been merged into one. The new *Eurosurveillance* is published every Thursday, with rapid communications on major public health events and news items alongside longer scientific articles and reviews. At the same time we are updating our editorial policy (http://www.eurosurveillance.org/editorial_policy/index.asp) and reviewing the types of articles (http://www.eurosurveillance.org/authors/index.asp) to better reflect our commitment to covering all aspects of epidemiology, prevention and control of communicable diseases from a European perspective.

The new Eurosurveillance is published every Thursday, with rapid communications on major public health events and news items alongside longer scientific articles and reviews

This is a logical step in the process that started three years ago in January 2005, when the two journals *Eurosurveillance Monthly* and *Eurosurveillance Weekly* were merged into one single publication having a weekly electronic release with short articles, a monthly electronic release with longer articles, and a quarterly print compilation comprising articles from both.

The merging of the two journals in 2005 was part of the strategic vision to make the journal stronger and more sustainable for the future, gaining on the respective strengths of the two journals: the timeliness of *Eurosurveillance Weekly* and the scientific reputation of *Eurosurveillance Monthly*. This decision also made it possible to have the weekly articles indexed by PubMed/Medline – a milestone for the journal. However, *Eurosurveillance* was still being published from two editorial offices in Paris and London and the change from two journals to one was not always obvious to the authors and readers – and quite often a source of confusion.

For almost a year now, *Eurosurveillance* has been published by a single editorial team based at the European Centre for Disease Prevention and Control (ECDC). The practical reasons for the distinction between the weekly and monthly releases have therefore disappeared. With only one electronic release, we will now be able to post the longer articles as soon as they are ready, thus reducing the time from final acceptance of an article to publication.

Alongside this change we are also making some improvements to the different article formats, enabling more extensive review articles, but also generally allowing for higher "word count" and a larger number of references in the articles, with a clearer grouping of the shorter articles – everything to make *Eurosurveillance* even more useful to its growing number of readers. The editorial team will continue its tradition of providing high quality and relevant information on infectious diseases in a very timely manner, and offering public health experts and scientists in the field a platform for exchange of data and good practice.

This article was published on 3 January 2008.

Citation style for this article: Ekdahl K, Steffens I. Eurosurveillance moves on.... Euro Surveill. 2008;13(1):pii=8001. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8001

Editorials

Observed oseltamivir resistance in seasonal influenza viruses in Europe interpretation and potential implications

A Nicoll[1], B Ciancio[1], P Kramarz[1], on behalf of the Influenza Project Team (influenza@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

In this week's issue of Eurosurveillance, Zambon and colleagues describe the first findings of the European Union-funded European Surveillance Network for Vigilance Against Viral Resistance (VIRGIL) of some seasonal influenza viral isolates resistant to the antiviral drug oseltamivir in Europe [1]. Since the winter of 2004-5, a sample of influenza viral isolates have been routinely monitored by VIRGIL for antiviral resistance in a number of EU member states and other European countries [2]. Testing of the isolates for the 2007-8 season began in late January, with the finding that in the specimens for the first 10 countries, four countries had a proportion of seasonal influenza A/H1N1 with a mutation that confers a high level of resistance to the drug oseltamivir. The proportion of A/H1N1 isolates that were resistant was especially high in Norway [1], both in genome sequencing and phenotypical testing.

An interim risk assessment was published by the European Centre for Disease Prevention and Control (ECDC) on 27 January based on these preliminary findings and the available science [3]. As of January 31, resistant isolates have been found in nine out of 18 of the European countries whose specimens were tested (Denmark, Finland, France, Germany, the Netherlands, Norway, Portugal, Sweden and the United Kingdom (UK)) [1]. Although a high proportion of isolates have been found resistant (overall figure of approximately 14%), the sample size was relatively small, meaning this may not accurately reflect the proportion that are resistant among all infections. Norway and VIRGIL alerted the World Health Organization (WHO) and all 27 EU and the other two EEA countries (Iceland and Liechtenstein) through the International Health Regulations and Early Warning Response System. Further testing has begun in the laboratories of the Centre of Infections of the UK's Health Protection Agency as well as the WHO Influenza Collaborating Centre in London, and through sequencing and phenotypic testing in national influenza centres. The WHO has held international consultations, and testing in WHO Collaborating Centres has identified similar findings in some other parts of the world, although not all. It is not yet clear from where these viruses emerged, or why. However, as they are in Europe, we must address them. The fact that the first findings came from Europe may simply be a reflection of the surveillance methods used here and the timeliness of the work. They should not be taken to imply that they emerged in Europe. The WHO is now coordinating further investigations at a global level, while the ECDC, working with the WHO European Region and the European Commission, is coordinating investigations in the EU and EEA/EFTA countries.

The oseltamivir resistance investigation is still in its early stages, with a small number of samples from several countries tested. A more accurate picture will only emerge when many more specimens have been tested and more epidemiological information is available. Influenza activity this season has only recently begun to significantly increase in Europe and A/H1N1 has been the predominant strain circulating so far [4]. From the samples examined to date, the proportions of the new virus A/H1N1 with the H274Y mutation appear to be low [1].

The resistance is unlikely to be related to antiviral medication use in individual patients in Europe

Oseltamivir is seemingly not frequently used in Europe, although better data needs to be acquired on this and the use of other antivirals. There has been no evidence to date that any of the Norwegian patients were exposed to the drug before their infection. Therefore, the resistance is unlikely to be related to antiviral medication use in individual patients in Europe. For the same reason, these findings have fewer clinical implications for routine clinical treatment of mild influenza infections than if oseltamivir was used more widely. The ECDC's interim risk assessment also emphasised that the findings are not related to avian influenza (the similarly named A/H5N1), pandemics or pandemic preparedness. However, they are a timely reminder of the ability of influenza viruses to develop antiviral resistance and the fact that it cannot be guaranteed that any novel influenza virus emerging will be sensitive to any particular antiviral medication [5,6,7,8].

Influenza seasons in which H1N1 viruses predominate are typically associated with less severe illness and lower overall mortality than seasons in which other influenza A viruses predominant. There is currently no evidence that the mutated H1N1 strain is any more virulent than other strains of seasonal influenza (all the Norwegian patients had typical influenza illnesses), but any influenza A can nevertheless cause severe disease or be fatal for vulnerable people, including infants, the elderly and those with chronic debilitating disease.

The circulating A/H1N1 viruses, including the oseltamivir-resistant ones, are well matched with the current seasonal influenza vaccine, meaning that those who have been vaccinated are already at a lower risk of contracting the disease or developing severe complications than those who have not yet been immunised. The

tests conducted so far have also shown that the mutated viruses are fully susceptible to the other currently available antiviral drugs, zanamivir and the adamantanes (amantadine and rimantadine) [1]. However, it is agreed that there is currently insufficient evidence for authorities to consider changes to clinical guidelines.

Resistant viruses carrying the same mutation have been seen in previous seasons but, as with most resistant viruses, were few in number, 'unfit' and transmitted poorly. Consequently, 'fitter' non-resistant viruses eventually predominated. The cautious use of antiviral medication may have contributed to this. These A/H1N1 isolates with the H274Y mutation are fitter. They are in several countries and are transmitting in the community [1]. The specimens tested to date are from early in the season and it may be that as the season progresses ordinary A/H1N1s predominate. Equally, the resistant viruses may come to predominate, as did the adamantane-resistant viruses in other H-types in some parts of the world, notably North America [5]. Careful virological and epidemiological surveillance should continue for the rest of this and other seasons. The ECDC will revise its assessment as more information on this issue emerges and comments are received. In collaboration with VIRGIL and the European Influenza Surveillance Scheme (EISS), the Centre will also regularly update the figures on resistance in Europe, initially on a weekly basis. More information about seasonal influenza can be found on the websites of the ECDC (http://www.ecdc.europa.eu) and the WHO (http://www.who.int).

* The Influenza Project Team includes also: K Fernandez de la Hoz, P Kreidl, H Needham, F Plata, C Varela, A Würz, C Yilmaz

References

1. Lackenby A, Hungnes O, Dudman SG, Meijer A, Paget WJ, Hay AJ, Zambon MC. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Euro Surveill 2008;13(5). Available from: http://www.eurosurveillance.org/edition/v13n05/080131_2.asp
2. Meijer A, Lackenby A, Hay A, Zambon M. Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season. Euro Surveill 2007;12(4)[Epub ahead of print]. Available from: http://www.eurosurveillance.org/em/v12n04/1204-222.asp
3. Interim ECDC Risk Assessment. Emergence of seasonal influenza viruses type A/H1N1 with oseltamivir resistance in some European countries at the start of the 2007-8 influenza season. 27 January 2008. Available from: http://www.ecdc.europa.eu/pdf/080127_os.pdf
4. Arkema JMS, MeijerA, Paget WJ, van Casteren V, Hungnes O, Mazick A and van der Velden J. The influenza season has started in a number of European countries. Euro Surveill 2008;13(4). Available from: http://www.eurosurveillance.org/edition/v13n04/080124_2.asp
5. Deyde VM, Xu X, Bright RA, Shaw M, Smith CB, Zhang Y, Shu Y, Gubareva LV, Cox NJ, Klimov AI. Surveillance of resistance to adamantanes among influenza A(H3N2) and A(H1N1) viruses isolated worldwide. J Infect Dis. 2007 Jul 15;196(2):249-57. Epub 2007 Jun 7.
6. Bright RA, Shay DK, Shu B, Cox NJ, Klimov AI. Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. JAMA. 2006 Feb 22;295(8):891-4. Epub 2006 Feb 2.
7. Bright RA, Medina MJ, Xu X, Perez-Oronoz G, Wallis TR, Davis XM, Povinelli L, Cox NJ, Klimov AI. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet. 2005 Oct 1;366(9492):1175-81. Epub 2005 Sep 22.
8. Fiore AE, Shay DK, Haber P, Iskander JK, Uyeki TM, Mootrey G, Bresee JS, Cox NJ. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep. 2007 Jul 13;56(RR-6):1-54.
9. European Centre for Disease Prevention and Control. Seasonal influenza information. Available from: http://ecdc.europa.eu/Health_topics/Seasonal%20Influenza/Seasonal_Influenza.html

This article was published on 31 January 2008.

Citation style for this article: Nicoll A, Ciancio B, Kramarz P, on behalf of the Influenza Project Team . Observed oseltamivir resistance in seasonal influenza viruses in Europe interpretation and potential implications. Euro Surveill. 2008;13(5):pii=8025. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8025

Editorials

Epidemic intelligence in the European Union: strengthening the ties

D Coulombier (Denis.Coulombier@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

Two articles in this issue of Eurosurveillance refer to the challenges of epidemic intelligence activities in European Union Member States.

Public health surveillance remains the cornerstone of the detection of health threats requiring public health action. The routine notification by health care providers or laboratories of patients presenting with a clinical picture meeting a case definition enables public health officers to implement public health measures to prevent further spread. At the European level, the Early Warning and Response System (EWRS) is a tool allowing mutual notification and exchange of information on threats detected in the European Member States that require co-ordination of public health measures among the EU Member States.

Internet-based tools (IBT) for epidemic intelligence have, over the past decade, led to the enhancement of traditional surveillance

Internet-based tools (IBT) for epidemic intelligence have, over the past decade, led to the enhancement of traditional surveillance by accessing real-time information originating from the media, mailing lists and other internet sources (such as blogs and discussion fora). These IBT have provided those working in epidemic intelligence with a large amount of potentially useful information for the detection of threats.

However, the reliability and validity of the information provided by these sources remains a concern, and raises the question of whether national public health authorities should react and implement measures as a result of information gathered in this way. One epidemic intelligence tool, ProMED-mail, a global electronic reporting system for outbreaks of emerging infectious diseases and toxins maintained by the International Society for Infectious Diseases, is discussed in the article by Zeldenrust et al [1]. The authors examined the use of ProMED-mail by the Netherlands' Early Warning Committee over a period of more than one year, and showed that in two instances ProMED-mail's notification was timelier than any of the Early Warning Committee's other sources, but did not lead to more prompt intervention.

At the EU level, the experience of the European Centre for Disease Prevention and Control(ECDC) in epidemic intelligence has shown that the European Early Warning and Response System (EWRS) remains by far the most timely notification process for health threats concerning several Member States. The added value of screening IBT is marginal for threats confined to the EU. However, IBT remain important and a basis for detecting international threats and allowing for enhancing preparedness in order to prevent or mitigate their emergence in the EU. The outbreak of chikungunya in Italy in summer 2007 is a good example: reports of large numbers of cases of chikungunya in India during the spring, reported through ProMed-mail, GPhin and other sources, led to the strengthening of EU Member States' capacity to diagnose the disease, as well as chikungunya's inclusion in the list of diseases under notification in countries where the vector is present.

For many years, public health surveillance had remained the main tool for the detection and response to public health threats. During the 1990s, with the increased trade and travel within the EU, the need for a mechanism for prompt notification among EU Member States has emerged (EWRS) and proven to be effective in ensuring the coordination of public health measures. Concomitantly, IBT have allowed those working in epidemic intelligence to enhance their capacity to recognise potential threats originating outside of the EU and their ability to anticipate and prepare for it. The two articles presented in this issue stress the need for a better understanding of the added value of IBT and for developing an EU network of epidemic intelligence contact points to use these tools in the most efficient way.

This article was published on 7 February 2008.

Citation style for this article: Coulombier D. Epidemic intelligence in the European Union: strengthening the ties. Euro Surveill. 2008;13(6):pii=8030. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8030

Editorials

Is there room for improving case management for contacts of meningococcal disease in the European Union?

P L Lopalco (pierluigi.lopalco@ecdc.europa.eu)[1]
1. Programme on Vaccine-Preventable Diseases, European Centre for Disease Prevention and Control, Stockholm, Sweden

Invasive meningococcal disease (IMD) is a severe illness primarily affecting children and young adults. It has a high case fatality rate (10%-14%) and 11%-19% of patients who recover experience permanent hearing loss, mental retardation, loss of limbs or other serious sequelae [1]. Every individual meningococcal case, therefore, is an important public health issue; furthermore, meningococcal infection is a severe threat because of the possibility of generating clusters among close contacts (school, work, household, etc.).

To date, safe and effective vaccines have been developed for serogroups A, C, W135 and Y. Immunisation programmes have also been effective in reducing the overall burden of disease. However, a vaccine against B serotype is still far from coming on the market and universal vaccination strategies using the meningococcal C vaccine have only been implemented in a few European countries.

Secondary preventive measures – regarding public health management of cases and their close contacts – are still paramount

For this reason, secondary preventive measures – regarding public health management of cases and their close contacts – are still paramount.

In this issue of Eurosurveillance, Hoek and colleagues [2] report results of an interesting survey that reveals several gaps in this field, including on the use of antibiotics in children and pregnant women, uncertainties in defining "close contacts" and inertia in national policy changes reaching the local level.

In another article in today's issue, Stefanoff and colleagues [3] – focusing only on household contacts – underline again the need for clear evidence-based recommendations for public health case management and surveillance. Although the preliminary data suggest that the situation has improved in 2007, the proportion of cases in which chemoprophylaxis was administered to close contacts in Poland is still not satisfactory.

Finally, a recent article by Petsas and colleagues [4] on a case of IMD in a health care worker raised an interesting discussion highlighting once more the lack of a common agreement on how to define "close contacts" of IMD cases. Fusco and Puro, in a letter to the Editor [5], suggest that ambulance workers giving assistance to a suspect IMD case should be considered at high risk and be offered chemoprophylaxis, especially when they are not advised to wear face masks.

In conclusion, we believe that in this field there is a clear need for evidence-based public health policies and recommendations that should be effectively communicated and implemented on the basis of a large consensus at national and regional level.

The European Centre for Disease Prevention and Control is committed to supporting European Union Member States in developing the best policies on public health management for cases of IMD and their contacts, filling the gaps highlighted by several scientists in the field.

References

1. Centers for Disease Control and Prevention, United States. Meningococcal Disease. Fact-sheet. March 30 2006. Available from: http://www.cdc.gov/ncidod/dbmd/diseaseinfo/meningococcal_t.htm
2. Hoek M, Hanquet G, Heuberger S, Stefanoff P, Zucs P, Ramsay M. et al. A European survey on public health policies for managing cases of meningococcal disease and their contacts. Euro Surveill 2008;13(10). Available from: http://www.eurosurveillance.org/edition/v13n10/080306_4.asp
3. Stefanoff P, Rosinska M, Karczewski G, Zielinski A. The detection of meningococcal household clusters and their prophylaxis in the changing epidemiological situation of invasive meningococcal disease in Poland. Euro Surveill 2008;13(10). Available from: http://www.eurosurveillance.org/edition/v13n10/080306_3.asp
4. Petsas A, Sharma A, Aghadiuno O, Abid M, Paranthaman K. A secondary case of meningococcal disease in an ambulance worker, Berkshire, November 2007. Euro Surveill 2008;13(4). Available from: http://www.eurosurveillance.org/edition/v13n04/080124_1.asp
5. Fusco FM, Puro V. Letter: Meningococcal disease in an ambulance worker. Euro Surveill 2008;13(10). Available from: http://www.eurosurveillance.org/edition/v13n10/080306_5.asp

This article was published on 6 March 2008.

Citation style for this article: Lopalco PL. Is there room for improving case management for contacts of meningococcal disease in the European Union?. Euro Surveill. 2008;13(10):pii=8057. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8057

Editorials

Tackling tuberculosis: progress made and challenges remaining for the European Union

Z Jakab[1]
1. Director, European Centre for Disease Prevention and Control, Stockholm, Sweden

World Tuberculosis Day on 24 March commemorates the date in 1882 when Robert Koch presented his findings on the causing agent of tuberculosis (TB) – *Mycobacterium tuberculosis*. This celebration provides a good opportunity to take stock of the achievements in controlling the disease so far – and the remaining challenges at global, regional, national and local level.

Within the European Union (EU), most activities regarding the control of TB rely on national efforts since the key measure to combat the disease is to ensure appropriate diagnosis and treatment for all. However, the European Centre for Disease Prevention and Control (ECDC) can provide an EU added value to the fight against TB as a catalyst for EU organisations and other partners working on TB control. Since 2008, ECDC together with the World Health Organization's Regional Office Europe (WHO EURO) is co-ordinating the surveillance of TB in the European Region by collecting, validating and analysing TB data and further improving other surveillance activities. This follows on the work done by the European Commission and the Institute de veille sanitaire-funded network EuroTB (www.eurotb.org), which has been in charge of surveillance in the WHO European Region since 1996. The ECDC also supports countries in other areas such as enhancing laboratory services, proposing priorities for research or facilitating the tracing of people and other necessary activities when multi-country investigations are required.

The EU is far from reaching the goal of TB elimination

In recent decades, TB has been on the decline in the EU. In 2006, the current 27 EU Member States plus the European Economic Area/European Free-Trade Association (EEA/EFTA) countries reported 88,113 TB cases. Despite some signs of convergence, we are still facing a diverse situation in the EU, where many countries show low notification rates whereas others still have TB rates of over 30 per 100,000 population. These and other data derived from the latest EuroTB report can be found in an article by Falzon et al [1] in this special issue of Eurosurveillance. The data show that there is no room for complacency. The EU is far from reaching the goal of TB elimination. Reasons for remaining active include the presence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB in the EU and its neighbouring countries; rising TB/human immunodeficiency virus (HIV) co-morbidity in some Member States; and EU countries with low notification rates in which TB is concentrating in vulnerable populations such as immigrants from areas with a high TB burden, the urban poor, prisoners and immuno-suppressed people. Attention should be paid to those threats and also to the increasing numbers of TB cases in countries neighbouring the EU which are described in a second article by Falzon and van Cauteren [2] on trends in TB in the World Health Organization's (WHO) European Region from 1995 to 2005. The article analyses surveillance data of the EuroTB network.

Besides surveillance, well functioning laboratory services are key for the success in fighting TB. An article by Drobniewski *et al.* [3] maps the current National Reference Laboratory activities and points out the added value of cooperation and networking at the EU level with regard to strengthening laboratory services.

Following a request from the European Commissioner for Health in March 2007, the ECDC, in collaboration with many experts across Europe, developed a *Framework Action Plan to Fight TB in the EU*. The plan offers an excellent opportunity to invigorate the fight against TB in the EU and indicate the necessary steps towards controlling and ultimately eliminating TB in the EU. It is based on four main principles: ensuring prompt and quality TB care for all; strengthening health systems; developing and assessing new tools; and building partnerships and international collaboration. A rapid communication in this issue gives more details [4], and the plan, launched on 17 March, can be found at http://ecdc.europa.eu/pdf/080317_TB_Action_plan.pdf.

In the context of the *Framework Action Plan*, ECDC will support the Member States and collaborate with the relevant stakeholders in the assessment of the TB situation and the development and implementation of regional and national strategies. The next step in that direction will be to set up indicators and a 'framework for national plans' to enable the Member States to strengthen their current plans, effectively channel TB control activities and monitor their progress. The *Framework Action Plan* will be presented for information at the upcoming EU Council meeting in June 2008.

References

1. Falzon D, Kudjawu Y, Desenclos JC, Fernandez de la Hoz K, Dadu A, Zaleskis R. Stopping TB in Europe: some progress but still not there. Euro Surveill. 2008;13(12). Available from: http://www.eurosurveillance.org/edition/v13n12/080318_2.asp
2. Falzon D, Van Cauteren D. Demographic features and trends in tuberculosis cases in the European Region, 1995-2005. Euro Surveill. 2008;13(12). Available from: http://www.eurosurveillance.org/edition/v13n12/080318_4.asp
3. Drobniewski FA, Nikolayevskyy V, Hoffner S, Pogoryelova O, Manissero M, Ozin AJ. The added value of a European Union tuberculosis reference laboratory network – analysis of the National Reference Laboratory activities. Euro Surveill. 2008;13(12). Available from: http://www.eurosurveillance.org/edition/v13n12/080318_5.asp
4. Fernandez de la Hoz K, Manissero D on behalf of the Tuberculosis Disease Programme. A Framework Action Plan to fight Tuberculosis in the EU. Euro Surveill. 2008;13(12). Available from: http://www.eurosurveillance.org/edition/v13n12/080318_3.asp

This article was published on 18 March 2008.

Citation style for this article: Jakab Z. Tackling tuberculosis: progress made and challenges remaining for the European Union. Euro Surveill. 2008;13(12):pii=8072. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8072

Surveillance and outbreak reports

Demographic features and trends in tuberculosis cases in the European Region, 1995-2005

D Falzon (d.falzon@invs.sante.fr)[1], D van Cauteren[1,2]

1. Département des maladies infectieuses, Institut de veille sanitaire (Department of infectious diseases, French Institute for Public Health Surveillance), Saint-Maurice, France
2. Programme de formation à l'épidémiologie de terrain (PROFET), Département des maladies infectieuses, Institut de veille sanitaire (Department of infectious diseases, French Institute for Public Health

In 2005, 426,457 tuberculosis (TB) cases were notified in the World Health Organization (WHO) European Region, with a wide variation and an incremental west-to-east gradient in notification rates also reflected in TB mortality rates. In the enlarged European Union ('EU-27') and other western countries - where 19% of cases were of foreign origin in 2005 (>50% in 13 countries) - overall TB notification rates decreased by 2.4% yearly between 2000 and 2005, compared to 1.6% in 1995-2000, reflecting a declining incidence in all age groups and in most countries. Half the cases notified by the 12 ex-republics of the former Soviet Union in the East in 2005 were reported by the Russian Federation. In the East, the mean annual increase in 1995-2000 (10.0%) was higher than in 2000-2005 (3.9%), and in recent years the number of new cases stabilised while previously treated cases have increased. Efforts are still needed to improve and standardise TB surveillance across the Region. The collection of additional data on risk factors of TB may be useful for surveillance and control.

Introduction

The last years of the 20th century saw the resurgence of TB incidence in different parts of the world. In western countries of the World Health Organization (WHO) European Region where rates had been falling steadily for many years, the rate of decline decreased and, in some countries, a perceptible increase was observed [1]. At that time, countries in the central and eastern part of the Region were experiencing profound economic upheavals which impacted negatively upon their public health [2]. TB notification rates started increasing in the Baltic States (Estonia, Latvia and Lithuania) and in certain central Asian states after the end of the 1980s [3]. This heralded an upturn in TB rates in other former Soviet Union republics, which was sharper and more protracted than that seen further west. The true extent of the epidemic was difficult to assess since case definitions and completeness of reporting differed. In the wake of these developments, a TB surveillance network – EuroTB (http://www.eurotb.org) – was established in 1996 through funding by the European Commission to support TB surveillance across the WHO European Region. This article uses data from this network and from the WHO to describe the main demographic features and trends in TB between 1995 and 2005 in the Region.

Methods

Until 2007, the coordinating hub of EuroTB, located at the Institut de veille sanitaire in France, collected TB data from European national surveillance authorities in coordination with the WHO. In this article the 53 countries of the WHO European Region have been grouped into three geographic areas, based on epidemiological and geographic features (Table 1)

- the European Union and West (EU and West), composed of the 27 current Member States of the EU as well as other industrialized countries of Western Europe (Andorra, Iceland, Israel, Monaco, Norway, San Marino, Switzerland);
- the Balkans (Albania, Bosnia and Herzegovina, Croatia, Former Yugoslav Republic of Macedonia, Montenegro, Serbia, Turkey); and
- the East, made up of 12 republics of the former Soviet Union (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan).

Data used were updated until 31 December 2007. Population estimates used for calculating TB notification rates were obtained from the United Nations Population Division,4 with the exception of Serbia, which provided its own estimates for 1998-2005. Updates in notification and population data may account for slight differences in values compared to those published earlier. Data about TB deaths were obtained from the WHO Mortality Database website [5].

The definitions and methodology recommended for use in TB surveillance have been described elsewhere [6,7]. TB cases enumerated in this article include both those which were laboratory confirmed as well as others diagnosed only on clinical/radiological grounds. In 2005, 58% of TB cases in the EU and West (country range: 28-100%) were culture positive, as opposed to 34% in the Balkans (24-57%) and 20% in six countries in the East (4-36%). The geographic origin of TB cases was assigned as 'national' or 'foreign' in relation to the country of report on the basis of patients' place of birth or citizenship. Previously treated cases were those who received curative, combination anti-TB chemotherapy for one month or more prior to the current episode.

Rates of notification and mortality are expressed per 100,000 total population and stratified by age group and sex where indicated. No adjustment for reporting completeness was made. In 2006, countries reported completeness of TB notification to be 70-100% in the EU and West (23/34 countries), 90-98% in the Balkans (2/7 countries) and 48-100% in the East (8/12 countries). Methods used to derive estimates of completeness differed between countries and were sometimes not described. The time trend in notification rates was expressed as the mean of the percentage difference in rates (un-rounded) from one year to the next, and was not shown

for Montenegro (data first reported separately for 2005) and for individual countries reporting less than 60 cases in 2005.

The contribution of HIV to TB morbidity was expressed as the proportion of all notified TB cases known to be positive for HIV. The availability of HIV-testing results among TB patients depends on testing policies and the methodology used to collect the test results, which differed between countries. Only deaths coded ICD-9 010-018 (BTL 020-025, 029) or ICD-10 A15-19 were considered in the calculation of TB mortality. Indicators on other clinical characteristics of TB cases, on laboratory confirmation, on anti-TB drug resistance, and on treatment outcome were beyond the focus of this report.

Results

Of all the 426,457 TB cases reported in the WHO European Region in 2005, 72% were from the East, 12% from 12 countries joining the EU since 2004, 10% from countries in the original 'EU-15' and West, and 6% from the Balkans including Turkey (Table 1). The overall TB notification rate in 2005 was 47/100,000 population, with an incremental gradient when moving from west to east (country range: 4-205/100,000), which was also reflected in TB mortality (0-25/100,000; Table 2).

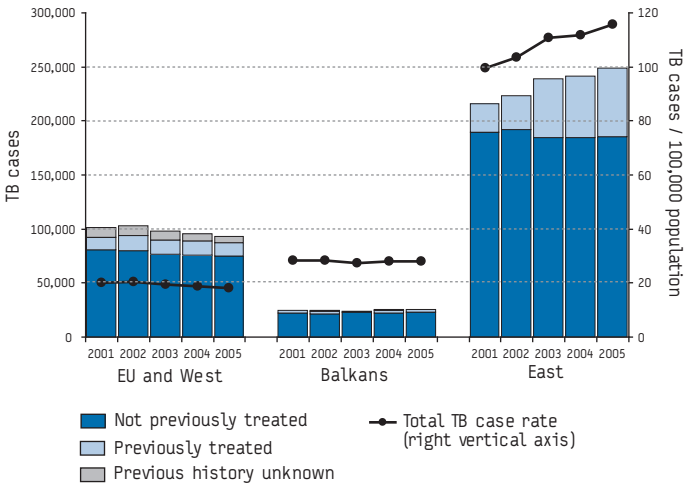
Overall the number of TB cases reported yearly in the Region has increased markedly since 1995. This increase however was not uniformly distributed over the years or between the countries. Total notification rates have continued to diverge between the EU and West and the East in recent years (Figure 1).

EU and West

In 2005, the overall notification rate in the EU and West was 18/100,000, with a rate of 10/100,000 or lower in 15 countries and higher than 30/100,000 in Romania (135), the Baltic States (39-75), Bulgaria (43), and Portugal (34). Scandinavian countries and countries on the Mediterranean littoral had some of the lowest notification rates in the area. The overall rate in the 12 countries joining the EU since 2004 was over four times that in the original 15 Member States. Despite the inclusion of countries with a higher TB incidence, the overall notification rate in the EU and West in 2005 was 10% lower than it was in 2001, reflecting a downward trend in 20 countries. Overall rates in the 'EU15' and West decreased by a similar gradient in 1995-2000 and in 2000-2005. Greece, Ireland and Sweden had a net increase in 2000-2005 after a decline in 1995-2000 The United Kingdom had an increase throughout 1995-2005, particularly between 2003 and 2005. In the Baltic States, rates decreased in 2000-2005

FIGURE 1

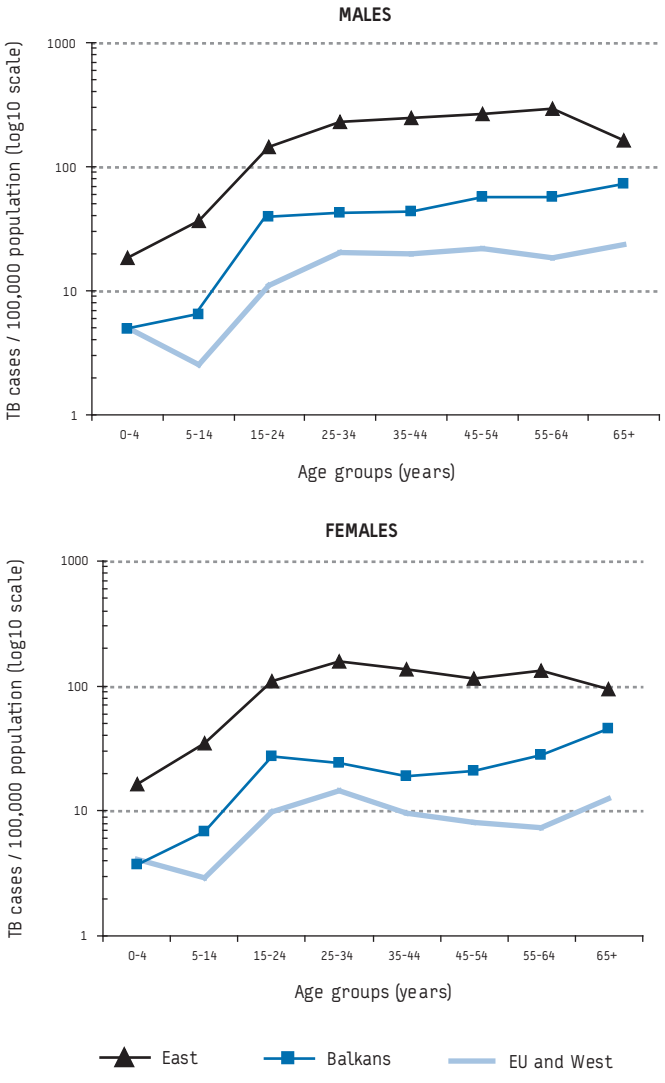
TB notification by area and treatment history, WHO European Region*, 2001-2005



* excluding countries with missing data for any year: Cyprus, Monaco, San Marino (EU and West); Bosnia and Herzegovina (Balkans); Belarus, Tajikistan, Ukraine (East)

FIGURE 2

Age-group and sex specific TB notification rates, WHO European Region*, 2005



* N=170,795; excluding cases without information on age or sex (407) and cases from countries without age-group distribution of TB cases or population: Andorra, Monaco, San Marino (EU and West); Belarus, Kyrgyzstan, Moldova, Russian Federation, Tajikistan, Ukraine (East). Romania excluded as the age-specific rates are very different from the rest of the EU and West.

Table 1

Total tuberculosis notifications and notification rates, WHO European Region, 1995-2005

		Total TB notifications											Total TB notification rates (per 100,000 population)										
		1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
'EU-15' (pre-2004)																							
	Austria	1,383	1,489	1,398	1,306	1,245	1,225	1,075	1,076	980	1,061	999	17	18	17	16	15	15	13	13	12	13	12
	Belgium	1,380	1,352	1,263	1,203	1,270	1,313	1,321	1,294	1,117	1,198	1,107	14	13	12	12	12	13	13	13	11	12	11
	Denmark	448	484	554	529	536	548	511	419	393	385	422	9	9	11	10	10	10	10	8	7	7	8
	Finland	662	644	573	629	566	537	494	473	412	331	361	13	13	11	12	11	10	10	9	8	6	7
	France	8,723	7,656	6,832	6,651	6,674	6,714	6,465	6,322	6,098	5,514	5,374	15	13	11	11	11	11	11	10	10	9	9
	Germany[a]	12,198	11,814	11,163	10,440	9,974	9,064	7,539	7,701	7,166	6,542	6,020	15	14	14	13	12	11	9	9	9	8	7
	Greece[a]	**939**	**945**	**767**	1,152	952	703	617	582	620	774	769	**9**	**9**	**7**	11	9	6	6	5	6	7	7
	Ireland	458	434	416	424	469	403	406	408	407	432	450	13	12	11	11	12	11	11	10	10	11	11
	Italy	5,225	5,152	5,176	4,795	4,429	4,759	4,505	4,212	4,518	4,220	4,137	9	9	9	8	8	8	8	7	8	7	7
	Luxembourg	32	36	38	44	42	44	32	32	54	31	37	8	9	9	10	10	10	7	7	12	7	8
	Netherlands	1,619	1,678	1,486	1,341	1,535	1,404	1,436	1,401	1,321	1,344	1,155	10	11	9	9	10	9	9	9	8	8	7
	Portugal	5,577	5,248	5,112	5,260	5,160	4,494	4,399	4,501	4,148	3,854	3,573	56	52	51	52	51	44	43	44	40	37	34
	Spain[b]	8,764	8,331	9,347	9,111	8,393	8,395	7,453	7,626	7,467	7,766	7,820	22	21	24	23	21	21	18	18	18	18	18
	Sweden	564	493	456	446	493	458	428	407	408	461	559	6	6	5	5	6	5	5	5	5	5	6
	United Kingdom	6,161	6,240	6,355	6,176	6,287	6,792	7,017	7,263	7,220	7,609	8,317	11	11	11	11	11	12	12	12	12	13	14
	Subtotal 'EU-15'	**54,133**	**51,996**	**50,936**	**49,507**	**48,025**	**46,853**	**43,698**	**43,717**	**42,329**	**41,522**	**41,100**	**14**	**14**	**14**	**13**	**13**	**12**	**11**	**11**	**11**	**11**	**11**
New EU countries (since 2004)																							
	Bulgaria	3,245	3,109	3,437	4,117	3,530	3,349	3,862	3,335	3,263	3,232	3,302	39	38	42	51	44	42	49	42	42	41	43
	Cyprus	36	24	47	45	39	33	40	20	35	30	37	5	3	6	6	5	4	5	2	4	4	4
	Czech Republic	1,851	1,936	1,834	1,805	1,631	1,442	1,350	1,200	1,162	1,057	1,007	18	19	18	18	16	14	13	12	11	10	10
	Estonia[c]	608	683	744	818	754	791	812	713	623	594	519	42	48	53	59	55	58	60	53	46	44	39
	Hungary	4,339	4,278	4,240	3,999	3,914	3,598	3,150	2,838	2,582	2,340	1,964	42	41	41	39	38	35	31	28	25	23	19
	Latvia[c]	1,541	1,761	2,003	2,182	1,968	2,063	2,082	1,855	1,726	1,610	1,443	62	72	82	90	82	87	88	79	74	70	63
	Lithuania[c]	2,362	2,608	2,926	3,016	2,903	2,981	2,989	2,844	2,821	2,514	2,574	65	72	82	85	82	85	86	82	82	73	75
	Malta	10	29	11	16	22	18	16	24	7	19	25	3	8	3	4	6	5	4	6	2	5	6
	Poland	15,959	15,358	13,967	13,302	12,179	11,477	10,672	10,475	10,124	9,493	9,280	41	40	36	35	32	30	28	27	26	25	24
	Romania	23,271	24,113	23,903	25,758	26,870	27,667	30,440	33,595	31,039	31,034	29,289	103	107	106	115	121	125	138	153	142	143	135
	Slovakia	1,537	1,499	1,298	1,282	1,218	1,111	1,076	1,053	983	705	760	29	28	24	24	23	21	20	20	18	13	14
	Slovenia	525	563	481	449	438	380	371	350	293	263	278	27	29	24	23	22	19	19	18	15	13	14
	Subtotal New EU countries	**55,284**	**55,961**	**54,891**	**56,789**	**55,466**	**54,910**	**56,860**	**58,302**	**54,658**	**52,891**	**50,478**	**52**	**53**	**52**	**54**	**53**	**52**	**54**	**56**	**53**	**51**	**49**
	Subtotal all EU ('EU-27')	**109,417**	**107,957**	**105,827**	**106,296**	**103,491**	**101,763**	**100,558**	**102,019**	**96,987**	**94,413**	**91,578**	**23**	**22**	**22**	**22**	**21**	**21**	**21**	**21**	**20**	**19**	**19**

West, non-EU																							
	Andorra	-	17	19	8	9	11	5	5	11	7	10	-	26	29	12	14	17	7	7	16	10	14
	Iceland	12	11	10	17	12	13	13	8	5	12	11	4	4	4	6	4	5	5	3	2	4	4
	Israel[a]	398	415	422	656	520	591	564	511	529	519	406	7	7	7	11	9	10	9	8	8	8	6
	Monaco	1	0	0	0	3	0	0	0	1	-	-	3	0	0	0	9	0	0	0	3	-	-
	Norway	236	217	205	244	273	237	288	251	337	302	288	5	5	5	6	6	5	6	6	7	7	6
	San Marino	2	0	1	0	0	1	0	1	1	0	-	8	0	4	0	0	4	0	4	3	0	-
	Switzerland	830	764	747	749	772	629	611	658	623	593	567	12	11	10	10	11	9	8	9	8	8	8
Total EU & West		**110,896**	**109,381**	**107,231**	**107,970**	**105,080**	**103,245**	**102,039**	**103,453**	**98,494**	**95,846**	**92,860**	**22**	**22**	**21**	**22**	**21**	**21**	**20**	**20**	**19**	**19**	**18**
Balkans																							
	Albania	664	707	655	694	765	631	572	612	561	581	540	21	23	21	22	25	20	19	20	18	19	17
	Bosnia and Herzegovina[d]	2,132	2,220	2,869	3,071	3,075	2,606	2,551	2,551	1,780[d]	2,382	2,160	62	65	83	86	83	69	66	66	- [d]	61	55
	Croatia	2,114	2,174	2,054	2,118	1,770	1,630	1,505	1,470	1,493	1,297	1,141	45	47	44	46	39	36	33	33	33	29	25
	Macedonia, Former Yugoslav Rep.	786	724	693	620	576	668	697	730	697	680	658	40	37	35	31	29	33	35	36	34	33	32
	Montenegro	-	-	-	-	-	-	-	-	-	-	170	-	-	-	-	-	-	-	-	-	-	28
	Serbia[e]	4,169	4,541	4,062	3,028	2,646	2,922	2,888	3,033	2,949	2,824	2,378	41	44	40	36	32	35	35	37	36	35	32
	Turkey	23,035	23,533	25,685	25,501	22,088	18,038	18,890	19,028	18,590	19,799	20,535	37	37	40	39	33	26	27	27	26	27	28
Total Balkans		**32,900**	**33,899**	**36,018**	**35,032**	**30,920**	**26,495**	**27,103**	**27,424**	**26,070**	**27,563**	**27,582**	**38**	**39**	**41**	**40**	**35**	**29**	**30**	**30**	**28**	**29**	**29**
East																							
	Armenia	836	935	1,026	1,455	1,499	1,344	1,401	1,455	1,570	1,701	2,322	26	29	33	47	48	44	46	48	52	56	77
	Azerbaijan	3,306	5,006	4,635	4,350	4,629	5,187	4,923	5,348	3,931	6,501	7,920	42	64	58	54	57	64	60	65	48	78	95
	Belarus	5,092	5,619	5,985	5,595	7,339	**6,084**	**5,505**	5,139	5,963	6,490	6,357	50	55	59	55	73	**61**	**55**	52	60	66	65
	Georgia	-	10,641	8,446	6,302	6,546	6,436	5,876	6,345	5,993	5,967	6,448	-	215	173	131	137	136	126	138	131	132	144
	Kazakhstan	**11,095**	**13,559**	16,109	20,623	25,060	28,265	31,254	32,936	32,169	32,131	31,187	**70**	**86**	104	135	166	189	210	221	214	213	205
	Kyrgyzstan	3,380	4,086	5,189	5,935	6,501	6,383	6,901	6,794	7,025	6,641	6,765	74	88	110	124	133	129	138	134	138	129	130
	Moldova	2,753	2,922	2,908	2,891	2,947	2,935	3,820	4,149	5,027	6,008	6,278	63	67	68	68	70	71	93	103	126	153	162
	Russian Federation	96,828	110,897	119,123	121,917	135,054	143,801	138,432	134,812	152,244	152,438	156,047	65	74	80	82	91	98	94	92	105	105	108
	Tajikistan	2,029	1,647	2,143	2,503	2,553	2,779	3,508	4,052	4,883	5,122	7,142	35	28	36	42	42	45	56	64	76	79	109
	Turkmenistan	2,009	2,149	3,438	3,712	4,092	3,967	4,922	4,635	4,759	4,172	3,291	48	50	79	85	92	88	108	100	101	88	68
	Ukraine	21,459	26,834	28,344	31,318	32,879	32,963	36,784	40,175	40,659	38,403	43,367	42	53	56	63	67	67	76	84	85	81	92
	Uzbekistan	9,866	11,919	13,352	13,958	16,959	15,912	18,106	27,009	26,172	25,714	28,891	43	51	56	58	70	64	72	106	101	98	109
Total East		**158,653**	**196,214**	**210,698**	**220,559**	**246,058**	**256,056**	**261,432**	**272,849**	**290,395**	**291,288**	**306,015**	**57**	**69**	**74**	**78**	**87**	**91**	**93**	**97**	**104**	**104**	**110**
WHO European Region		**302,449**	**339,494**	**353,947**	**363,561**	**382,058**	**385,796**	**390,574**	**403,726**	**414,959**	**414,697**	**426,457**	**35**	**39**	**41**	**42**	**44**	**44**	**45**	**46**	**47**	**47**	**48**

Information updated to 31 December 2007. Not including cases from Abkhazia, Greenland (99 cases in 2005), Northern Cyprus and S.Ossetia; neither cases from Kosovo (1 102 cases in 2005) after 1997.
Blue figures indicate new cases only.

a. important changes to reporting system in Germany (2001) and in Greece and Israel (1998)

b. 1995-1996: new respiratory cases only; 1997-2003: all respiratory and meningeal cases; 2004-2005: all cases

c. inclusion of retreated TB cases other than relapses from 2001

d. no data from Republika Srpska in 2003 (rate not shown)

e. included cases from Kosovo until 1997 and from Montenegro until 2004

Table 2

Tuberculosis notification and mortality, WHO European Region: selected indicators

		Mean annual % change in total notification rate		TB notification, 2005								TB mortality, 2005[a]	
									HIV status of TB cases				
	Country	1995-2000	2000-2005	% cases in males	% cases in <15y	% cases in >64y	% cases of foreign origin[b]	% cases treated for TB in past	Cases with HIV infection N	Cases with HIV infection %[c]	% HIV status unknown	N	Rate/ 100,000 population
'EU-15' (pre-2004)													
	Austria	-2.4%	-4.2%	66%	4.2%	20.9%	44%	3%	-	-	-	52	0.6
	Belgium	-1.1%	-3.5%	62%	6.6%	23.3%	52%	6%	52	4.5%	18%	-	-
	Denmark	3.9%	-5.0%	60%	9.0%	9.5%	61%	7%	9	2.1%	98%	-	-
	Finland	-4.1%	-7.4%	57%	1.4%	52.9%	10%	7%	3	0.8%	-	38	0.7
	France	-5.3%	-4.9%	60%	5.6%	23.2%	45%	7%	-	-	-	428 [d]	0.7
	Germany	-5.9%	-7.7%	60%	3.8%	28.2%	44%	8%	-	-	-	350 [d]	0.4
	Greece	-2.9%	2.3%	64%	8.1%	28.5%	28%	10%	-	-	-	75 [d]	0.7
	Ireland	-3.2%	0.5%	60%	6.2%	19.8%	34%	10%	2	0.4%	99%	15	0.4
	Italy	-1.8%	-2.9%	60%	3.9%	25.1%	44%	7%	-	-	-	-	-
	Luxembourg	-	-	57%	2.7%	10.8%	68%	0%	-	-	-	1	0.2
	Netherlands	-2.9%	-4.1%	59%	4.4%	16.9%	66%	4%	61	5.3%	78%	34 [d]	0.2
	Portugal	-4.5%	-5.0%	68%	2.8%	15.1%	12%	10%	546	15.4%	50%	211 [e]	2.0
	Spain	-1.0%	-2.7%	65%	6.4%	17.7%	19%	7%	394	5.0%	55%	334 [d]	0.8
	Sweden	-3.9%	4.2%	53%	6.6%	21.8%	73%	5%	-	-	-	16 [d]	0.2
	United Kingdom	1.7%	3.7%	55%	5.5%	14.9%	65%	7%	548 [e]	8.3%	-	384 [d]	0.6
	Subtotal 'EU-15'	**-3.1%**	**-3.0%**	**61%**	**5.1%**	**20.6%**	**41%**	**7%**	**-**	**4.8%**	**-**	**-**	**0.6**
New EU countries (since 2004)													
	Bulgaria	2.2%	0.8%	67%	5.5%	19.5%	0%	6%	10 [d]	0.3%	>99%	268 [d]	3.4
	Cyprus	-	-	68%	8.1%	16.2%	68%	8%	-	-	-	-	-
	Czech Republic	-4.5%	-6.8%	64%	0.6%	37.3%	13%	3%	5 [e]	0.4%	78%	68	0.7
	Estonia	6.7%	-7.5%	66%	0.2%	13.1%	16%	18%	33	6.4%	9%	49	3.6
	Hungary	-3.4%	-11.1%	69%	0.3%	25.2%	3%	18%	-	-	-	191	1.9
	Latvia	7.4%	-6.2%	70%	4.7%	9.8%	6%	14%	51	3.5%	96%	170	7.4
	Lithuania	5.7%	-2.3%	69%	3.5%	14.6%	3%	18%	7	0.3%	-	308 [d]	9.0
	Malta	-	-	88%	0.0%	24.0%	68%	4%	0	0.0%	0%	1	0.2
	Poland	-6.3%	-4.0%	66%	1.1%	27.3%	0%	11%	15 [e]	0.1%	>99%	806	2.1
	Romania	4.1%	1.9%	70%	3.8%	10.8%	0%	24%	187	0.6%	63%	2,089 [d]	9.6
	Slovakia	-6.3%	-6.5%	61%	2.9%	36.1%	4%	14%	1	0.1%	23%	47	0.9
	Slovenia	-6.1%	-5.9%	58%	2.5%	33.8%	17%	10%	0	0.0%	76%	17	0.6
	Subtotal New EU countries	**0.2%**	**-1.4%**	**68%**	**3.1%**	**16.2%**	**1%**	**19%**	**-**	**0.3%**	**-**	**-**	**2.1**
	Subtotal all EU ('EU-27')	**-1.6%**	**-2.4%**	**65%**	**4.0%**	**18.2%**	**19%**	**14%**	**-**	**0.7%**	**-**	**-**	**0.7**

West, non-EU													
	Andorra	-	-	30%	0.0%	0.0%	80%	0%	0	0.0%	20%	-	-
	Iceland	-	-	73%	0.0%	27.3%	64%	9%	1	9.1%	18%	0	0.0
	Israel	8.2%	-8.6%	56%	9.9%	29.3%	82%	2%	22	5.4%	-	24 [e]	0.4
	Monaco	-	-	-	-	-	-	-	-	-	-	-	-
	Norway	0.2%	4.9%	52%	6.3%	14.9%	78%	5%	-	-	-	7 [d]	0.2
	San Marino	-	-	-	-	-	-	-	-	-	-	-	-
	Switzerland	-5.4%	-2.4%	55%	3.9%	23.8%	60%	8%	-	-	-	16 [d]	0.2
Total EU and West		**-1.6%**	**-2.4%**	**65%**	**4.0%**	**18.2%**	**20%**	**13%**	**-**	**0.8%**	**-**	**-**	**0.7**
Balkans													
	Albania	0.0%	-3.3%	67%	6.1%	24.6%	*1%*	8%	1	0.2%	>99%	*12* [d]	*0.4*
	Bosnia and Herzegovina	3.0%	-5.3%	54%	1.7%	36.7%	*0%*	7%	-	-	-	-	-
	Croatia	-4.1%	-6.9%	63%	2.2%	33.5%	9%	8%	-	-	-	109	2.5
	Macedonia, F.Y.R.	-3.2%	-0.5%	59%	13.7%	16.0%	*0%*	16%	2	0.3%	94%	78 [e]	3.8
	Montenegro	-	-	61%	0.0%	26.5%	*1%*	16%	0	0.0%	95%	-	-
	Serbia	-2.5%	-1.7%	61%	0.8%	32.2%	*2%*	11%	3	0.1%	>99%	-	-
	Turkey	-5.8%	1.3%	65%	6.0%	9.5%	*0%*	9%	-	-	-	-	-
Total Balkans		**-4.7%**	**-0.2%**	**64%**	**5.2%**	**15.2%**	*1%*	**9%**	**-**	**0.2%**	**-**	**-**	**2.5**
East													
	Armenia	12.3%	12.6%	80%	4.6%	5.9%	*0%*	14%	46	2.0%	98%	*155* [e]	*4.8*
	Azerbaijan	10.3%	12.3%	67%	5.2%	6.4%	*0%*	40%	8 [e]	0.2%	-	-	-
	Belarus	5.3%	1.9%	72% [f]	1.2% [f]	11.1% [f]	*0%* [f]	17%	32 [f]	0.6%	-	1,027 [e]	10.4
	Georgia	-9.9%	1.4%	72%	6.3%	10.5%	*0%*	33%	13	0.2%	90%	-	-
	Kazakhstan[g]	22.2%	1.8%	58%	5.7%	4.5%	*0%*	28%	-	-	-	3,305 [d]	22.0
	Kyrgyzstan[g]	12.3%	0.2%	57% [f]	13.2% [f]	7.8% [f]	*0%* [f]	13%	-	-	-	*797*	*15.6*
	Moldova	2.4%	18.4%	76%	2.9%	5.1%	*1%*	28%	-	-	-	659	18.3
	Russian Federation	8.6%	2.3%	-	2.6% [f]	7.0% [f]	*1%* [f]	24%	1,544 [f]	1.3%	-	32,220	22.5
	Tajikistan[g]	6.4%	19.9%	56% [f]	8.1% [f]	5.3% [f]	*0%* [f]	25%	-	-	-	*622*	*9.5*
	Turkmenistan[g]	14.8%	-3.9%	65%	5.3%	3.3%	0%	4%	-	-	-	-	-
	Ukraine	10.2%	6.7%	-	-	-	*0%*	11%	-	-	-	11,896	25.4
	Uzbekistan[g]	8.9%	12.4%	56%	8.3%	8.4%	*0%*	31%	147	0.5%	>99%	*2,784*	*10.6*
Total East		**10.0%**	**3.9%**	**61%**	**4.3%**	**6.8%**	**0%**	**23%**	**-**	**0.6%**	**-**	**-**	**15.6**
Total WHO European Region		**4.8%**	**1.8%**	**63%**	**4.3%**	**10.5%**	**5%**	**20%**	**-**	**0.5%**	**-**	**-**	**0.9**

a. Source: WHO Mortality Database (WHOSIS, update October 2007). Codes included: ICD-9 010-018 (BTL 020-025,029) or ICD-10 A15-19. Italics indicate <80% coverage or / and data completeness. Totals show median values (rates) for countries grouped.
b. As defined by birth; italics indicate use of citizenship as criterion
c. Totals show median values (percentage) for countries grouped
d. Values for 2004
e. Values for 2003
f. Previously untreated cases only (for statistics other than HIV infection, including also cases with previous treatment unknown in Belarus and relapses in the Russian Federation)
g. Central Asian states

following an increase in 1995-2000, while in the Czech Republic, Hungary and Slovakia the decline was faster in the latter period than in earlier years. Bulgaria and Romania had smaller increases in rates in 2000-2005 than in 1995-2000.

In 2005, two thirds of notifications were among males, and rates among them increased after childhood, reaching a plateau in adulthood with a subsequent slight increase in old age (Figure 2). In females, rates were lower than in males after childhood, with a bi-modal pattern peaking in early adulthood and in old age. Rates decreased progressively in all age groups over time (Figure 3). This largely reflected the trend in many countries, including France, Germany, the Netherlands and Portugal. However, while rates in cases aged 55 or older decreased sharply in all countries, differences were noted in the progression of rates in children and young adults between countries (data not shown). In Romania (not included in Figure 3), rates increased in all age groups until 2002, after which they declined. In this country, the proportion of previously treated cases increased progressively in 1995-2005 to reach 24% in 2005, by far the highest in all the EU and West.

The Baltic States experienced a substantial rise in notification rates in the 1990s after their independence from the Soviet Union, which has only abated in recent years. In Latvia and Lithuania, which accounted for most cases from the Baltic States, TB notification rates increased in under-5 year olds, but decreased in adults in recent years. In the United Kingdom, rates remained stable at low levels in children but increased progressively in all age groups between 15 and 54, with a doubling in rates in the 25-34 year olds over the period, during which time the proportion of foreign TB cases increased steadily to 79% in 2005. The contribution of TB in immigrants to overall notification varied greatly between countries. While only 1% of cases reported by the central European countries in 2005 were not autochthonous (new EU countries excluding Cyprus and Malta; country range: 0-17%), in the other countries 42% of TB cases were of foreign origin (range: 12-82%). In 27 countries with data for 2005, two thirds of cases of foreign origin were equally distributed between Asia and Africa, 19% were from another country of the EU and West or the Balkans, and 9% from a former Soviet Union republic outside the EU. Half the foreign cases originated from only 11 countries, which included high-burden countries from the Indian Sub-continent and Sub-Saharan Africa as well as other populous countries within the WHO European Region itself.

Aggregated data on HIV sero-status of TB cases reported in 2003 to 2005 were available for 21 countries. The highest HIV prevalence among TB cases was reported by Portugal (15%) and Iceland (9%, 1 case), and was 2-8% in 8 countries and 0-1% in 11 countries. HIV prevalence among TB cases was reportedly stable in 2000-2005 in most countries, but increased markedly in Estonia (from 0.1% to 6.4%) and Latvia (from 0.7% to 3.5%).

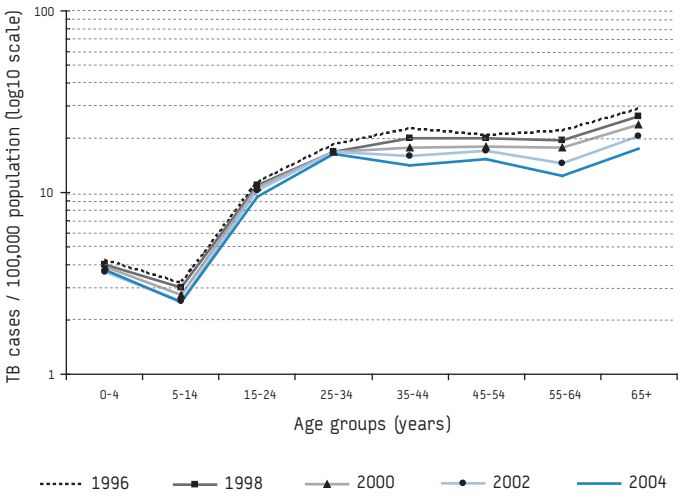
Total TB mortality rate was 1/100,000 population or less in most countries, but was higher in Bulgaria, Hungary, Poland, and Portugal (2-3), and even higher in the Baltic States and Romania (4-10). In the 'EU15' and West, mortality increased progressively by age, being more than four times higher in persons over 64 years when compared to those aged 55 to 64 years (Figure 4). In contrast, in the central European Member States, rates increased sharply from childhood to early middle-age but then more smoothly into old age.

The Balkans

In 2005, 27,582 TB cases were reported by the seven Balkan countries, 74% of these cases by Turkey alone. The overall TB

FIGURE 3

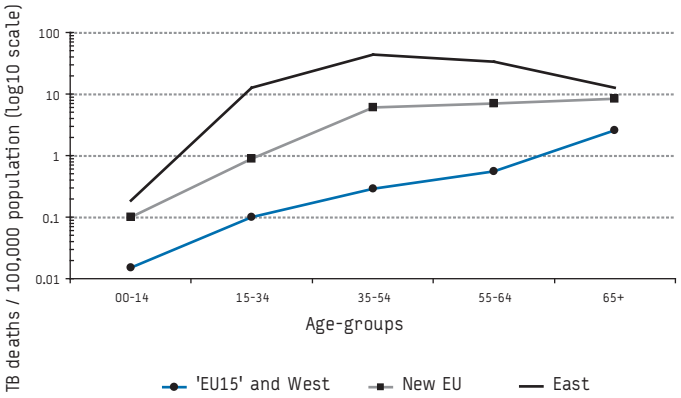
Age-group specific TB notification rates, EU & West*, 1996-2004



* excluding cases without information on age (769) and cases from countries without full age distribution for one or more years: Andorra, Bulgaria, Cyprus, Greece, Ireland, Monaco, San Marino, Spain. Romania excluded as the age-specific rates are very different from the rest of the EU and West.

FIGURE 4

TB mortality rates by age-group, EU & West and East,* latest available data



* excluding 438 TB deaths with age unknown and including latest data (2003-2005) for countries using ICD-10 coding: **'EU15' and West** (N=1,895): Austria, Finland, France, Germany, Israel, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom; **New EU** (N=3,739): Czech Rep, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia; **East** (N=52,252): Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russian Federation, Ukraine, Uzbekistan (Source: WHO Mortality Database, WHOSIS, update October 2007)

notification rate in the countries was 29/100,000, with rates higher in Bosnia and Herzegovina (55) than in the other countries (17-32). Between 2000 and 2005, rates decreased by 0.5-6.9% yearly in all countries, except for Turkey where they increased by 1.3%. A decline was observed in Bosnia and Herzegovina following an increase in the late 1990s.

Males predominated (range: 54-67%) among notifications. Children represented 5% of reported cases in 2005 but reached 14% in the Former Yugoslav Republic of Macedonia (overall rate 32/100,000). Notification rates in males increased sharply from childhood to early adulthood, and then increased slowly into old age. In females, rates were lower than in males in adults and decreased after early adulthood to rise again smoothly in the elderly.

As for central EU Member States, only 1% of cases overall were of foreign origin (9% in Croatia) and two thirds of these were from another Balkan country. HIV sero-prevalence among TB cases was reported by four countries and was low (range: 0.0-0.3%).

TB mortality rates were moderate in Croatia and the Former Yugoslav Republic of Macedonia (2.5 and 3.8/100,000 population respectively).

East

In 2005, the overall TB notification rate in the 12 former Soviet Union republics in the East reached 110/100,000 population. Rates were higher than average in Kazakhstan (205), Moldova (162), Georgia (144) and Kyrgyzstan (130). Over half of the 306,015 cases reported in this area were from the Russian Federation. Notification rates in the East increased on average by 3.9% yearly between 2000 and 2005, but this ranged widely between countries (-3.9% to +19.9%). Much of the overall increase is attributable to increasing inclusion of previously treated cases, the proportion of which increased from 12% to 25% over this period as the number of new cases remained stable (Figure 1). However, the mean annual increase in rates was 2.5 times lower in 2000-2005 than that observed between 1995 and 2000.

While there was a male predominance among notified cases this is lower in the central Asian republics than in the other countries (57% vs. 72% respectively). Children accounted for 4% of the cases overall, but reached 13% in Kyrgyzstan among previously untreated cases. Most cases aggregated in the ages 15-44 years with only 7% of cases being over 64 years. Rates in males increased from childhood to middle age by a factor of 10 and then decreased sharply in the older ages. Notification rates in childhood were similar between the sexes but much higher in adult males than in females, in whom they peaked in young adulthood and in middle-age.

Most Eastern countries do not report TB in foreign citizens. In Moldova and the Russian Federation, foreign citizens represented 1% of notified cases. Information on TB-HIV comorbidity was sparse. Six countries reported results of HIV testing in TB patients, in which 0.2-2.0% of notified TB cases were HIV positive in recent years.

Mortality data for TB were available for nine countries, of which four had low coverage or completeness. Total TB mortality rates in the other five countries varied between 10.4 and 25.4/100,000 in the latest available year. Mortality rates increased rapidly from childhood to peak at age group 35-54 years, and then decreased at old ages.

Discussion

The reversal in the decline in TB notification rates observed in the early 1990s in western countries of the WHO European Region persisted for some years but, with some notable exceptions, most countries have experienced a steady decrease in newly-diagnosed TB cases in recent years. As notifications among nationals decreased or remained stable in nearly all countries, cases of foreign origin came to represent a larger proportion of all TB cases reported. Immigration from countries with high TB prevalence has been one of the most important recent developments concerning TB in much of the industrialised EU. Thus, the recent increase in total TB cases observed in Sweden and the United Kingdom reflect the incremental trend in foreign-born cases as rates largely stabilised among the indigenous population. Populations of foreign origin generally experience higher TB notification rates than nationals [8]. The bi-modal pattern in age-specific notification rates in the western countries reflects the superimposition of patterns from foreign (largely young adult) and autochthonous (mostly elderly) populations. These changes in the profile of TB patients in the western countries are likely to impact negatively on treatment outcome. Foreign patients are more likely to have drug resistance [9]. Treatment interruption is more common in immigrants [10]. Furthermore, the increasing age of TB patients has a negative impact on likelihood of treatment success [11]. In Finland, deaths among TB cases - half of whom are nowadays elderly - are higher than elsewhere [12].

TB surveillance data and trends in the East have to be interpreted carefully, as in several countries TB notification has been influenced differently by changes in TB control systems since the early 1990s. Stabilisation or increase in notification rates may thus reflect improved case detection or changes in case definitions rather than actual incidence. The wide range in the proportion of notified cases having had TB in the past reflects differences in patient recruitment and in the definition of a notifiable case. Much of the increment in case reports in the East in recent years was due to the increased inclusion of previously treated cases while the number of newly diagnosed cases levelled off. This explains the spike in the Russian Federation in 2003, which influenced overall rates in the East given the large share of cases coming from this country alone (Figure 1). Similarly, the Baltic States started including forms of previously treated cases in addition to relapses midway in the period under study partly explaining a peaking of total notification rates around this time. Despite these artifacts, the high notification rates in young adults in the East still indicate intense transmission in recent years.

Testing for HIV among TB patients and for TB among HIV-positive individuals is problematic and comment on trends of TB/HIV comorbidity are impeded by incomplete information. In most countries the HIV status is known for only a small proportion of TB cases. The proportion of TB cases infected with HIV when calculated by including all notified TB cases in the denominator gives a conservative estimate in countries where HIV testing is offered only to a selection of patients based on risk. Retrieval of testing results is also incomplete. Notwithstanding, a number of observations can be made. In Balkan countries, the low prevalence of HIV among TB cases is associated with a low HIV prevalence in the general population of these countries up to now [13,14]. The increase in HIV prevalence among TB cases observed elsewhere reflects separate processes of particular concern. In the United Kingdom, there has been increasing immigration from countries with high prevalence for both TB and HIV in recent years [15]. In

western countries injecting drug users (IDUs) usually predominate among HIV cases with TB, suggesting a higher risk for developing TB among this HIV transmission group [16]. The same appears to be the case in the former Soviet Union republics where a dramatic increase in newly diagnosed HIV infections has occurred since the mid-1990s, mostly among IDUs [17]. Being an IDU was a strong predictor of HIV infection in younger adults with TB in Kiev city (Ukraine) in 2004-2005, and TB/HIV comorbidity among IDUs has reportedly increased since 2002 [18]. In 2002-2003, 92% of 49 TB/HIV cases detected in a cross-sectional survey of St Petersburg (Russian Federation) had injected drugs [19]. In Estonia, which has endured a sharp HIV-epidemic in the early years of this decade mostly in IDUs, [20] the steady rise in TB/HIV comorbidity is likely to represent an overlap of the HIV and TB epidemics in the indigenous population. And in Latvia, where cases having TB and HIV increased, 31 of 51 TB/HIV cases detected in 1998-2001 were in IDUs [21].

TB mortality rates follow roughly the same geographic gradient as TB morbidity. All former Soviet Union republics had high TB death-to-notification ratios. In contrast to countries further west mortality rates and death-to-notification ratios peaked before old age. This may reflect a higher lethality due to drug-resistant disease, the prevalence of which is high in countries like Kazakhstan [22]. In Ukraine, a country which has been particularly affected by the HIV epidemic for a number of years [13], this may be the effect of comorbidity. Despite these observations, some limitations are noted when comparing data between countries. The practice of coding the cause of death varies between vital registration systems in different countries. For instance Lithuania attributes much more TB deaths to miliary disease than neighbouring Estonia and Latvia. Most countries in the East never use codes for death from the late effects of TB (i.e. ICD-9 137 or ICD-10 B90), in contrast to many Western countries, some of which - like Norway and Sweden - register more deaths in these categories than under the standard tuberculosis codes used in this article [5].

Conclusion

Countries in the East, with their high TB morbidity and mortality, remain a priority for TB surveillance in the WHO European Region. Surveillance systems need to be reinforced and modernized, and data collection increasingly automated. Access of TB patients to health care facilities with reliable laboratory facilities to perform culture examination and HIV testing, and the reporting of these test results should become more widespread. Cases of foreign origin should be more widely reported. The male predominance among adult TB cases, albeit more or less ubiquitous in the world [23], should serve as an alert to investigate possible barriers to access to care for women, especially when sex-ratios differ markedly between neighbouring countries with similar epidemiological patterns.

Today's EU presents a wide spectrum of TB patterns. Notification rates in the Baltic States remain high even if in decline, and these countries are particularly concerned by TB/HIV comorbidity and drug resistance. Central European countries, several bordering the former Soviet Union, need to be vigilant regarding a possible re-emergence of TB. The low TB incidence in much of the EU and West are no reason for complacency. The elimination of TB (<1 TB case/1,000,000 population) is still a distant prospect for all countries. The measurement of progress towards elimination will necessitate sensitive indices of disease activity in sub-populations at increased risk of TB infection. These groups need to be better profiled at the supranational level. Similar to the way geographical origin has been built into international reporting, the collection of additional variables that are amenable to adequate standardisation can be useful for targeting public health action. These could include indices of social deprivation, history of imprisonment, use of tobacco, use of alcohol, injecting drug use, contact with active TB and area of residence within the country.

Despite efforts throughout the lifetime of EuroTB to standardise the European case definition for TB case reporting, more work is required. The Regional network of national TB surveillance authorities has provided a useful forum for discussion and exchange of experiences in the past, including the revision of the European case definition in 2006. This resource should be developed in future to enhance the process of routine data collection, conduction of surveys and standardisation of methodology.

Acknowledgements

The EuroTB network was jointly funded by the European Commission (DG-SANCO) and the Institut de veille sanitaire of France. The following correspondents, in place at the end of 2007, had the opportunity to comment on an advanced draft of this article: M Coll Armangué (Andorra), H Hafizi (Albania), V Pogosian (Armenia), JP Klein (Austria), F Agaev (Azerbaijan), G Gurevich (Belarus), M Wanlin (Belgium), Z Dizdarevic, M Duronjic (Bosnia and Herzegovina), V Milanov (Bulgaria), A Simunovic (Croatia), C Hadjianastassiou (Cyprus), J Wallenfels (Czech Republic), P Andersen (Denmark), V Hollo (Estonia), P Ruutu (Finland), D Antoine (France), A Salakaia (Georgia), W Haas, B Brodhun (Germany), G Spala (Greece), J Strausz (Hungary), T Blondal (Iceland), J O'Donnell (Ireland), D Chemtob (Israel), MG Pompa (Italy), Sh Ismailov (Kazakhstan), A Alisherov (Kyrgyzstan), J Leimans (Latvia), E Davidavicienė (Lithuania), P Huberty-Krau (Luxembourg), S Talevski (the Former Yugoslav Republic of Macedonia), A Pace Asciak (Malta), D Sain (Moldova), A Negre (Monaco), O Bojovic (Montenegro), C Erkens (the Netherlands), B Winje-Askeland (Norway), M Korzeniewska-Kosela (Poland), A Fonseca Antunes (Portugal), D Chiotan (Romania), E Kakorina (Russian Federation), A Sorcinelli (San Marino), G Radosavljevic-Asic (Serbia), I Solovic (Slovakia), D Erzen (Slovenia), E Rodriguez Valin (Spain), V Romanus (Sweden), P Helbling (Switzerland), S Saidaliev (Tajikistan), F Gümüslü (Turkey), B Jumaev (Turkmenistan), M Golubchykov (Ukraine), J Watson, J McMenamin, R Salmon, B Smyth (United Kingdom), D Usmanova (Uzbekistan). Likewise other members of the EuroTB Advisory Committee not already mentioned: L Clancy, F Drobniewski, E Ibraim, M Forssbohm, V Kuyvenhoven and R Zaleskis. We also acknowledge the comments on this article made by J-C Desenclos and D Che of the Department of Infectious Diseases at the Institut de veille sanitaire.

References

1. Raviglione MC, Sudre P, Rieder HL, Spinaci S, Kochi A. Secular trends of tuberculosis in Western Europe. Bull World Health Organ 1993; 71(3-4):297-306.
2. Coker RJ, Atun RA, McKee M. Health-care system frailties and public health control of communicable disease on the European Union's new eastern border. Lancet 2004;363(9418):1389-92.
3. Raviglione M, Rieder HL, Styblo K, Khomenko AG, Esteves K, Kochi A. Tuberculosis trends in Eastern Europe and the former USSR. Tuber Lung Dis. 1994 Dec;75(6):400-16.
4. United Nations Population Division. Annual Populations 1950-2050 (The 2006 Revision), United Nations, New York. 2007.
5. World Health Organization. Mortality Database. Available from: http://www3.who.int/whosis/en (updated 15 October 2007, accessed 18 December 2007).

6. Rieder HL, Watson JM, Raviglione MC, Forssbohm M, Migliori GB, Schwoebel V, et al. Surveillance of tuberculosis in Europe. Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting on tuberculosis cases. Eur Respir J. 1996;9(5):1097-104.
7. The Commission of the European Communities. Commission Decision of 19 March 2002 laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (2002/253/EC). Official Journal of the European Communities 2002; 86:44-62.
8. Infuso A, Falzon D, on behalf of the EuroTB network. [European surveillance of tuberculosis: description of the network and recent results] Med Mal Infect. 2005;35(5):264-8. French.
9. Falzon D, Infuso A, Aït-Belghiti F, for the EuroTB correspondents. In the European Union, TB patients from former Soviet countries have a high risk of multidrug resistance. Int J Tuberc Lung Dis. 2006;10(9):954-8.
10. Borgdorff MW, Veen J, Kalisvaart NA, Broekmans JF, Nagelkerke N. Defaulting from tuberculosis treatment in the Netherlands: rates, risk factors and trend in the period 1993-1997. Eur Respir J. 2000;16(2):209-13.
11. Falzon D, Le Strat Y, Belghiti F, Infuso A, for the EuroTB correspondents. Exploring the determinants of treatment success for tuberculosis cases in Europe. Int J Tuberc Lung Dis 2005;9(11):1224-1229.
12. Vasankari T, Holmström P, Ollgren J, Liippo K, Kokki M, Ruutu P. Risk factors for poor tuberculosis treatment outcome in Finland: a cohort study. BMC Public Health. 2007;7(147):291.
13. EuroHIV. HIV/AIDS surveillance in Europe. End-year report 2005. No. 73 (www.eurohiv.org). Saint-Maurice: Institut de veille sanitaire; 2006. Available from: http://www.eurohiv.org/reports/report_73/pdf/report_eurohiv_73.pdf
14. UNAIDS Annual Report 2006: making the money work. Geneva: UNAIDS; 2006. Available from: http://data.unaids.org/pub/Report/2007/2006_unaids_annual_report_en.pdf
15. Ahmed AB, Abubakar I, Delpech V, Lipman M, Boccia D, Forde J, et al. The growing impact of HIV infection on the epidemiology of tuberculosis in England and Wales: 1999-2003. Thorax. 2007;62(8):672-6.
16. Kirk O, Gatell JM, Mocroft A, Pedersen C, Proenca R, Brettle RP, et al. Infections with Mycobacterium tuberculosis and Mycobacterium avium among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group JD. Am J Respir Crit Care Med. 2000;162(3 Pt 1):865-72.
17. Hamers FF, Downs AM. HIV in central and eastern Europe. Lancet 2003;361(9362):1035-1044.
18. van der Werf MJ, Yegorova OB, Chentsova N, Chechulin Y, Hasker E, Petrenko VI, et al. Tuberculosis-HIV co-infection in Kiev City, Ukraine. Emerg Infect Dis. 2006;12(5):766-8.
19. Van Rie A, Zhemkov V, Granskaya J, Steklova L, Shpakovskaya L, Wendelboe A, et al. TB and HIV in St Petersburg, Russia: a looming catastrophe? Int J Tuberc Lung Dis. 2005;9(7):740-5.
20. Uuskula A, Kalikova A, Zilmer K, Tammai L, DeHovitz J. The role of injection drug use in the emergence of human immunodeficiency virus infection in Estonia. Int J Infect Dis 2002;6(1):23-27.
21. Morozova I, Riekstina V, Sture G, Wells C, Leimane V. Impact of the growing HIV-1 epidemic on multidrug-resistant tuberculosis control in Latvia. Int J Tuberc Lung Dis 2003;7(9):903-906.
22. World Health Organization/International Union Against TB and Lung Disease Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Anti-Tuberculosis Drug Resistance in the World: Fourth Global Report. 2008. Available from: http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf
23. Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. Int J Tuberc Lung Dis 1998;2(2):96-104.

This article was published on 18 March 2008.

Citation style for this article: Falzon D, van Cauteren D. Demographic features and trends in tuberculosis cases in the European Region, 1995-2005. Euro Surveill. 2008;13(12):pii=8075. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8075

Research articles

The added value of a European Union tuberculosis reference laboratory network – analysis of the national reference laboratory activities

F A Drobniewski[1], V Nikolayevskyy[1], S Hoffner[2], O Pogoryelova[1], D Manissero[3], A J Ozin (amanda.ozin@ecdc.europa.eu)[3]
1. Health Sciences Research and Health Protection Agency, London, United Kingdom
2. Department of Bacteriology, Smittskyddsinstitutet (Swedish Institute for Infectious Disease Control, SMI), Solna, Sweden
3. European Centre for Disease Prevention and Control, Stockholm, Sweden

National reference laboratories (NRL) and other laboratories are the cornerstones of well-functioning tuberculosis programmes and surveillance activities. However, the scope and activity of NRL services for mycobacterial identification and drug susceptibility testing (DST) has not been examined in detail across the European Union (EU), nor has the added value of cooperation and networking at the European level been explored with regard to strengthening laboratory services. Therefore, the European Centre for Disease Prevention and Control (ECDC) has commissioned a survey to explore these issues and to identify areas of work that could bring added value by supporting networking activities of tuberculosis (TB) reference laboratories in the EU. Structured questionnaires were sent to TB reference laboratory experts in the EU and European Economic Area (EEA) countries, and in three additional countries selected on the basis of their networking activities with EU projects and other initiatives (Switzerland, Croatia and Israel). The compiled results describe the activities and structure of 32 NRLs (29 countries replied, a response rate of 91%). The analysis of the survey led to the following recommendations for strengthening TB laboratory services: (1) implementing of the published European standards for TB laboratory services with respect to infrastructure, national reference functions, biosafety, human resources, quality assurance, operational research (including evaluation of new medical diagnostics), accuracy and speed, appropriately trained staff; (2) ensuring that laboratories only perform activities for which they have demonstrated proficiency; (3) implement validated and standardised second-line drug susceptibility testing (DST), including drugs used to define extensively drug-resistant tuberculosis (XDR TB); (4) aiming to identify *Mycobacterium tuberculosis* complex (MTBC) and rifampicin (RIF) resistance in over 90% of cultures and cases from smear-positive sputum directly within one to two working days. To realise some of the above recommendations and to strengthen links of TB surveillance and microbiology activities in the EU, a list of suggested generic areas of activities for an EU network of reference laboratories is presented. Such a network would build on and link to existing networks and initiatives at the European and global level.

Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality in Europe. In 2005, 51 of 53 countries in the World Health Organization (WHO) European region reported 426,717 cases (an overall notification rate of 48 TB cases per 100,000 population or 8% of the total number of cases reported globally) [1,2]. In the same year the countries of the current European Union (EU) and European Economic Area (EEA) reported 93,129 cases (an average notification rate of 18/100,000) with notification rates and numbers significantly higher in the East than the West [2] (apart from Portugal). Higher rates were seen in the Baltic States, Romania, and Bulgaria with the latter two countries (EU accession states at the time) accounting for 35% of the cases. Even in low incidence countries [18] notification rates in vulnerable and high-risk populations can be as high as those reported in high burden countries globally [2].

In the context of the heterogeneous epidemiological setting in the EU, the situation of TB control is further complicated by the presence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. High MDR TB rates are reported mainly in the Baltic States, but drug-resistant cases are found throughout the whole of the EU, with occasional outbreaks in countries with a low incidence of TB [2-8].

An integrated TB surveillance system already exists across the EU and European region, initially organised by the EuroTB project funded by the Directorate General for Health and Consumer Affairs (DG SANCO) and co-financed by the Institute de Veille Sanitaire, France (InVS) [2], and currently by a joint effort of the European Centre for Disease Prevention and Control (ECDC) and WHO European Region (WHO EURO). However, the scope and activity of national reference laboratory services for mycobacterial identification and drug susceptibility testing, on which much of this surveillance activity is based, has not been examined in detail across the EU Member States (MS), nor has the added value of cooperation and networking at EU level and with neighbouring countries been explored with regard to strengthening laboratory services.

In addition to its role in TB surveillance, the laboratory is the cornerstone of TB diagnosis, essential for both the management of individual patients and effective TB control. This requires access to accurate and timely laboratory diagnosis, including DST and, in particular, faster methods for the diagnosis of TB and MDR/XDR TB. Given this essential role, laboratory services, in the EU and globally, clearly need further strengthening and support in order to achieve the goals of national TB programmes and ensure quality diagnosis for patients [9,10].

We therefore conducted a situation analysis of national TB reference laboratory (NRL) services across the member states of the EU/EEA countries (including Norway and Iceland), and selected

non-EU countries (Switzerland, Croatia and Israel) that were linked to EU projects. It was aimed at determining the range and availability of primary and reference diagnostic services that offer identification of mycobacterial cultures as *Mycobacterium tuberculosis* complex (MTBC; usually *M. tuberculosis*, or M. bovis) and first- and second-line drug susceptibility testing. Information on the existence of standard operating procedures (SOPs), standardisation and quality control of procedures was sought and respondents were asked what they believed the NRL service should do and whether they thought these activities were currently being undertaken.

Materials and Methods

A structured questionnaire was sent electronically to TB reference laboratory experts within the EU/EEA countries as well as to Switzerland, Croatia and Israel, countries that are involved in other EU-supported initiatives relevant to this survey. These experts were identified through the following sources or criteria: (1) They were included on lists of directors of NRLs held by EuroTB and WHO EURO; (2) They were the recipients of specimen panels which are sent to NRLs globally by the WHO Global Project on TB Drug Resistance. Within the EU, the identity of the director of the NRL and whether they were qualified to comment on the national TB reference service was additionally confirmed, wherever possible, by the recently established forum of ECDC National Microbiological Focal Points (a consultation group of microbiologists, appointed by the MS, who know the systems and structures of public health microbiology services in their countries well and can support ECDC in strategic and technical issues) [11].

A pilot survey was conducted that involved only a small number of EU and non-EU countries (Croatia, Denmark, Germany, Italy, Latvia, Sweden and the United Kingdom). The questionnaire was subsequently modified for clarity and precision to produce a final questionnaire that was made available in English, French and Russian. These final questionnaires were completed electronically and contained a total of 83 questions. Most questions required choosing between "Yes", "No", "Don't know", and "Not applicable" from a drop-down menu, and some required entering numerical data *and/or* additional comments.

A list of all activities typically performed by TB laboratories was compiled and the respondents were asked whether they believed the activity was appropriate for an NRL ("ideal" activity). They were then asked if their NRL performed this activity ("actual" activity). The responses were graded on a five-point scale with a maximum score of 160 points per activity in case all laboratories agreed that this activity should be performed (32 laboratories x 5 points).

Those aspects of the survey that referred to functions expected of the NRL services and to areas of added value from networking of NRLs at EU level, were discussed in working groups and plenary sessions at a meeting of TB surveillance correspondents in Stockholm, September 2007 ["ECDC - WHO EURO - EuroTB: Annual Meeting on Tuberculosis Surveillance in Europe"]. The participants were TB microbiology experts, including those who had received and responded to the questionnaire and those from other TB microbiological centres, as well as TB surveillance experts.

Results

Responses were received from 32 TB reference laboratory experts, situated in laboratories in the cities indicated below, and representing 27 EU/EEA countries as well as two countries outside the EU (29 countries overall, a response rate of 91%):

- EU: Belgium (Brussels and Antwerp), Bulgaria (Sofia), Cyprus (Nicosia), Czech Republic (Prague), Denmark (Copenhagen), Estonia (Tartu), Finland (Turku), France (Paris), Germany (Borstel), Hungary (Budapest), Ireland (Dublin), Italy (Rome and Milan), Latvia (Riga), Lithuania (Vilnius), Luxembourg (Luxembourg), Malta (Valetta), Netherlands (Bilthoven), Poland (Warsaw), Portugal (Lisbon and Oporto), Romania (Bucharest), Slovakia (Nitra), Slovenia (Golnik), Spain (Zaragoza), Sweden (Stockholm), United Kingdom (London);
- EEA: Iceland (Reykjavik), Norway (Oslo);
- non-EU/EEA: Croatia (Zagreb), Israel (Tel Aviv).

Laboratory activities

The respondents provided data on cultural and molecular diagnostic methods used in their laboratories for the isolation, detection and speciation of Mycobacteria, and for DST.

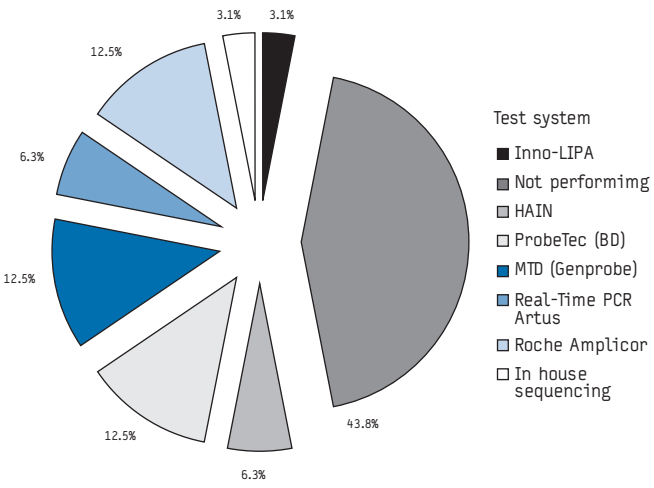
Detection of MTBC and drug susceptibility analysis in clinical specimens

Twenty-seven of 32 laboratories perform smear microscopy and microbiological culture of primary clinical specimens. Laboratories that do not analyse clinical specimens routinely include Bilthoven, Brussels, Oslo, Stockholm, and Turku. Eighteen of 31 laboratories of those testing primary specimens) use rapid methods for detection of MTBC in direct specimens (Figure 1). Most laboratories (14/18) used commercially available assays including reverse-phase hybridisation of labelled PCR products with DNA probes immobilised on membranes (Inno-LiPA, Innogenetics, Belgium and HAIN, Germany) or microplates (Roche Amplicor Mycobacteria), strand displacement amplification (BD ProbeTec ET), amplification and detection of specific rRNA fragments (MTD Genprobe), and real-time PCR (Artus).

Commercial molecular assays used for the diagnosis of drug resistance are all based on the detection of mutations in specific genes associated with drug resistance. Rapid identification of RIF *and/or* isoniazid (INH) resistance in clinical specimens is particularly important for early detection of MDR TB. These tests are performed by 13 (RIF) and 11 (INH) laboratories, using commercial reverse-

Figure 1

Rapid detection of *Mycobacterium tuberculosis* in direct clinical specimens



hybridisation assays such as Inno-LIPA RifTB assay for detection of RIF resistance only, and the HAIN MTBDR and MTBDR+ assays for detection of resistance to RIF and INH together.

A non-commercial reverse hybridisation assay (macroarray) for detection of both RIF and INH resistance is in use in the laboratory in London, six laboratories (Antwerp, Bilthoven, Brussels, London, Milan and Paris) use in-house DNA-sequencing (rpoB gene) for detection of RIF resistance only, and one laboratory (Milan) uses multiplex PCR for the detection of mutations in genes associated with INH resistance (katG and inhA).

Reference culture identification

Identification of isolates can be performed either by using conventional phenotypic methods based on isolation of bacterial cultures on liquid or solid media followed by biochemical tests, or by using molecular methods based on detection of highly specific nucleotide sequences in certain genes (e.g. 16S RNA or rpoB).

Identification of cultures as MTBC with conventional methods is performed by 30 of the 32 laboratories (Reykjavik submits their isolates for identification to Copenhagen and Valetta to London). Five laboratories do not differentiate isolates further to species level within the MTBC (Riga, Vilnius, Antwerp, Rome, and Reykjavik). Rapid identification of MTBC isolates is performed by all but four laboratories (Sofia, and Bucharest do not identify isolates rapidly; cultures from Reykjavik and Valetta are rapidly identified in Copenhagen and London, respectively), using a variety of commercial (Accuprobe, HAIN, Inno-LiPA) and non-commercial molecular assays (DNA sequencing and in house PCR) with most laboratories (16/28) using more than one method: as a first choice method, 13, 11, two, and two laboratories used Accuprobe, HAIN, Innolipa, and in-house molecular methods, respectively.

Non-tuberculous mycobacteria from cultures are identified at all but three laboratories (Vilnius does not perform identification of non-tuberculous mycobacteria; cultures from Reykjavik and Valetta are identified in Copenhagen and London, respectively).

Drug susceptibility testing on cultures

Conventional phenotypical drug susceptibility tests for first-line drugs isoniazid , rifampicin, streptomycin, and ethambutol are performed by all laboratories, and for pyrazinamide by all but four laboratories (first and second-line DST of cultures from Reykjavik, Valetta and Nicosia are performed in Copenhagen, London and Borstel, respectively). The range of second-line (and "third-line") drugs tested for resistance is more limited (Figure 2): Most laboratories test (or submit isolates for testing) for susceptibility to ofloxacin (27 laboratories), cycloserine, para-aminosalicylic acid (PAS) and capreomycin (26 laboratories each), amikacin (25 laboratories), ethionamide (23 laboratories), kanamycin (19 laboratories), and ciprofloxacin (17 laboratories).

Susceptibility tests for 10 other drugs are performed by between one and 11 laboratories (Figure 2). As a consequence, seventeen laboratories are unable to identify all potential XDR TB isolates. However, taking into account recent findings on molecular mechanisms of cross-resistance between aminoglycosides (e.g. kanamycin and amikacin) and cyclic peptides (capreomycin) [12], those laboratories that do not perform tests for all injectable second-line drugs may still be able to detect most XDR TB cases.

Rapid identification of RIF resistance is performed by 19 laboratories and of INH resistance by 15 laboratories, using molecular methods including the Inno-LIPA (RIF), HAIN (RIF and INH), and pyrosequencing commercial assays, or in-house sequencing (rpoB, katG, inhA genes) as the principal molecular method for the detection of drug resistance.

Quality issues

The respondents were requested to provide information on their accreditation, links to WHO supranational reference laboratories

FIGURE 2

Laboratories performing (or submitting isolates for) second- and third-line drug susceptibility testing

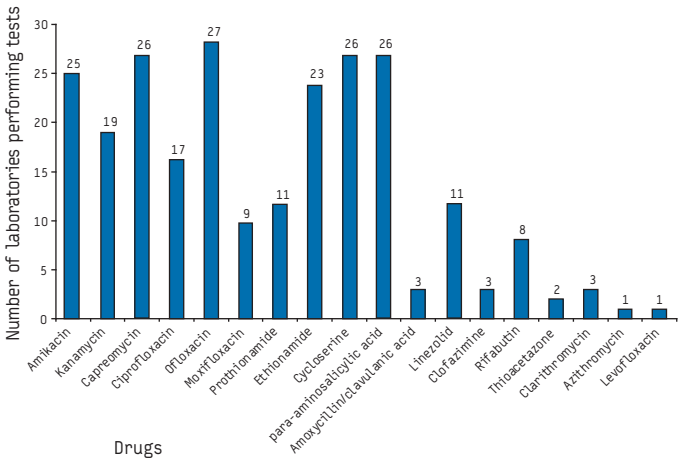
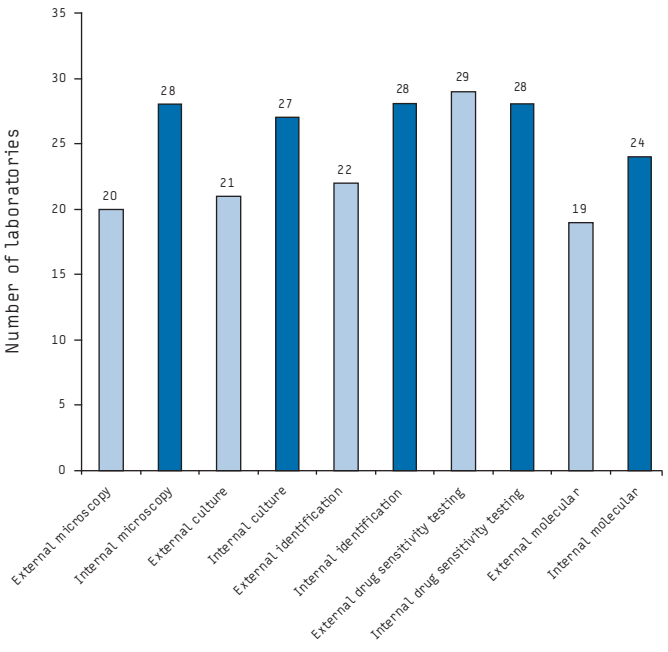


FIGURE 3

External and internal quality control in tuberculosis reference laboratories (n=31)



(SNRL), availability of written SOPs, and their participation in external and internal quality control programmes.

Fifteen laboratories received accreditation from their authorised national bodies. The remaining laboratories did not report formal accreditation (Brussels, Budapest, Dublin, Lisbon, Luxembourg, Nicosia, Nitra, Oporto, Reykjavik, Riga, Golnik, Sofia, Tel-Aviv, Turku, Valetta, Warsaw, and Zagreb. Nine laboratories (Antwerp, Bilthoven, Borstel, London, Oporto, Paris, Prague, Rome (with Milan), and Stockholm) have WHO SNRL status. Of the remaining 23 laboratories, 19 are connected to a defined SNRL (with three laboratories collaborating with Borstel, seven with Stockholm, five with London, one with Barcelona, one with Prague, one with Paris, and one with Bilthoven).

Availability of SOPs, biosafety and participation in Quality Control programmes

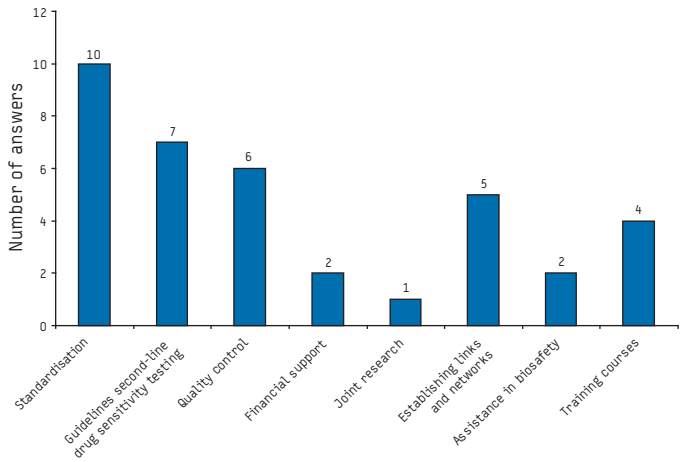
Written SOPs for microscopy, culture, species identification, DST, and molecular methods are available at all laboratories performing these tests, except Tel-Aviv (which does not have SOPs for DST and molecular methods). Most laboratories participate in external quality control systems and have appropriate policies for internal quality control for the different methods they use (Figure 3).

External quality control systems for DST cover all 29 laboratories performing these tests, whereas coverage for other techniques, especially microscopy, molecular methods, and culture is poorer, with 20, 19, and 21 laboratories, respectively (n=32) (Figure 3). Internal quality control policies for microscopy, identification and DST are available at almost all laboratories performing these tests, with fewer laboratories having these policies for culture, and molecular methods (27 and 24, respectively, of a total of 32 laboratories.) (Figure 3).

Written biosafety protocols are available at all but one laboratory (Oporto). Nevertheless, staff working on TB is at risk from being exposed, and seven active TB cases from six laboratories were reported within the last five years. Five of those cases were laboratory-acquired.

FIGURE 4

Most frequently voiced opinions on how ECDC could assist in improving tubercolosis reference services across Europe (more than one answer possible)



Service continuity *and/or* disaster recovery plans are available in 24 laboratories.

Role of ECDC

All respondents but one believed that ECDC could assist in improving laboratory services across Europe by assisting in the development of standards of laboratory practice, and of DST in particular, assisting in the implementation of quality control systems, establishing links between laboratories across Europe, organising training courses, implementing joint research activities and providing financial support (Figure 4). Most laboratories (24/31) reported that they conduct research with just over a quarter of staff (93 persons) being active in research. One respondent felt that assistance with research implementation could be facilitated by ECDC.

TB National reference laboratory – status, primary functions and activities

In this section of the questionnaire, the respondents were asked whether NRLs existed in their country and whether their laboratory was the NRL, how the NRL in their country was selected, and what types of activities the respondents believed should be performed by NRL.

Of the 32 laboratories that participated in the survey, 29 indicated they considered themselves as the NRL, and 25 of the 32 were formally recognised as the NRL.

The principles of NRL selection (n=16) differed significantly between countries, with six laboratories appointed directly by the Ministry of Health, four by a national committee of clinical bacteriologists or other governmental bodies, and six laboratories selected on the basis of quality assessment, formal review *and/or* tendering processes.

National (regional) TB laboratory networks exist in 22 countries (Cyprus, Denmark, Iceland, Israel, Luxembourg, Malta, and Portugal do not have a network, but in most of these cases this is because a single laboratory performs all primary and reference mycobacterial work). Twenty-one laboratories do not have a specific budget for reference activities. Twenty-three laboratories participate in the implementation of the National TB Programme (NTP) and in the provision of formal training/supervision within the laboratory network.

The respondents were asked about the obstacles in performing reference functions. Budget constraints were considered by the majority of respondents (27 of the 32) as the major obstacle to performing the reference functions of a NRL. Other problems such as lack of equipment, poor infrastructure, and human resources issues, were mentioned by 13, 13, and 17 laboratories, respectively. Some laboratories mentioned additional obstacles to performing reference functions, for instance the absence of formal national recognition, poor administrative support (four laboratories), decentralised TB services (one laboratory), and poor cooperation with the epidemiology service (one laboratory).

Core functions and activities of NRL

Figure 5 summarises the core, or primary, functions and activities of NRLs from two perspectives: the participants' opinion regarding the activities that their NRLs actually perform; and their opinion regarding the "ideal" core functions of NRLs. The responses were graded on a five-point scale. Overall, there was good agreement between current activity at NRLs and ideal activity, i.e. agreement on the importance of accurate and timely identification of MTBC,

drug susceptibility testing, appropriate infrastructure and staffing, involvement and control of laboratory budgets, and supporting the national TB programme in laboratory areas. However, there were some differences: fewer respondents agreed, for example, that NRLs should perform microscopy and culture of clinical specimens.

Discussion and conclusion

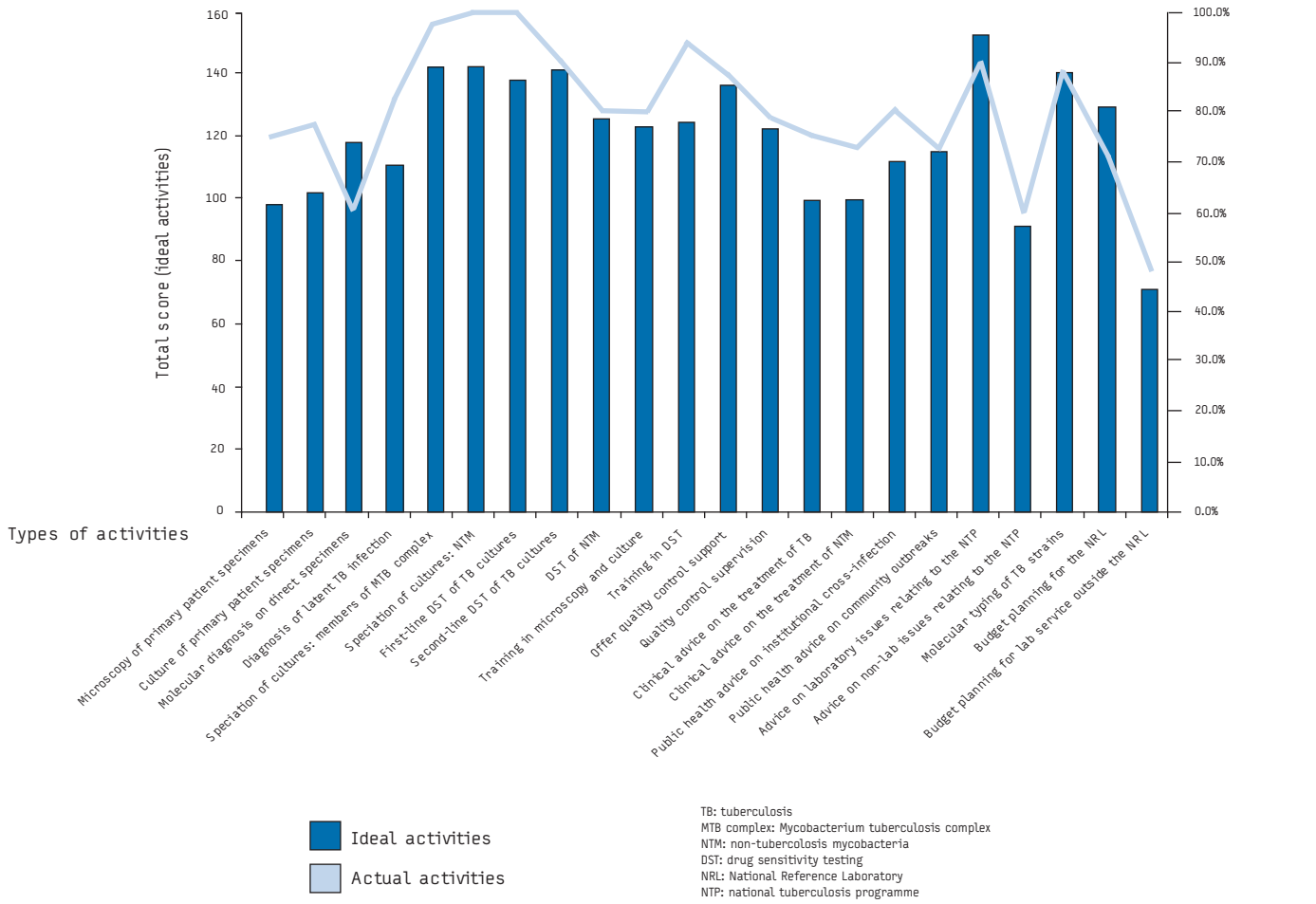
In the EU, and in Europe in general, the strengthening of laboratory services will include the development of an appropriate infrastructure, methodology, training and quality assurance controls for laboratories, providing both conventional (i.e. smear microscopy, culture and drug susceptibility testing) and rapid diagnostic tests. High quality diagnosis is the first priority, however emphasis on more wide-spread introduction of existing, high quality, rapid tests for TB and RIF resistance/MDR TB identification would greatly facilitate earlier identification of MDR TB patients and their enrolment on appropriate treatment. Implementation of such rapid diagnostic tests will need investment in infrastructure, equipment, training, reagents, supplies, and adequate biosafety measures. [7,13]. Given the circumstances described above, there was a need to carefully assess the current mycobacterial laboratory services and quality control practices throughout the EU. A situational analysis of this kind provides a starting point for identifying needs and gaps in laboratory methods/services and for exploring the added value of EU reference laboratory networking activities.

There was general agreement that the key roles of a NRL and service were: (1) to identify of mycobacterial cultures as *M. tuberculosis* or non-tuberculous mycobacteria; (2) to analyse first- and second-line drug resistance of TB cultures; (3) to perform rapid identification and detection of at least RIF resistance in patient specimens; (4) to develop protocols and SOPs; (5) to set standards and to run external quality control and assurance schemes (with partners); (6) to be involved in operational research such as the validation of new diagnostics; (7) to provide clinical and relevant public health advice on the treatment of TB; (8) to advise on laboratory issues relating to national TB programmes; and (9) to perform molecular typing of *M. tuberculosis* strains in support of public health actions, *and/or* in geographically *and/or* time defined settings, for example a city, *and/or* to answer specific focused questions on transmission.

Achieving the above requires the use of good laboratory practice and a commitment to: (1) meeting or developing adequate standards

Figure 5

Ideal and actual activities performed by National Reference Laboratories across Europe



for laboratory diagnosis, be it microscopy, bacterial culture, DST or molecular diagnosis [13,14]; (2) ensuring appropriate and safe laboratory infrastructures; and (3) providing adequate numbers of sufficiently trained staff to perform the work.

In addition to strengthening TB reference laboratory services, an increased effort is required to increase the TB case detection rate and to improve the speed of TB and MDR TB diagnosis (especially in individuals co-infected with human immunodeficiency virus (HIV)) and the proper management of multidrug-resistant (MDR and XDR) TB cases. Therefore, both basic diagnostic and specialised reference laboratories will need to be significantly upgraded, and quality laboratory maintenance and management sustained thereafter.

The extent of the necessary improvements varies considerably among the EU Member States, and the small number of non-EU countries invited to participate in this current survey. It would be beneficial to extend this analysis across the whole European region in order to obtain a consistent picture of the national reference services across Europe and of how larger centres may be able to support smaller ones.

Biosafety continues to be an issue seeing as several laboratory staff have developed active TB during their employment. Human resources also remain a significant problem and will be presented and discussed in a separate analysis of data obtained in the current survey.

Several countries, in particular those of the former Soviet Union, have high rates of drug resistance amongst their TB patients [1,3,4,7]. Many of these countries, for example the Baltic States, are now part of or bordering the EU.

Measuring resistance to first- and second-line drugs is complex and for many second-line drugs lacks standardisation. Most countries have few MDR TB cases and maintaining the technical expertise needed for accurate analysis is difficult.

There remains a need to standardise second-line drug resistance testing across the EU and beyond, using agreed and standardised methodology [15-17], and such testing should only be performed at NRLs due to the relatively small number of cases and the difficulty

Box 1

General recommendations and principles to improve the access to and performance of mycobacterial laboratories with the aim to ensure reliable and timely diagnostic services

- Implement the European standards for TB laboratory services [13] with respect to infrastructure, national reference functions, biosafety, human resources, quality assurance, accreditation, operational research including evaluation of new medical devices, accuracy and speed;
- Ensure safe, secure and adequate laboratory infrastructures and sufficiently trained staff to perform the work;
- Recognise that high quality laboratory services are an integral part of the surveillance chain;
- Support surveillance systems in routine reporting, optimising case detection and identification of antimicrobial resistance, and understanding the spread of the resistance in various settings;
- Support the application of appropriate national and international quality assurance schemes with agreed testing panels;
- Ensure political commitment and investment in infrastructure and human resources to improve and sustain laboratory services in the long term, through the training of sufficient numbers of staff in appropriate TB laboratory procedures with forward planning for the replacement of retired staff or staff who have resigned.

Box 2

Recommendations for the development of a well functioning EU reference laboratory network with added pan-European value

Create an EU reference laboratory network, with the capacity to serve and support the EU Member States and the European Region. Such a network should build on, synergise with, and not duplicate activities covered by other supranational/global initiatives with a special focus on the challenges of TB control and elimination in the EU setting. The network would add pan-European value by supporting the following types of activities:

- international laboratory technical support and access to diagnostic services (i.e. access to drug susceptibility testing through twinning or other contractual arrangements);
- strengthened routine and enhanced surveillance initiatives and links to microbiological laboratories;
- training opportunities through workshops, staff exchanges, access to training material;
- possibilities for peer-review of laboratory performance and implementation of standards;
- development and/or maintainance of standardised and harmonised methods (n.b. while this is a particularly high priority for second-line drug testing, it is relevant for the whole spectrum of new and traditional diagnostic methods);
- promotion of the implementation of existing WHO and other external quality assurance systems;
- development of new external quality assurance systems (e.g. typing and rapid molecular diagnosis);
- development of an infrastructure for operational research (e.g. development and/or validation of new diagnostic methods or devices).

Box 3

Recommendations to ensure access to culture methods and drug susceptibility testing (DST) for first- and second-line drugs with proper implementation of new diagnostic tools

- Improve universal access to mycobacterial culture and use of routine drug susceptibility analysis;
- Perform accurate, timely, high quality drug resistance analysis for all new TB cases for first-line drugs on specimens taken before initiating treatment, if the patient continues to be culture-positive after two to three months and if there is a history of prior TB treatment (a major risk factor for drug resistance);
- As a minimum for laboratories supplying DST data from reference cultures to clinicians, governments, the WHO, and for surveys or surveillance, correctly identify resistance to isoniazid and rifampicin in over 90% of quality control samples in two out of the last three quality control rounds;
- Rapidly identify mycobacterial cultures as M. tuberculosis complex (mainly M. tuberculosis and M. bovis) and identify rifampicin resistance as the first priority within one or two working days; Modern molecular techniques allow the successful identification of isoniazid resistance in at least 75% of M. tuberculosis complex isolates within one or two working days; It is now technically possible to rapidly (1-2 days) identify MDR-TB;
- Implement validated and standardised second-line drug DST (including drugs used to define XDR-TB);
- Develop and implement appropriate quality assurance for second-line drugs and determine the underlying reasons for programmatic failures leading to the need for DST for second-line drugs;
- Accelerate the development and implementation of techniques for the rapid diagnosis of TB, rifampicin resistance, and MDR/XDR-TB in primary patient specimens, in particular for the most infectious cases; aim, as a minimum, to identify MTBC and rifampicin resistance in over 90% of cases from smear positive sputum directly, where logistic resources are available, within one or two working days;
- Support appropriate operational and translational research (clinical research, programme management in the context of laboratory services, barriers to the implementation of appropriate therapy), development, and application of new tools, i.e. of diagnostic methods (particularly for children or individuals co-infected with HIV and meningitis), new treatments, proof of cure in patients with drug resistant TB, and prevention tools).

of maintaining testing proficiency in a setting where multiple centres perform this activity.

Box 1 shows general principles and recommendations to improve the access and performance of mycobacterial laboratories to ensure reliable and timely diagnostic services.

Box 2 and 3 provide detailed recommendations drawing on the participants' responses, a round table discussion focussing on drug resistance, the specific European Standards for mycobacterial laboratories [13] that need to be achieved, and the implementation of new tools which will help to achieve them.

The laboratory remains at the centre of TB control activities, and laboratory activities in Europe could be further developed and strengthened through the creation of an EU reference laboratory network (Box 2) with the capacity to serve and support the EU Member States and the European Region, demonstrated proficiency in their activities, and appropriate links with other relevant technical and scientific support bodies in the EU as well as Europe in general.

Acknowledgements

We would like to acknowledge the support and contributions to this work from the ECDC, particularly the team members of the ECDC Tuberculosis Programme, the EuroTB project, Dr Lucica Ditiu and colleagues at WHO EURO, and the ECDC National Microbiology Focal Points. We would especially like to thank all the TB laboratory experts who so kindly completed the questionnaire. No actual or implied endorsement is made for commercial products mentioned in this article.

References

1. World Health Organization. Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Report. Geneva; 2007. Report No.: WHO/HTM/TB/2007.376. Available from: http://www.who.int/entity/tb/publications/global_report/2007/en/index.html
2. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Institut de veille sanitaire, Saint-Maurice. March 2007. p.114. Available from: http://www.eurotb.org/rapports/2005/full_report.pdf
3. Drobniewski F, Balabanova Y, Nikolayevsky V, Ruddy M, Kuznetzov S, Zakharova S, et al. Drug-resistant tuberculosis, clinical virulence, and the dominance of the Beijing strain family in Russia. JAMA. 2005;293(22):2726-31.
4. Kruuner A, Sillastu H, Danilovitsh M, Levina K, Svenson SB, Kallenius G, et al. Drug resistant tuberculosis in Estonia. Int J Tuberc Lung Dis. 1998;2(2):130-3.
5. Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martin-Casabona N, et al. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg Infect Dis. 2007;13(3):380-7.
6. Aziz MA, Wright A, Laszlo A, De Muynck A, Portaels F, Van Deun A, et al. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet. 2006;368(9553):2142-54.
7. World Health Organization. The Global MDR-TB & XDR-TB Response 2007–2008 Plan. Geneva; 2007. Report No.: WHO/HTM/TB/2007.387. Available from: http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.387_eng.pdf
8. Ruddy MC, Davies AP, Yates MD, Yates S, Balasegaram S, Drabu Y, et al. Outbreak of isoniazid resistant tuberculosis in north London. Thorax. 2004;59(4):279-85.
9. Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess. 2007;11(3):1-196.
10. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet. 2007;369(9578):2042-9.
11. ECDC founding document. Regulation (EC) no 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control. Official Journal of the European Union. 2004. L 142. Available from: http://eur-lex.europa.eu/pri/en/oj/dat/2004/l_142/l_14220040430en00010011.pdf
12. Maus CE, Plikaytis BB, Shinnick TM. Molecular analysis of cross-resistance to capreomycin, kanamycin, amikacin, and viomycin in Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2005;49(8):3192-7.
13. Drobniewski FA, Hoffner S, Rusch-Gerdes S, Skenders G, and Thomsen V. Recommended standards for modern tuberculosis laboratory services in Europe. Eur Respir J. 2006; 28(5):903-9.
14. Drobniewski F, Rusch-Gerdes S, Hoffner S. Antimicrobial susceptibility testing of Mycobacterium tuberculosis (EUCAST document E.DEF 8.1)--report of the Subcommittee on Antimicrobial Susceptibility Testing of Mycobacterium tuberculosis of the European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Clin Microbiol Infect. 2007;13(12):1144-56.
15. Kruuner A, Yates MD, Drobniewski FA. Evaluation of MGIT 960-based antimicrobial testing and determination of critical concentrations of first- and second-line antimicrobial drugs with drug-resistant clinical strains of Mycobacterium tuberculosis. J Clin Microbiol. 2006;44(3):811-8.
16. Rusch-Gerdes S, Pfyffer GE, Casal M, Chadwick M, Siddiqi S. Multicenter laboratory validation of the BACTEC MGIT 960 technique for testing susceptibilities of Mycobacterium tuberculosis to classical second-line drugs and newer antimicrobials. J Clin Microbiol. 2006;44(3):688-92.
17. Johansen IS, Larsen AR, Sandven P, Petrini B, Soini H, Levina K, et al. Drug susceptibility testing of Mycobacterium tuberculosis to fluoroquinolones: first experience with a quality control panel in the Nordic-Baltic collaboration. Int J Tuberc Lung Dis. 2003;7(9):899-902.
18. Broekmans JF, Migliori GB, Rieder HL, Lees J, Ruutu P, Loddenkemper R, et al. European framework for tuberculosis control and elimination in countries with a low incidence. Eur Respir J. 2002;19(4):765-75.

This article was published on 18 March 2008.

Citation style for this article: Drobniewski FA, Nikolayevskyy V, Hoffner S, Pogoryelova O, Manissero D, Ozin AJ. The added value of a European Union tuberculosis reference laboratory network – analysis of the national reference laboratory activities. Euro Surveill. 2008;13(12):pii=8076. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8076

Rapid communications

Stopping TB in Europe: some progress but still not there

D Falzon (d.falzon@invs.sante.fr)[1], Y Kudjawu[1], J C Desenclos[1], K Fernandez de la Hoz[2], A Dadu[3], R Zaleskis[3]

1. Département des maladies infectieuses, Institut de veille sanitaire (Department of infectious diseases, French Institute for Public Health Surveillance), Saint-Maurice, France
2. Tuberculosis Programme, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
3. Communicable Disease Unit, World Health Organization, Regional Office for Europe (WHO/EURO), Copenhagen, Denmark

Overview of the epidemiological situation in 2006

The latest available information from countries in the World Health Organization (WHO) European Region carries important signals about the tuberculosis (TB) situation in this part of the world [1]. The total number of TB cases reported in the Region was slightly lower in 2006 than in 2005 (422,830 versus 426,457), reflecting a decrease in three-fourths of the reporting countries. Most TB cases in 2006 (73%) were reported by 12 former Soviet Union republics in the East, 21% by the European Union and West (EU and West) and 6% by the remaining countries in the Balkans (Table 1; for the composition of geographical areas see Box). National TB notification rates ranged from 4 to 282 per 100,000 population. The total TB notification rate for the whole Region has increased very slightly between 2002 and 2006,

Table 1

Tuberculosis surveillance indicators by geographic area, WHO European Region

Country	Geographic area*							
	European Union and West		Balkans		East		Total	
	N†		N†		N†		N†	
Total population (millions)	34	513.1	7	95.6	12	278.3	53	887.0
Demographic and clinical features of TB cases, 2006								
Total number of cases notified	32	89,032	7	26,911	12	306,887	51	422,830
Total TB notifications/100,000 population	32	17.4	7	28.1	12	110.3	51	47.7
Mean annual % change in notification rate (2002-2006)	32	-4.0%	7	-1.4%	12	+3.2%	51	+0.9%
Foreign origin	32	20%	7	1%	12	0%	51	4%
Age over 64 years, nationals	32	20%	7	15%	11	7%	50	10%
Age over 64 years, foreign born/citizens	32	9%	7	22%	2	2%	41	9%
Not previously treated (diagnosed) for TB	32	80%	7	90%	12	75%	51	77%
HIV infection among TB cases (latest available data 2003-2006)	23	2.5%	4	0.3%	9	1.9%	36	2.0%
TB deaths/100,000 (median, latest available rates 2002-2006) ‡	28	0.7	4	3.3§	5	22.0	37	0.8%
Multidrug-resistant TB (MDR TB), 2006 ‡								
Primary MDR TB (median)	23	1.1%	3	0.0%	1	6.8%	27	0.9%
Nationals, combined MDR TB (median)	23	0.5%	3	0.6%	1	15.4%	27	0.6%
Foreign-born/citizens, combined MDR TB (median)	23	1.8%	1	1.0%	0	-	24	1.7%
Outcome, new definite pulmonary cases, 2005 ‡#								
Success (cure or treatment completion)	25	79%	5	89%	8	74%	38	79%
Death	25	6%	5	3%	8	6%	38	5%
Failure	25	2%	5	1%	8	9%	38	4%
Still on treatment	25	2%	5	1%	8	2%	38	2%
Loss to follow up (default, transfer, unknown)	25	10%	5	6%	8	9%	38	9%

from 46 to 48 cases per 100,000, although rates of previously untreated TB cases appear to be on the decrease in both the East and West (Figure 1). We describe the main epidemiological features of TB cases notified in each of the abovementioned areas using surveillance data reported by the countries themselves.

East

While half of the TB cases in the East in 2006 were reported by the Russian Federation, the total notification rates per 100,000 population were higher in Kazakhstan (282), Moldova (160), Georgia (142) and Kyrgyzstan (127). The mean annual increase in total notification rates in 2002-2006 (+3%) was lower than that observed in 1998-2002 (+6%).

One fifth of cases in the East had been previously treated, but the proportion varied considerably between countries (6-46%), reflecting different practices in defining cases and recruiting patients. The number of previously untreated cases decreased between 2005 and 2006 in nine countries.

TB mortality rates were high (10-25/100,000 in 5 countries in 2003-2006).

HIV infection was reported in 1% or less of TB cases in seven countries (2003-2006), but was higher in the Russian Federation and Ukraine (1.7% and 5.1% respectively among new TB cases in 2006). Additionally, these two countries reported increasing numbers of AIDS cases diagnosed with TB as initial indicative illness between 2000 and 2006.

Recent data on drug resistance from nearly all Eastern countries reveal a widespread problem. In Georgia and certain regions of the Russian Federation and Ukraine, 7-16% of previously untreated TB cases surveyed in 2005-2006 had resistance to at least isoniazid and rifampicin (multidrug–resistant TB; MDR TB). MDR TB was more common in previously treated cases (16-61% in 10 countries with data in 2006).

Among previously untreated sputum smear-positive pulmonary cases in 2005, Kyrgyzstan and Turkmenistan reported achieving the WHO global target of 85% treatment success, while another nine countries had a lower success ratio (59-82%). High levels of failure or prolonged treatment (4-17% of cases) probably reflect the frequency of drug resistance in these countries.

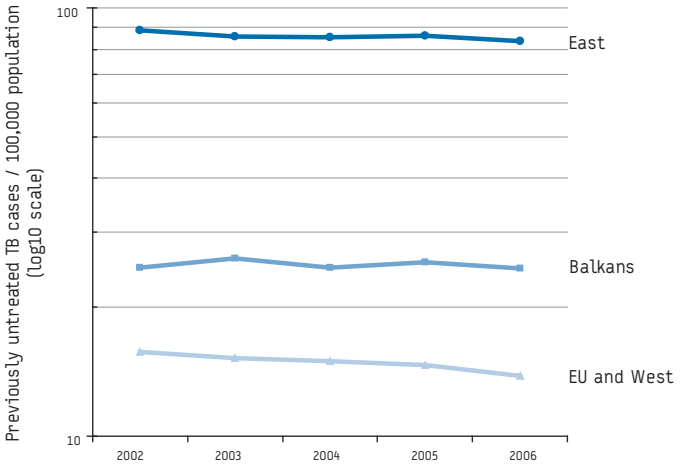
EU and West

The lowest TB mortality and incidence in the Region were reported by countries in the EU and West, but the rates were higher in the Baltic States (Estonia, Latvia and Lithuania), Bulgaria and Romania than elsewhere in this area. Fifteen countries had total notification rates lower than 10/100,000 in 2006. The mean rate in the 12 countries which joined the EU since 2004 was over four times higher than in the EU-15 Member States. Nonetheless, the average annual decrease in total notification rates in the EU and West between 2002 and 2006 was significantly larger than that observed between 1998 and 2002 (-4.0% versus -1.3% respectively).

Between 2000 and 2005, the number of TB cases reported in 'nationals' (as defined by place of birth or citizenship) decreased steadily but the number of cases of foreign origin increased slightly (pooled data for 24 countries, Figure 2). As a result, the proportion of foreigners among the total number of cases has increased over time. Between 2005 and 2006, the number of cases reported in foreigners decreased overall, although not in all countries. A sharp

FIGURE 1

Rates of previously undiagnosed tuberculosis cases, by geographic area, WHO European Region*, 2002–2006



Proportion of TB cases with previous treatment history unknown

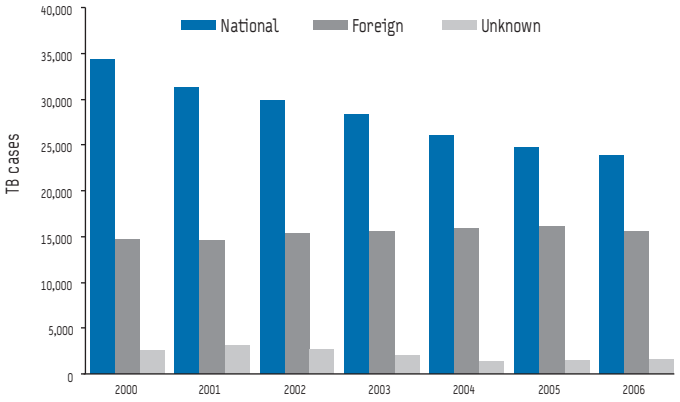
	2002	2003	2004	2005	2006
EU and West	9%	9%	7%	6%	7%
Balkans	2%	0%	0%	0%	0%
East	0%	0%	0%	0%	6%

* Excluding Cyprus, Monaco, San Marino (EU and West); Bosnia and Herzegovina (Balkans); Belarus, Tajikistan, Ukraine (East).

All countries included reported data on previous treatment history of TB cases. Proportion of cases with unknown treatment history varied in certain countries in the EU and West over time, while in the East nearly all cases with unknown treatment history in 2006 were reported by Kazakhstan and the Russian Federation.

FIGURE 2

Total number of tuberculosis cases by geographic origin, European Union and West*, 2000–2006



* Excluding countries with incomplete data for any one year or change in criterion of origin: Andorra, Bulgaria, Cyprus, Greece, Luxembourg, Monaco, Poland, San Marino, and Spain. Cases from Romania (>25,000 yearly, <0.1% foreign) are not included.

drop in notifications in foreigners was reported between 2005 and 2006 in Austria, Denmark and Sweden, following an increase in the previous years, while a steadier decline occurred since at least 2003 in France, Germany, Israel, the Netherlands, Portugal and Switzerland. In contrast, the number of cases of foreign origin increased progressively and substantially in Italy and the United Kingdom since at least 2002.

HIV prevalence among TB cases increased between 2000 and 2006 in Estonia and Latvia (from less than 1% to 9% and 3% respectively) and doubled in the United Kingdom between 2000 and 2003 (from 4% to 8% in England and Wales; no further data reported since). In 2006, it was 0-1% in eight other countries, 2-7% in another nine, 15% in Iceland (2 cases), and 14% in Portugal. As in previous years, MDR TB remained more frequent in the Baltic States (combined MDR TB: 15-19%) than in the other countries (0-2% in 18 countries; 7% in Israel, and 14% in Malta – 2 cases), where it was generally more common in cases of foreign origin. In 25 countries with complete outcome data (2005), success was reported in 79% of new culture-positive pulmonary cases. Loss to follow up was more frequent among foreign cases than nationals (16% vs. 9% respectively; P<0.01) while death was less commonly reported (4% vs. 6%, P<0.01).

Balkans

In 2006, three-fourths of TB cases notified by the Balkan countries were reported by Turkey, where the total notification rate has stabilised recently as the national TB control programme expanded. Between 2002 and 2006, the total number of TB cases in the other Balkan countries decreased, and the notification rates declined by a mean of 4-11% yearly.

TB mortality rates have been moderate in recent years (2-4/100,000 in 4 countries providing data).

In 2006, HIV prevalence among TB cases was low (0.0-0.6% in 4 countries with data), and combined MDR TB was 0.4-1.9% in three countries with representative data. Treatment success ratios among new definite pulmonary cases in 2005 were 85-97% in Bosnia and Herzegovina, Serbia and Turkey, but lower in the rest of the area (30-84%) largely as a result of incomplete information on follow-up.

Conclusion

The stabilisation in TB incidence in the WHO European Region as a whole in the last few years marks a degree of progress in TB control. A 'birth cohort' effect partly explains this trend, particularly among the indigenous TB cases in western countries [2]. The TB caseload and incidence, however, vary considerably across the Region and weigh disproportionately on certain countries where information and resources are insufficient to implement the best-suited control measures. Rates are not decreasing everywhere, partly as a result of improved detection and fluxes in migration. These are major characteristics of the TB situation in the Region which will need increased attention in future. Moreover, our data indicate certain features which will have important implications for the direction of future surveillance and efforts in TB control. A high frequency of MDR TB as well as the presence of extensively drug-resistant TB (XDR TB), has now been well documented in patients presenting for treatment in most countries of the former Soviet Union [3]. A sizeable proportion of TB patients being detected in these countries require more intensive treatment and costly support. The response to this challenge will involve mobilisation of clinical, laboratory and public health capacity. Comprehensive monitoring of patients' outcomes becomes all the more necessary, requiring the prolongation of follow-up beyond 12 months and due vigilance for early recurrence [4]. The HIV epidemic in countries of the former Soviet Union, predominantly among injecting drug users, is having a perceptible impact on TB. Providing joint TB and HIV management for more patients in countries already burdened by drug-resistant TB will present a formidable challenge. While, with some exceptions, TB mortality rates in the EU are low, a recent study showed that TB still contributes heavily to death from infectious diseases in 12 EU countries in which the mean number of reported TB deaths in 2003-2004 was twice as high as that attributed to HIV infection [5].

It seems that the increasing trend of TB cases reported among persons of foreign origin in several western countries has reached a turning point, as numbers declined between 2005 and 2006. This has to be observed carefully over the next few years to see how the situation evolves, as it may be affected by access to care, immigration policy and factors influencing migration in the countries of origin. While the collection of data on foreigners with TB at European level has a long history and is appreciably well standardised, other sub-populations at increased risk of infection or unfavourable outcomes of treatment could benefit from targeted surveillance and outreach programmes. These include prisoners, injecting drug users and socially disadvantaged persons. The collection of data on these risks at the supranational level should be seriously considered as well.

Box

Countries of the WHO European Region by geographic area

EU and West:

EU: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom;

West: Andorra, Iceland, Israel, Monaco, Norway, San Marino, Switzerland.

Balkans: Albania, Bosnia and Herzegovina, Croatia, Former Yugoslav Republic of Macedonia, Montenegro, Serbia, Turkey.

East: Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan.

Acknowledgements:

We thank the national Contact Points who provided the data [2], and the past and present members of EuroTB Advisory Committee for their long-standing support of the network. We also thank other members of the WHO and the ECDC Tuberculosis Programme who collaborated closely with the EuroTB team over the years.

References

1. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2006, Institut de veille sanitaire, Saint-Maurice, France. March 2008. Available from: http://www.eurotb.org/rapports/2006/full_report.pdf

2. Falzon D, Van Cauteren D. Demographic features and trends in tuberculosis cases in the European Region, 1995-2005. Euro Surveill 2008;13(12). Available from: http://www.eurosurveillance.org/edition/v13n12/080318_4.asp

3. World Health Organization/International Union Against TB and Lung Disease Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Anti-Tuberculosis Drug Resistance in the World: Fourth Global Report. 2008. Available from: http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf

4. Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. BMJ 2008;336(7642):484-487.

5. van Lier E, Havelaar A, Nanda A. The burden of infectious diseases in Europe: a pilot study. Euro Surveill 2007;12(12). Available from: http://www.eurosurveillance.org/em/v12n12/1212-222.asp

This article was published on 18 March 2008.

Citation style for this article: Falzon D, Kudjawu Y, Desenclos JC, Fernandez de la Hoz K, Dadu A, Zaleskis R. Stopping TB in Europe: some progress but still not there. Euro Surveill. 2008;13(12):pii=8073. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8073

Rapid communications

A Framework Action Plan to fight Tuberculosis in the European Union

K Fernandez de la Hoz[1], D Manissero[1], on behalf of the Tuberculosis Disease Programme* (tuberculosis@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

Many European Union (EU) Member States show a decline in tuberculosis (TB) incidence and many have low incidence rates (15 countries reported less than 10 cases per 100,000 population in 2006). However, despite the progress in curbing the TB epidemic, the disease remains a public health threat in the EU. The epidemiological patterns are still very diverse between countries and control efforts are challenged by problems such as multidrug-resistant (MDR TB) and extensively drug-resistant tuberculosis (XDR TB), TB/HIV co-infection and the concentration of cases within vulnerable groups.

In this context, in March 2007 the EU Health Commissioner called on the European Centre for Disease Prevention and Control (ECDC) to work on a proposal for an action plan to fight TB in the EU. Following the call, the ECDC has developed a Framework Action Plan to fight Tuberculosis in the European Union [1]. The document covers the essential elements that need to be addressed to control TB effectively and finally to eliminate the disease (defined as less than one case per 1,000,000 population) in the EU. It has been developed by the ECDC Tuberculosis Disease Programme, in close collaboration with the European Commission and with the extensive contribution of other experts from ECDC, the EuroTB network, EU Member States and European Economic Area EEA/EFTA countries, the World Health Organization (WHO) and other key stakeholders. In addition, the Round Table on Health Strategies in Europe organized by the Portuguese Presidency of the EU in July 2007 provided valuable expert input on the topic of MDR/XDR TB.

The long-term goal of the Framework Action Plan to fight Tuberculosis in the European Union is to control and ultimately eliminate TB in the EU. Specifically, the plan aims at:

- Increasing political and public awareness of TB as a public health issue in the EU;
- Supporting and strengthening EU Member States' efforts against TB in line with national epidemiological situation and challenges; and
- Contributing to the control of TB in the EU by supporting those countries from which imported cases originate.

The plan is based on four principles: ensuring prompt and quality care for all; strengthening capacity of health systems; developing new tools; and building partnerships and collaboration with countries and stakeholders. Eight areas for strategic development are linked to the four basic principles described in the document. These eight areas (Box) recognise the need to consider the heterogeneous epidemiological picture in the EU and to recognise the different needs of those countries with high, and those with low, TB incidences in order to direct actions appropriately. The four principles and the underpinned strategies are in line with the content of the United Nations' Millennium Development Goals and the WHO Stop TB Strategy and is complementary to the 'Plan to Stop TB in 18 High Priority Countries in the WHO European Region 2007–2015' [1].

The plan is meant as a first step in a process that will need to continue over the coming years with more detailed activities implemented at regional, national and Community level. Close collaboration with countries neighbouring the EU and other countries will be essential in the implementation of this plan in order to contribute to the global reduction of TB. The 'Framework Action Plan to fight Tuberculosis in the European Union' is posted on the ECDC website (http://ecdc.europa.eu/pdf/080317_TB_Action_plan.pdf) and will be presented to the European Council in June 2008.

* Tuberculosis Disease Programme members: A Amato-Gaucci, K Fernandez de la Hoz, V Hollo, C Kodmon, D Manissero, A Nanda, J O'Toole, A Ozin, V Prikazsky, I Steffens, A Würz

Box

Eight Strategic Areas

- Area 1. TB control commitment, TB awareness and capacity of health systems
- Area 2. Surveillance
- Area 3. Laboratory services
- Area 4. Prompt and quality TB care for all
- Area 5. MDR- and XDR TB
- Area 6. TB/HIV co-infection
- Area 7. New tools for TB control
- Area 8. Build partnership and collaboration with countries

References

1. European Centre for Disease Prevention and Control. A Framework Action Plan to fight Tuberculosis in the EU. Stockholm; 2008. Available from http://ecdc.europa.eu/pdf/080317_TB_Action_plan.pdf
2. World Health Organization. Plan to Stop TB in 18 priority countries of the WHO European Region, 2007–2015. Copenhagen; 2007. Available from: http://www.euro.who.int/document/E91049.pdf

This article was published on 18 March 2008.

Citation style for this article: Fernandez de la Hoz K, Manissero D, on behalf of the Tuberculosis Disease Programme*. A Framework Action Plan to fight Tuberculosis in the European Union. Euro Surveill. 2008;13(12):pii=8074. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8074

Human Listeria monocytogenes infections in Europe - an opportunity for improved European surveillance

J Denny[1], J McLauchlin (jim.mclauchlin@hpa.org.uk)[2]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
2. Food Safety Microbiology Laboratory, Health Protection Agency, Centre for Infections, London, United Kingdom

The 2006 Community Summary Report from the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) was published recently with the latest trends and figures on the occurrence of zoonotic infections and agents, antimicrobial resistance and foodborne outbreaks in the then 25 European Union (EU) Member States and five non-EU countries [1]. This article seeks to expand further upon reports of human listeriosis (Listeria monocytogenes infections) and changes in the epidemiology of this disease, and to inform of important developments as they relate to an opportunity for the establishment of a formalized listeriosis surveillance network in Europe.

Introduction

Listeria monocytogenes is a ubiquitous organism in the environment and a rare cause of human disease. In 2006, listeriosis was reported in 23 EU Member States and was the fifth most common zoonotic infection in Europe, after Campylobacter, Salmonella, Yersinia, and VTEC infections [1]. Even though listeriosis occurs infrequently (0.3 cases per year per 100,000 of the population for the whole of the EU, Table 1), it is characterised by a high case-fatality rate which can exceed 30% percent [2,3]. It also carries one of the highest hospitalisation rates among known foodborne pathogens, 91%, with additional long term sequelae in some patients [4]. Cases occur in well-defined risk groups, including immunocompromised individuals, elderly (aged 65 years and older), pregnant women, unborn infants and neonates [5]. The high morbidity and mortality of this infection make a strong case for the importance and priority of improved surveillance of the disease.

The Zoonoses Community Summary Report [1] also contains data on identified L. monocytogenes in food and animals. Microbiological criteria providing limits to the levels of this bacterium in food were introduced in 2005 [6]. In 2006, this bacterium was reported to occur in ready-to-eat products in 2.4% of bovine meat, 3.9% of pork meat, 2.7% of poultry, 2.7% of other or unspecified meats, 1.3% of cheese, and 12.6% of fishery products [1]. Since listeriosis is predominantly transmitted by the consumption of contaminated foods (although other modes of transmission such as vertical transmission do occur), active responses are essential to control this organism in the food chain.

In addition to the collection of data via the Zoonoses Community Summary Report, an active surveillance system combining food and human surveillance activities is required to respond to changes in the incidence of the disease and to promptly recognize foodborne outbreaks, particularly those that involve more Member States.

Methods

There is a statutory obligation for Member States to report cases of human listeriosis to the European Union (EFSA) as part of the Zoonoses Directive [7]. Cases are typically defined as those microbiologically confirmed by the isolation of L. monocytogenes from a normally sterile site and by classifying a mother-baby pair as a single case. There is, however, variation on how each country classifies and confirms cases, given that the EU has not yet approved and put to use a common set of case definitions [8].

Analysis in this study was performed by a SPSS 15.0 statistical analysis using data from the 2006 and 2004 Zoonoses Community Summary Reports [1,6]. When looking at overall and disease-specific EU trends, numbers of cases per 100,000 were analyzed from 1999 to 2006 using a linear regression method and Pearson's R correlation to assess for significance. Those with statistical significance of $p<0.05$ are reported and graphed. Population sizes for EU Member States and other European countries were obtained from Eurostat [9].

Listeria trends across Europe

The numbers of cases of human listeriosis reported from European countries between 1999 and 2006 are shown in Table 1. In 2006, cases of human listeriosis were reported from 23 EU Member States as well as from Bulgaria (in EU since 2007) and Norway, all of which were laboratory-confirmed. The data were reported as case-based from all countries except Austria and Lithuania who reported aggregated data.

In 2006, Member States reported the highest number of cases (1,583) over the past eight years, representing an increasing and statistically significant trend. More complete longitudinal reporting exists for some Members States, including data from ten MS which acquired membership in 2004, and therefore it is possible to observe long-term trends for these countries. Cases from Germany, France and the United Kingdom accounted for 64% of the total number of cases reported in EU in 2006, a proportion similar to that observed in 2005. Denmark, Finland and Luxembourg reported the highest incidence rates of >=0.9 cases per 100,000 population in 2006 (Table 2).

Table 1

Human cases of listeriosis reported in Europe in 1999–2006

Country	Number of confirmed cases							
	2006	2005	2004	2003	2002	2001*	2000*	1999*
Austria	10	9	19	8	16	9	14	13
Belgium	67	62	70	76	44	57	48	64
Cyprus	1							
Czech Republic+	78	15	16					
Denmark	56	46	41	29	28	38	39	44
Estonia+	1	2	2					1
Finland	45	36	35	41	20	28	18	46
France	290	221	236	220	218	187	261	275
Germany	508	510	296	256	240	216	33	31
Greece	6		3		5	3	2	1
Hungary+	14	10	16					
Ireland	7	11	11	6	6	7	7	
Italy	51	51	25			31	13	17
Latvia+	2	3	5	8	16		36	
Lithuania+	4	2	1	2				
Luxembourg	4							
Malta+	0							
Netherlands	64	96	55	52	32	16		
Poland+	28	22	10	5	31			
Portugal			38					
Slovakia+	12	5	8	6	7			
Slovenia+	7		1	6				
Spain	78	68	100	52	49	57	35	32
Sweden	42	35	44	48	39	67	46	27
United Kingdom	208	223	232	255	158	156	115	116
EU Total	**1583**	**1427**	**1264**	**1070**	**909**	**872**	**586**	**667**
Bulgaria[x]	6							
Iceland								
Liechtenstein								
Norway	27	14	21*	18*	17*	18*		

All data from 2006 Zoonoses Community Summary Report, except:
* Data from 2004 Zoonoses Community Summary Report
x European Union Member State since 2007
+ European Union Member State since 2004

Table 2

Incidence of human listeriosis per 100,000 population in the European Union, in 1999–2006

Country	2006	2005	2004	2003	2002	2001	2000	1999
Austria	0.1	0.1	0.2	0.1	0.2	0.1	0.2	0.2
Belgium	0.6	0.6	0.7	0.7	0.4	0.6	0.5	0.6
Cyprus	0.1	0.0	0.0	0.0	0.0	0.0		
Czech Republic+	0.8	0.1	0.2	0.0	0.0	0.0		
Denmark	1.0	0.9	0.8	0.5	0.5	0.7	0.7	0.8
Estonia+	0.1	0.1	0.2	0.0	0.0	0.0		0.1
Finland	0.9	0.7	0.7	0.8	0.4	0.5	0.4	0.9
France	0.5	0.4	0.4	0.6	0.4	0.3	0.4	0.5
Germany	0.6	0.6	0.4	0.3	0.3	0.3	0.0	0.0
Greece	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0
Hungary+	0.1	0.1	0.2	0.0	0.0	0.0		
Ireland	0.2	0.3	0.3	0.2	0.2	0.2	0.0	
Italy	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0
Latvia+	0.1	0.1	0.2	0.3	0.7	0.0	0.2	
Lithuania+	0.1	0.1	0.0	0.1	0.0	0.0		
Luxembourg	0.9	0.0	0.0	0.0	0.0	0.0		
Malta+	0.0	0.0	0.0	0.0	0.0	0.0		
Netherlands	0.4	0.6	0.3	0.3	0.2	0.1		
Poland+	0.1	0.1	0.0	0.0	0.1	0.0		
Portugal		0.0	0.4	0.0	0.0	0.0		
Slovakia+	0.2	0.1	0.1	0.1	0.1	0.0		
Slovenia+	0.3	0.0	0.1	0.3	0.0	0.0		
Spain	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1
Sweden	0.5	0.4	0.5	0.5	0.4	0.8	0.5	0.3
United Kingdom	0.3	0.4	0.4	0.4	0.3	0.3	0.2	0.2
EU Total	**0.3**	**0.3**	**0.3**	**0.2**	**0.3**	**0.2**	**0.1**	**0.2**

+ European Union Member State since 2004

Considering the past eight years, statistically significant and increasing trends were noted in Germany, Ireland, Lithuania, the Netherlands, Spain and the UK (Figure 1). During this period, a decrease of the number of cases in 2001 and 2002 followed by an increase in 2006 was detected in data from Belgium, Denmark, Finland and France (Table 1). An unusual increase in the number of cases was reported in the Czech Republic in 2006 compared to 2004 and 2005. 78 cases including 13 deaths in 2006 were associated with a single outbreak caused by contaminated soft cheese [1,10]. No other large foodborne outbreaks were identified in the European Union during 2006.

In 2006, human cases of listeriosis occurred more frequently later in the year, while in 2005 they were evenly distributed (Figure 2). The incidence and the number of cases of listeriosis in patients aged 65 and older were approximately 2.5 times higher than those reported in any other age group (Figures 3 and 4). Patients aged 65 years and older constituted 64% of all listeriosis cases in Belgium, 32% in the Czech Republic, 64% in Finland, 55% in France, 59% in Germany, 69% in Italy, 52% in the Netherlands, 46% in Spain, 69% in Sweden, 56% in the United Kingdom and 47% in the remaining 12 Member States (combined). More than half (54%) of the reported cases were male.

Discussion

The collection of European surveillance data represents a potentially very powerful tool for informing interventions to control infectious diseases. The comparison of national data, however, can be problematic since there are wide variations in the numbers of cases and incidence rates among reporting countries, thus emphasizing the advantage of comparing data over time within each Member State and across the European Union. When making comparisons between Member States, account should be taken of such factors as the variability of case definitions, reporting requirements, surveillance systems and microbiological methods employed by reporting countries. Efforts are currently underway to harmonise case definitions within the EU [8], and it is envisaged that these will improve the comparability of national surveillance data in the future. It is currently not possible to categorise the cases of listeriosis further than by age. However since data from some

Figure 1

Listeriosis incidence, European Union countries with statistically significant increases, 1999–2006

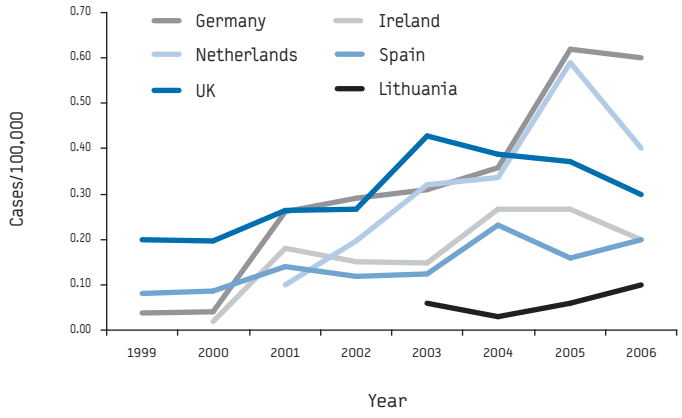


Figure 2

Seasonal distribution of human cases of listeriosis in the European Union in 2005 and 2006

Figure 3

Incidence of human listeriosis by age group, European Union, 2006

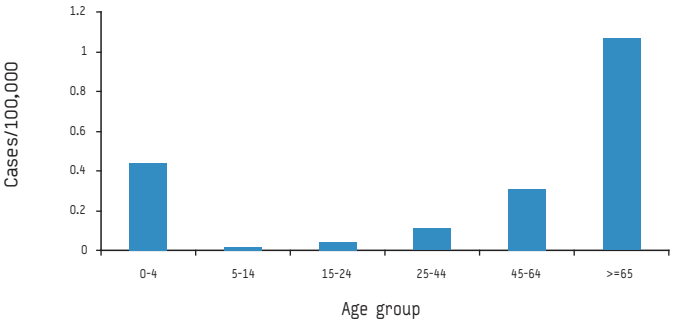
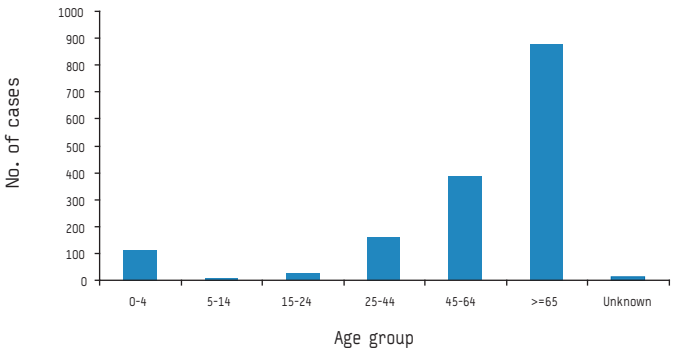


Figure 4

Number of cases of human listeriosis by age group, European Union, 2006



Member States have been associated with marked changes in the numbers and proportion of cases in different patient groups [5,11] more sophisticated data gathering is necessary to characterise both the trends and affected patients further.

Data from 2006 show an increase in the number of cases of listeriosis in Europe. In order to respond to these findings, it is first of all important to establish if this represents a true increase in incidence. As sustained surveillance activities for listeriosis have been in place in a number of EU Member States since the 1980s and similar, increasing trends have been noted across different countries, it is likely that this represents a true change. However additional surveillance is necessary to investigate this further.

If the increase is real, it is important to establish whether it can be associated with changes in susceptible populations, medical investigations conducted (i.e. improved diagnostic procedures) or treatment. Changes may also have occurred within the food chain to increase the risk of acquiring infection, such as alteration of eating habits, legislative changes, an increase in ambient temperature and/or alternation of food formulations and storage conditions such as refrigeration temperature or shelf life. It is therefore essential to conduct a more extensive and comprehensive investigation of the possible contributing factors affecting the incidence of listeriosis across Europe, performed in a way that the answers to these questions would readily facilitate the prioritization of efforts taken in order to respond to the rise.

Since listeriosis is predominantly foodborne, it is possible to prevent cases of this disease either by removing a single contaminated food source associated with common source outbreaks [12], or by general improvements in food-production hygiene which reduce the levels of L. monocytogenes contamination in ready-to-eat foods [13,14,15]. These intervention strategies showed success in reducing the numbers of cases in both Europe and North America during the 1990s. The data presented here, however, suggests a reversal of this trend in Europe with independent rises in the numbers of cases reported across several EU Member States. A more detailed analysis of national data has been described for Germany [5] and England and Wales [11], providing additional insights into the increases which are not currently possible from the centrally collected data. The increase in Germany was suggested to have occurred despite changes in surveillance and raised diagnostic awareness (listeriosis became a notifiable disease in 2001), and resulted in a more than a doubling of the numbers of reported cases between 2001 and 2005. The German increase occurred almost exclusively in patients >=60 years of age and did not appear to be linked to any single common-source outbreak; the cases were therefore predominantly sporadic in nature. The increase in England and Wales [11] showed similar characteristics to that in Germany, although there is no evidence supporting a relationship between these two national trends. The increase in England and Wales also occurred predominantly in patients aged >=60 years and in those who presented with bacteraemia but without central nervous system infection. The numbers of cases reported amongst patients <60 years of age, those with infections of the central nervous system, and those associated with pregnancy have remained similar since 1990. Increases occurred in most regions of England and Wales, occurred amongst both genders, were due to multiple subtypes of L. monocytogenes, could not be explained by common source outbreaks and were predominantly sporadic in nature. The increase was independent of demographic changes and has resulted in an approximate tripling of the age-specific rates of listeriosis in England and Wales between 1990 and 2006.

The Scientific Panel on Biological Hazards (BIOHAZ) of the European Food Safety Authority (EFSA) recently recommended that efforts to reduce risks to human health should focus on risk reduction practices both during the production process of ready-to-eat foods (RTE) and at home by consumers [16]. The report recommended to further investigate listeriosis cases and to generate and analyse data on ready-to-eat foods where L. monocytogenes was most commonly found. Additional key areas for attention may include food packaging and preparation practices along the food chain (such as the handling and slicing of RTE meat products), changes to food formulation (such as the salt or other preservative contents), storage temperatures, general industrial good hygiene practices and the education and training of food handlers. Consumers are also believe to benefit from clear recommendations on good food hygiene practice (i.e. at what temperature to keep food chilled at all times), and from being encouraged to take careful note of the shelf-life of food in their refrigerators. Such educational messages targeted at those in the older sections of the population may prevent cases, yet care needs to be taken so as not to dissuade this group from making good nutritional choices.

The increase in listeriosis cases, together with the need for further research and the recommendations from the Scientific Panel on Biological Hazards all emphasize the need for enhanced surveillance at the EU level to better estimate the burden of disease and the presence of this bacterium in the food chain. A first step in this process should be to convene expertise from EU Member States, ECDC and EFSA in order to share common efforts, to prioritize research activities, and to decide upon an enhanced and standardised variables to be collected by the Member States and reported at the EU level to ECDC. Now is an opportune time for the ECDC to coordinate these activities. The former Europe-based international surveillance network for the enteric infections Enter-net, now steered by ECDC, provides an ideal mechanism to enhance the surveillance of listeriosis and thus to ensure that the current EU-wide research activities are directed towards a shared vision of listeriosis surveillance and response to reducing the incidence of the disease.

Conclusion

In view of the increase in cases of listeriosis reported from EU Member States over the past five years, the capacity of ECDC to perform disease surveillance at the international level offers a unique opportunity. Surveillance across Europe must include improved reporting of confirmed cases of human listeriosis; centralised collection of data on the characterisation of L. monocytogenes; shared best practices for the detection, investigation and control of foodborne outbreaks, and methods to reduce the incidence of this bacterium throughout the food chain. It is an opportune time for coordinated action between EU Member States, EFSA and ECDC to effectively target risk reduction strategies at the sections of the European population at highest risk of contracting listeriosis.

Acknowledgements

We would very much like to acknowledge the helpful contributions to this paper from: Véronique Goulet and Henriette de Valk of the department of Infectious Diseases, Institut de Veille Sanitaire, Saint-Maurice, France; Johanna Takkinen, Andrea Ammon and Andrew Amato of

the European Centre for Disease Prevention and Control in Stockholm, Sweden; and Iain Gillespie at the Health Protection Agency Centre for Infections, London, United Kingdom.

References

1. The Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents, Antimicrobial resistance and Foodborne outbreaks in the European Union in 2006. Available from: http://www.efsa.europa.eu/EFSA/DocumentSet/Zoon_report_2006_en.pdf
2. De Valk H, Jacquet C, Goulet V, Vaillant V, Perra A, Simon F, et al. Surveillance of listeria infections in Europe. Euro Surveill 2005;10(10):251-5. Available from: http://www.eurosurveillance.org/em/v10n10/1010-225.asp
3. Goulet V, Marchetti P. Listeriosis in 225 non-pregnant patients in 1992: clinical aspects and outcome in relation to predisposing conditions. Scand J Infect Dis. 1996;28(4):367-74
4. Jemmi T, Stephan R. Listeria monocytogenes: food-borne pathogen and hygiene indicator. Rev Sci Tech. 2006;25(2):571-80.
5. Koch J, Stark K. Significant increase of listeriosis in Germany - Epidemiological patterns 2001-2005. Euro Surveill 2006;11(6):85-8. Available from: http://www.eurosurveillance.org/em/v11n06/1106-224.asp
6. The Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Antimicrobial resistance in the European Union in 2004. Available from: http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620772157.htm
7. Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:325:0031:0040:EN:PDF
8. ECDC. Case definitions for reporting communicable diseases to the Community Network, 2006. 8 September 2006 (proposal).
9. Eurostat. 2006. Populations and social conditions: Population structure indicators on 1st January 2006. Available at: http://epp.eurostat.ec.europa.eu/portal/page?_pageid=0,1136184,0_45572595&_dad=portal&_schema=PORTAL
10. Vít M, Olejník R, Dlhý J, Karpíšková R, Cástková J, Príkazský V, et al. Outbreak of listeriosis in the Czech Republic, late 2006 – preliminary report. Euro Surveill 2007;12(2):E070208.1. Available from: http://www.eurosurveillance.org/ew/2007/070208.asp#1
11. Gillespie IA, McLauchlin J, Grant KA, Little CL, Mithani V, Penman C, et al. Changing pattern of human listeriosis, England and Wales, 2001-2004. Emerg Infect Dis. 2006;12(9):1361-6.
12. McLauchlin J, Hall SM, Velani SK, Gilbert RJ. Human listeriosis and paté: a possible association. BMJ. 1991;303(6805):773-5.
13. de Valk H, Vaillant V, Goulet V. [Epidemiology of human Listeria infections in France]. Bull Acad Natl Med. 2000;184(2):267-74. [French]
14. McLauchlin J. The role of the Public Health Laboratory Service in England and Wales in the investigation of human listeriosis during the 1980s and 1990s. Food Control. 1996;7(4-5):235-239.
15. Tappero JW, Schuchat A, Deaver KA, Mascola L, Wenger JD. Reduction in the incidence of human listeriosis in the United States. Effectiveness of prevention efforts? The Listeriosis Study Group. JAMA. 1995;273(14):1118-22.
16. EFSA. Panel on biological hazards (BIOHAZ). Request for updating the former SCVPH opinion on Listeria monocytogenes risk related to ready-to-eat foods and scientific advice on different levels of Listeria monocytogenes in ready-to-eat foods and the related risk for human illness - Scientific Opinion of the Panel on Biological Hazards. 2007. Available from: http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178680093176.htm

This article was published on 27 March 2008.

Citation style for this article: Denny J, McLauchlin J. Human Listeria monocytogenes infections in Europe - an opportunity for improved European surveillance. Euro Surveill. 2008;13(13):pii=8082. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8082

Reflections on an evaluation of the Dutch infectious diseases surveillance information system

BHB van Benthem (birgit.van.benthem@rivm.nl)[1], J A van Vliet[1]

1. Department of Epidemiology and Surveillance, Centrum Infectieziekte-bestrijding (Centre for Infectious Diseases Control, CIb), Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and Environment, RIVM), Bilthoven, the Netherlands

The Netherlands' Infectious diseases Surveillance Information System (ISIS) was developed 12 years ago as an early warning system for the country. The initial objective was to establish a surveillance system that gathered the test results of all micro-organisms from all medical microbiology laboratories (MMLs) in the Netherlands on a daily basis in order to create an early warning system. This paper analyses the most important results of a recent evaluation of the system. The evaluation was based on an analysis of early warning signals to detect outbreaks, number of visits to the ISIS website, and interviews with stakeholders, documentation on the ISIS system, and analyses of the ISIS MML database. While the daily collection of data on all micro-organisms for early warning has been achieved, the connection of all 85 MMLs in the Netherlands to the central ISIS MML database has not been achieved – only 18 MMLs have been connected. This has resulted in a low coverage and non-representative selection of MMLs for the Netherlands and therefore national outbreaks were missed. Data were used to determine trends in antimicrobial resistance over time. The ISIS system was not found suitable for early warning since outbreaks were detected via other systems. However, with some adaptations the ISIS system could be suitable for the surveillance of antimicrobial resistance. Furthermore, the discontinuation of this network would cause the loss of the most important data system for antimicrobial resistance in the Netherlands, since there is no other national system that gathers data on this topic. This evaluation resulted in a restart of the network.

Introduction

ISIS presents current information on the presence of infectious diseases in the Netherlands online. The system was developed by the National Institute of Public Health and the Environment (RIVM) as an information technology infrastructure for the continuous collection and analyses of data, the distribution of surveillance information and early warning of outbreaks, and monitoring of trends. MMLs play an important role in early warning of outbreaks of infectious diseases since results from MMLs are on average faster available than results from disease notifications gathered by Municipal Health Services.

The idea was that all 85 medical microbiology laboratories in the Netherlands would send data on all micro-organisms on a daily basis.

At the ISIS website, professionals were able to view daily updated trends in the occurrence of certain micro-organisms via algorithms. The complete surveillance cycle was computerized [1].

The ISIS MMLs' database contained both positive and negative test results, unlike most laboratory surveillance systems, which only contain positive test results. The daily transport of data took place from the Laboratory information management systems (LIMS) to the central database at RIVM. As a result of technical problems that required investments in maintenance and doubts about the cost-effectiveness and usefulness of ISIS MMLs for the Centre for Infections Diseases Control (CIDC), it was decided to evaluate the system and report the most important results of that evaluation in English in this paper [2].

Methods

The evaluation was done by comparing the original objective with the current situation [3], partly using guidelines for the evaluation of public health surveillance system as defined by CDC [4]. Information concerning ISIS MMLs and the performance of the system is based on an analysis of early warning signals [5]. ISIS website visits and interviews by means of an open-structured questionnaire with stakeholders, documentation on ISIS MMLs, and analyses of ISIS MMLs' data. The evaluation focused on the contents of the system: representativeness, quality of data, and use of the system for public health purposes.

Results

The original objective was to set up a surveillance system that gathered test results of all micro-organisms of all MMLs on a daily basis. The daily collection of data on all micro-organisms for early warning has been fully achieved. However, the participation of all 85 MMLs has not been achieved: only 18 MMLs participated over the 12-year period. The connection of MMLs to the central system turned out to be a custom-made procedure and the time schedule for connecting all MMLs was too optimistic. Laboratory information management systems (LIMS) of seven software providers were linked to ISIS MML. Participation was voluntary, which resulted in a low coverage and a non-representative sample of MMLs for the Netherlands. Coverage changed over the years due to new connections and disconnections since a change in LIMS implied a reconnection of that LIMS to ISIS MML. A comparison between all early warning signals of ISIS MMLs and outbreaks notified by other networks such as the early warning committee showed that

all 10 nationwide outbreaks that were described in the Netherlands in 2004 and 2005 were missed by ISIS MMLs [6]. In the same period, ISIS MMLs produced 222 early warning signals, but none of them induced any response from the national outbreak management team or any other response actions.

In addition to the non-representativeness of the system, the evaluation revealed that the quality of the data was insufficient. This was due to several reasons. Firstly, the standards for notation and data structure, as defined by the Dutch Society of Clinical Microbiology, were only partly followed. Secondly, routine data quality control was not performed and thirdly recoding from local LIMS to the central database system contained errors.

The main advantage of ISIS was that the system collected both positive and negative test results from MMLs and relevant epidemiological information so that diagnostic strategies and testing behaviour could be evaluated. However, the disadvantages of ISIS MMLs were that data not routinely gathered in a LIMS were not available. The interpretation of trends, especially for microorganisms were no other surveillance systems are available in the Netherlands (such as *Giardia*, *Cryptosporidium* and *Yersinia*), was hampered by low coverage and lack of clinical information, reason for diagnostic tests, type of test and the interpretation of a test result. Data in the ISIS MMLs' database were most suitable for analyses on the level of test results (micro-organisms and not patient level) as is necessary for the surveillance of antimicrobial resistance. Although the system was not primarily and not optimally designed for the surveillance of antimicrobial resistance, it was most often used for that purpose [7].

Discussion

The design of ISIS can be considered as path-finding. Despite the fact that the original objective was not met, much has been learned from the project. The objective was defined too broadly, which brought the project out of control. It is possible to design a system like ISIS, but regular investments in hardware and software are essential for the continuity of such a system. The control and maintenance of a fully computerized surveillance system such as ISIS MML is costly. Sustainable financial support is therefore essential. Surveillance benefits from standardization. Control of the data process and its translations needs to be a continuous process. Quality control should precede computerized data-analyses. Furthermore, communication between stakeholders of such a complex system is the key to success. The organisation of the system and communication between stakeholders are the limiting factors, rather than the information technology. The quality of the system could easily be improved if the collaboration and communication between stakeholders were improved, a clinical microbiologist was part of the project team and regular feedback to the connected MMLs was given. However, these improvements would be costly.

All of these issues should be carefully considered when launching an early warning surveillance system based on data originating from several laboratory systems.

Conclusion

ISIS MML was not found suitable for early warning, since outbreaks were detected via other networks. The system is suitable for the surveillance of antimicrobial resistance, and its discontinuation would cause the loss of the most important data system for antimicrobial resistance in the Netherlands. This is not a desirable option, as antimicrobial resistance is increasing and the European Union strongly recommends the surveillance of antimicrobial resistance.

Based on the results of the evaluation, it was decided to discontinue ISIS by the end of 2007. A new system will replace the old one, focusing on the prevalence of resistance in clinical-relevant bacteria and the monitoring of trends in resistance. Feedback to participating MMLs will be given regularly; close collaborations with medical microbiologists have already been established. In the new system, data will be gathered in a technically simple way, with a focus on quality control. All stakeholders approved the new format. The new system will start modestly, with possibilities for expansion in the future (See the box below).

Recommendations for national electronic laboratory surveillance systems:

- One SMART (Specific, Measurable, Attainable, Results-focused and Timely) objective;
- Standardization of data;
- Personal communication between participation laboratories and national centre;
- Continuous developments and adaptations necessary.

References

1. M'ikanatha NM, Lynfield R, van Beneden CA, Valk H, editors. Infectious disease surveillance. London, United Kingdom: Blackwell publishing; 2007. p. 294.
2. Van Benthem BHB. Evaluatie ISIS MML. 2007, RIVM rapportnummer 210211001. In Dutch.
3. Sprenger MJW, van Pelt W. Infectieziekten Surveillance Informatie Systeem. 1994, RIVM rapportnummer 214670001.
4. Centre for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems. MMWR 2001;50:RR-13.
5. Widdowson MA, Bosman A, van Straten E, Tinga M, Chaves S, van Eerden L, et al. Automated, laboratory-based system using the Internet for disease outbreak detection, the Netherlands. Emerg Infect Dis. 2003;9(9):1046-52.
6. Rahamat-Langendoen JC, van Vliet JA, Suijkerbuijk AW. Recognition of threats caused by infectious diseases in the Netherlands: the early warning committee. Euro Surveill 2006;11(12):242-5. Available from: http://www.eurosurveillance.org/em/v11n12/1112-230.asp
7. SWAB. NethMap 2007 – Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. Available from: http://www.swab.nl/swab/swabcms.nsf/(WebFiles)/D552D3B6190D0461C12572FF0024F246/$FILE/NETHMAP_2007.pdf

This article was published on 13 March 2008.

Citation style for this article: van Benthem BH, van Vliet JA. Reflections on an evaluation of the Dutch infectious diseases surveillance information system. Euro Surveill. 2008;13(11):pii=8070. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8070

A quarterly update on food- and waterborne diseases in Europe - summary of data for the third quarter of 2007

J Denny[1,2], G Hernández Pezzi (gloria.hernandez-pezzi@ecdc.europa.eu)[1], J Threlfall[3], T Westrell[1], I Fisher[3]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden
2. on behalf of network participants listed below, under acknowledgements
3. Health Protection Agency Centre for Infections, London, United Kingdom

This paper highlights findings from the first quarterly report on food- and waterborne diseases produced by the European Centre for Disease Prevention and Control (ECDC). In the past such reports had been generated by Enter-net, a Europe-based international surveillance network for the enteric infections. The quarterly reports are an important surveillance tool for the network participants and other public health professionals to use in order to identify emerging trends and changes taking place in a shorter interval than one year.

Introduction

The report discussed here brings data from the third quarter of 2007 on cases of *Salmonella*, Verocytotoxin-producing *Escherichia coli* (VTEC) and *Campylobacter* in the European Union (EU) and European Fair Trade Association (EFTA) countries. For this period, 25 countries provided data on *Salmonella*, 16 on VTEC, and 15 on *Campylobacter* (see the list of contributors). In 2006, respectively 27, 17 and 17 countries reported data for the third quarter of the year. As different countries reported in both years, direct comparisons and comments on trends in the data between these two years are avoided. At the time of writing this paper, ECDC does not yet have access to all historical data collected by Enter-net. Comparison across quarters from different years will be possible in future reports, once this data is available.

Methods

The former Enter-net surveillance hub collected data on *Salmonella*, VTEC and *Campylobacter* until 2 October, 2007. These data were collated in the Enter-net databases and included microbiological and epidemiological data on each laboratory case confirmed by the national reference laboratories. The *Salmonella* database has been in existence since 1995, the VTEC database since 2000 and the *Campylobacter* database since 2005 [1]. Data collected from the beginning of October 2006 were transferred to the ECDC on 2 October, 2007. Data for the third quarter of 2007 were submitted from countries directly to ECDC, where they were analysed and summarized before being returned to the network participants for approval.

Public domain versions of the quarterly reports are posted on the ECDC website [2]. When making comparisons between countries, one should take into account such factors as the variability of case definitions, reporting requirements, surveillance systems and microbiological methods employed.

Results

Salmonella

The total number of human *Salmonella* isolates reported in the third quarter of 2007 was 29,294 by 25 countries. For comparison, 34,854 cases were reported in the same period of 2006. The majority of isolates were *S.* Enteritidis or *S.* Typhimurium (Table 1). With respect to emerging serotypes, 239 cases of *Salmonella* Java were reported in the third quarter of 2007, compared to 75 cases in the analogous period of 2006. This is believed to be related to an outbreak of 172 cases of *S.* Java occurring in Sweden, associated with a common exposure to imported spinach, although this has not been confirmed with microbiological evidence [3]. The majority of cases of *Salmonella* were reported in persons aged between 15

Table 1

***Salmonella* serotypes most frequently reported in Europe in the third quarter of 2007 (data from 25 countries) and 2006 (data from 27 countries)**

Serotype	3rd quarter of 2007		3rd quarter of 2006	
	Number of cases	Percentage of the total	Number of cases	Percentage of the total
Enteritidis	17,722	64.4	23,531	67.5
Typhimurium	3,616	13.1	4,537	13.0
Infantis	351	1.3	314	0.9
Virchow	309	1.1	378	1.1
Java	239	0.9	77	0.2
Newport	193	0.7	242	0.7
Stanley	182	0.7	148	0.4
Typhi	162	0.6	213	0.7
Hadar	143	0.5	231	0.7
Agona	133	0.5	125	0.4
Other	4,455	16.2	5,058	14.5
Total	27,505*	100.0	34,854	100.0

* This sub-analysis was performed on cases received by February 2008 and therefore the total in this table (and the denominator used to calculate percentages) is lower than the total number of reported cases given in the text, due to later updates.

and 64 years (45%), which is also the largest age group. Cases younger than five years constituted approximately a quarter of all cases (25%).

Most frequently, *Salmonella* isolates were found to be resistant to sulphonamides (20% of all isolates tested), nalidixic acid (16%) and tetracyclines (16%) (Table 2). In the third quarter of 2006, the highest proportions of isolates were resistant to sulphonamides (24%), ampicillin (17%) and tetracyclines (16%).

Multi-drug resistance (MDR), defined as resistance to four or more unrelated antimicrobials, was found most frequently among *S.* Group B (48%) and *S.* Haifa (46%). Among the more common serotypes, MDR was highest in *S.* Kentucky (41%), *S.* Virchow (39%) and *S.* Typhimurium (38%).

Verocytotoxin-producing Escherichia coli (VTEC)

The total number of VTEC cases reported in the third quarter of 2007 was 594 from 16 countries. During the same period in 2006, 605 cases were reported from 17 countries. The most commonly identified serogroup was E. coli O157, which in the third quarter of 2007 represented the majority of all reported serogroups (56%) and of all known serogroups (65%) (Table 3). In the same period in 2006, E. coli O157 represented 42 % of all serogroups. Phage Types 8, 32 and 4 were reported most frequently in the third quarter of 2007, whereas phage type 21/28 was reported most frequently in the third quarter of 2006.

In the third quarter of 2007, the highest proportion of VTEC isolates was resistant to sulphonamides (31%), streptomycin (24%) and tetracyclines (19%). The proportion of reported MDR isolates

Table 2

Antimicrobial susceptibility of *Salmonella*, third quarter of 2007 (14 countries reporting)

Antimicrobial agent	Total number of isolates tested	Number of resistant isolates (%)	Number of intermediate isolates (%)	Number of sensitive isolates (%)
Ampicillin	9,636	1,337(13.9)	19 (0.2)	8,280 (85.9)
Cefotaxime	8,337	28 (0.3)	8 (0.1)	8,301 (99.6)
Chloramphenicol	8,556	430 (5.0)	9 (0.1)	8,117 (94.9)
Ciprofloxacin	9,369	185 (2.0)	155 (1.7)	9,029 (96.4)
Gentamicin	8,529	198 (2.3)	24 (0.3)	8,307 (97.4)
Kanamycin	8,149	81 (1.0)	26 (0.3)	8,042 (98.7)
Nalidixic acid	7,857	1,285 (16.4)	7 (0.1)	6,565 (83.6)
Streptomycin	7,528	980 (13.0)	224 (3.0)	6,324 (84.0)
Sulphonamides	7,798	1,561 (20.0)	53 (0.7)	6,184 (79.3)
Tetracyclines	8,469	1,330 (15.7)	454 (5.4)	6,685 (78.9)
Trimethoprim	8,318	443 (5.3)	11 (0.1)	7,864 (94.5)

Table 3

Verotoxin-producing *Escherichia coli* (VTEC) serotypes most frequently reported in Europe in the third quarter of 2007 (data from 16 countries) and 2006 (data from 17 countries)

Serotyp	3rd quarter of 2007		3rd quarter of 2006	
	Number of cases	Percentage of the total	Number of cases	Percentage of the total
O157	334	56.2	253	41.8
O26	48	8.1	61	10.1
O103	22	3.7	20	3.3
O145	17	2.9	30	5.0
O111	12	2.0	10	1.7
O91	11	1.9	16	2.6
O121	7	1.2	13	2.1
O128	6	1.0	6	1.0
O55	6	1.0	9	1.5
O113	4	0.7	3	0.5
Other	44	7.4	72	11.9
NT*	83	14.0	107	17.7
Total	**594**	**100.0**	**605**	**100.0**

*NT stands for untyped, untypable or not definitively typed

Table 4

Antimicrobial susceptibility of Verotoxin-producing *Escherichia coli* (VTEC), third quarter of 2007 (five countries reporting).

Anti-microbial agent	Resistant		Intermediate		Sensitive		Number of isolates tested
	Number of isolates	Percentage of all isolates tested	Number of isolates	Percentage of all isolates tested	Number of isolates	Percentage of all isolates tested	
Ampicillin	12	7.3	82	50.0	70	42.7	164
Cefotaxime	1	0.6	-	-	162	99.4	163
Chloramphenicol	2	1.2	-	-	162	98.8	164
Ciprofloxacin	1	0.6	-	-	163	99.4	164
Gentamicin	3	1.8	2	1.2	159	97.0	164
Kanamycin	5	3.0	2	1.2	157	95.7	164
Nalidixic acid	4	2.4	-	-	160	97.6	164
Streptomycin	40	24.4	2	1.2	122	74.4	164
Sulphonamides	50	30.5	53	32.3	61	37.2	164
Tetracyclines	31	18.9	60	36.6	73	44.5	164
Trimethoprim	8	5.2	1	0.6	145	94.2	154

Table 5

Multidrug-resistant (MDR) Verotoxin-producing *Escherichia coli* (VTEC), by serogroup, third quarter of 2007 (five countries reporting)

Serogroup	Number of MDR isolates	Total number of isolates tested	Percentage of the total
O26	3	27	11.1
O91	2	9	22.2
O111	2	8	25.0
O18	1	1	100.0
O55	1	6	16.7
O92	1	1	100.0
NT*	2	6	33.3
Others	0	106	0.0
Total	**12**	**164**	**7.3**

MDR – resistant to >= 4 antimicrobial drugs
*NT stands for untyped, untypable or not definitively typed

Table 6

Clinical manifestations of Verotoxin-producing *Escherichia coli* (VTEC) infections, third quarter of 2007 (14 countries reporting)

Clinical manifestation	O157		non-O157		Unknown serogroup		All serogroups	
	Number of cases	Percentage of the total	Number of cases	Percentage of the total	Number of cases	Percentage of the total	Number of cases	Percentage of the total
Diarrhoea	61	38.9	73	75.3	23	62.2	157	54.0
Bloody diarrhoea	68	43.3	8	8.2	4	10.8	80	27.5
Haemolytic-uraemic syndrome (HUS)	17	10.8	11	11.3	7	18.9	35	12.0
Asymptomatic	11	7.0	5	5.2	3	8.1	19	6.5
Total	**157**	**100.0**	**97**	**100.0**	**37**	**100.0**	**291**	**100.0**

was 7% (Tables 4 and 5). The proportion of MDR isolates reported in the third quarter of 2006 was 11%.

VTEC infections manifested most commonly as bloody diarrhoea and haemolytic-uremic syndrome (HUS). Bloody diarrhoea was reported more frequently in cases with VTEC O157 infections, compared to non-O157 infections, while HUS was as common in O157 cases as among non-O157 cases.

The majority of VTEC O157 cases were reported in females (58%), whereas non-O157 cases were evenly divided between males and females. VTEC O157 cases were typically older and aged between 16 and 64 years (42%), whereas non-O157 cases were more frequently reported in children aged between one and five years (47%).

Campylobacter

The incidence rate of *Campylobacter* infections among 15 reporting European Union countries was 6.9 per 100,000 population in the third quarter of 2007. In the same period in 2006 the rate was 7.3 per 100,000 population. *C. jejuni* was the predominant species identified (representing 62% of the total and 93% of all known species) (Table 7). In the third quarter of 2007, most cases were reported in persons aged between 15 and 64 years (59%) and of male gender (53%). Data on 90% of travel-associated cases included a source country. The top three reported source countries were Spain (371 cases and 25% of all sources identified), Turkey (315, 21%) and Bulgaria (259, 17%).

In the third quarter of 2007, a total of 1,096 isolates were tested for antimicrobial resistance. In contrast, only 207 were reported to have been tested in the third quarter of 2006. The highest proportion of *C. jejuni* and *C. coli* isolates were resistant to tetracyclines, nalidixic acid and tetracyclines, with the proportion of resistant *C. coli* isolates nearly triple that of *C. jejuni*. Multidrug-resistance was identified in 10% of all isolates tested in the third quarter of 2007, and was most frequent among *C. coli* species (23%) (Table 8). In the third quarter of 2006, 18% of all isolates tested were reported to be MDR.

Conclusion

The first quarterly report by ECDC on cases of *Salmonella*, VTEC and *Campylobacter* is limited by its inability to compare data with prior reports due to a lack of consistency in reporting countries and systems. For the purpose of interpretation, however, we compared the findings from this report with those from the Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents, Antimicrobial resistance and Foodborne outbreaks in the European Union in 2006 (Zoonoses Report) [4]. We found that the proportions of *S.* Enteritidis and *S.* Typhimurium to other serotypes were similar, as was the breakdown of the ages of the reported cases. *S.* Java stands out for being reported more frequently than expected due to an outbreak occurring in Sweden briefly described in the report. *Salmonella* drug-resistance data is consistent with the findings from the 2006 third quarterly report, concerning levels of resistance to commonly used antibiotics, particularly sulphonamides and tetracyclines.

Other noteworthy findings in the present report are that VTEC O157 cases constitute a larger proportion of all reported serotypes in the third quarter of 2007 when compared with findings of the 2006 Zoonoses Report [4] where 47% were VTEC O157, and with the third quarterly report of 2006 in which 42% were reported as VTEC O157. To see more bloody diarrhoea among VTEC O157 cases than among non O157 cases is something to be expected. Finding as many HUS cases among both VTEC O157 and non-O157 cases,

Table 7

Cases of *Campylobacter*, by species, third quarter of 2007 (11 countries reporting)

Species	Number of cases	Percentage of total	Percentage of isolates typed
C. jejuni	12,494	61.7	92.9
C. coli	445	2.2	3.3
Other	510	2.5	3.8
Not typed	6,816	33.6	-
Total	**20,265**	**100.0**	**100.0**

Table 8

Multidrug-resistant (MDR) *Campylobacter*, by species, third quarter of 2007 (three countries reporting)

Species	Number of MDR isolates	Total number of isolates tested	Percentage of the total
C. jejuni	70	898	7.8
C. coli	36	159	22.6
Others	1	39	2.6
Total	107	1,096	9.8

MDR – resistant to >= 4 antimicrobial drugs

however, is unusual, as typically there are many more HUS cases associated with VTEC O157 than with non-O157. This finding may be explained partly by the fact that some countries have not been testing for non-O157 isolates and only now are beginning to do so [4]. The proportion of *C. jejuni* to *C. coli* cases reported, and their respective resistance patterns offer no deviations from findings over 2006 [4]. Yet the fact that few VTEC and *Campylobacter* specimens submitted in the third quarter of 2007 demonstrated multi drug-resistance is difficult to interpret, due to a small number of countries reporting this information and a need for many more samples to be analyzed before trends can be interpreted.

Acknowledgements

A special thank you to Henriette De Valk, Lisa King, Anja Siitonen, Yvonne van Duynhoven, Kassiani Mellou, Regina Vorou, Angelika, Johanna Takkinen, Andrew Amato and Andrea Ammon for their comments and improvements.

This paper could not have been prepared without the contribution of all network participants. The participants of the network are the microbiologists in charge of the National Reference Laboratories for *Salmonella*, Verocytotoxin-producing *Escherichia coli* and *Campylobacter* infections, and the epidemiologists with responsibility for their national surveillance. These individuals are only a part of large group of people contributing to the network. There are innumerable medics, scientists, laboratory technicians, epidemiologists and IT specialists working in each institute who provide support and input to the operation, development and success of the network.

Network participants:

- Austria[2]: Christian Kornschober, Reinhild Strauss, Robert Muchl, Sandra Jelovcan, Gabriela El Belazi, Burkhard Springer, Manfred Dierich, Reinhard Würzner;
- Belgium[1,2,3]: Françoise Wuillaume, Denis Piérard, Jean-Marc Collard, Sophie Bertrand;
- Bulgaria[1]: Kremena Parmakova, Petar Petrov, Katyusha Ivanova, Vania Mehandjieva;
- Cyprus[1]: Panayiota Maikanti Charalambous, Myrto Chronidou;
- Czech Republic[1,3]: Marta Prikazs, Renata Karpiskova, Daniela Dedicova;
- Denmark[1,2]: Eva Møller Nielsen, Steen Ethelberg, Flemming Scheutz, Kåre Mølbak;
- Estonia[1,2,3]: Jevgenia Epshtein, Inna Sarv, Unna Joks;
- Finland[1,2,3]: Markku Kuusi, Anja Siitonen;
- France[1,2,3]: Henriette De Valk, François-Xavier Weill, Nathalie Jourdan, Lisa King, Ingrid Filliol, Patricia Mariani, Francis Mégraud and Emmanuelle Espié;
- Germany[1,2,3]: Angelika Fruth, Alexander Friedrich, Klaus Stark;
- Greece[1]: Panayotis T. Tassios, Rengina Vorou, Kassiani Mellou, Alkis Vatopoulos, Georgia Mandilara;
- Hungary[1,2,3]: Katalin Krisztalovics, Maria Herpay, Maria Vidane Szucs;
- Ireland[1,2,3]: Paul McKeown, Anne Carroll, Martin Cormican, Eleanor Mcnamara;
- Italy[1]: Ida Luzzi, Alfredo Caprioli, Marta Ciofi degli Atti, Gaia Scavia, Pasquale Galetta;
- Latvia[1,3]: Sandra Magone, Solvita Selderina, Ruta Paberza, Bormane, Svetlana Makarova;
- Lithuania[1]: Galina Zagrebneviene, Vilma Jonaitiene, Indre Mackeviciute;
- Luxembourg[1]: Francois Schneider, Patrick Hau, Joel Mossong, Catherine Ragimbeau;
- Malta[1,3]: Anthony Gatt, Paul Cuschieri, Christopher Barbara, Charmaine Gauci;
- The Netherlands: Yvonne Van Duynhoven, Wilfrid Van Pelt, Wim Wannet;
- Poland: Malgorzata Sadkowska-Todys, Jolanta Szych, Grzegorz Madajczak, Sebastian Wardak;
- Portugal: Cristina Furtado, Jorge Machado;
- Romania[1]: Maria Damian, Zota Lavinia Cipriana, Tatu-Chitoiu Dorina, Adriana Pistol;
- Slovakia[1,2,3]: Lucia Hrivniakova, Margareta Slacikova, Dagmar Gavacova, Henrieta Kocianová;
- Slovenia[2]: Eva Grilc, Tjasa Zohar Cretnik, Marija Trkov;
- Spain[1,2,3]: Pilar Soler, M. Aurora Echeita;
- Sweden[1,2,3]: Sofie Ivarsson, Yvonne Andersson, Sven Lofdahl, Ralfh Wollin, Margareta Lofdahl, Lars Engstrand;
- United Kingdom[1,2,3]: Bob Adak, Tom Cheasty, John Cowden, Mary Hanson, John Coia, Tansy Peters, Paul McKeown;
- Iceland: Gudrun Sigmundsdottir, Hjordis Hardardottir;
- Liechtenstein: Erne Sabine;
- Norway[1,2,3]: Karin Nygard, Joergen Lassen, Line Vold;
- Switzerland[1]: Herbert Haechler, Karim Boubaker, Hans Schmid.

Data submitted for: [1]Salmonella, [2]VTEC and/or [3]Campylobacter for the third quarter of 2007.

References

1. Fisher I. The Enter-net international surveillance network – how it works. Euro Surveill 1999;4(5):52-55. Available from: http://www.eurosurveillance.org/em/v04n05/0405-222.asp
2. Food- and Waterborne Diseases Reports. Available from: http://ecdc.europa.eu/Activities/surveillance/ENTER_NET/reports.html
3. Denny J, Threlfall J, Takkinen J, Löfdahl S, Westrell T, Varela C, Adak B, Boxall N, Ethelberg S, Torpdahl M, Straetemans M, van Pelt W. Multinational Salmonella Paratyphi B variant Java (Salmonella Java) outbreak, August – December 2007. Euro Surveill 2007;12(12):E071220.2. Available from: http://www.eurosurveillance.org/ew/2007/071220.asp#2
4. The Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents, Antimicrobial resistance and Foodborne outbreaks in the European Union in 2006. Available from: http://www.efsa.europa.eu/EFSA/DocumentSet/Zoon_report_2006_en.pdf

This article was published on 13 March 2008.

Citation style for this article: Denny J, Hernández Pezzi G, Threlfall J, Westrell T, Fisher I. A quarterly update on food- and waterborne diseases in Europe - summary of data for the third quarter of 2007. Euro Surveill. 2008;13(11):pii=8069. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8069

The detection of meningococcal household clusters and their prophylaxis in the changing epidemiological situation of invasive meningococcal disease in Poland, 2003-2006

P Stefanoff (pstefanoff@pzh.gov.pl)[1], M Rosinska[1], G Karczewski[1], A Zielinski[1]
1. Department of Epidemiology, National Institute of Hygiene, Warsaw, Poland

Individual surveillance reports on meningococcal disease in Poland from 2003-2006 were screened for information on cluster detection and chemoprophylaxis administration, and a questionnaire was distributed to the country's regional health departments in order to summarize cluster investigation. The number of primary cases of meningococcal disease reported in 2003-2006 was 635, including 292 cases of meningitis, 185 cases of septicaemia, and 158 cases of meningitis with septicaemia. Chemoprophylaxis was administered to close contacts on average in 33.2% cases, the proportion increasing from 3.9% in 2003 to 43.8% in 2006. Between 2003 and 2006, there were five household clusters reported, involving a total of 10 cases. In one cluster, only co-primary cases were identified, and in the other four clusters, secondary cases were detected. Four of the five clusters were microbiologically confirmed, and the serogroup was established in two clusters (one C, one B). Chemoprophylaxis was correctly administered to household members in one cluster, after the diagnosis of the primary case, and a further case was recorded 42 days after the onset of disease in the primary case. Vaccination of contacts was not performed during the studied period. No deaths or serious disease sequelae were observed in the course of described household clusters.

Introduction

Invasive meningococcal disease (IMD) usually occurs sporadically, but can sometimes cause subsequent cases in close contacts. The detection and investigation of clusters is one of the most important aims of epidemiological surveillance of IMD, allowing the monitoring of the effectiveness of chemoprophylaxis and an assessment of the possible need for public health interventions, such as mass immunisation of the population when hyperepidemic strains are increasingly identified. In Poland, recommendations for IMD chemoprophylaxis were issued by the National Reference Centre for Bacterial Meningitis (NRCBM) in 2004 and were endorsed by the Chief Medical Officer for their national application [1]. Currently, the recommended prophylaxis of IMD cases includes the identification of close contacts and the referral of these individuals to general practitioners (GP) for observation and the administration of appropriate antibiotics. The drugs recommended for carriage eradication include rifampicin, ciprofloxacin, and ceftriaxone. IMD chemoprophylaxis is not free of charge for the patients, but is covered by the National Health Fund partial refund. Vaccination against IMD is neither included as a routine (free of charge) vaccine in the childhood immunisation schedule, nor recommended for the prevention of subsequent cases when vaccine-preventable strains are involved.

In recent years, the epidemiological situation of IMD in Poland has changed. The proportion of serogroup C among all Neisseria meningitis isolates and the incidence of infections caused by this serogroup in teenagers have increased [2], coinciding with an increased number of hyperinvasive strains of serogroup C (ST-11) meningococci detected in the NRCBM [3]. These changes were linked to larger community-based and institution-based outbreaks that attracted increased media attention [3,4,5].

The aim of the present study was to summarise the prophylactic measures undertaken within IMD surveillance and to describe the meningococcal household clusters identified in Poland in 2003-2006 in order to review the public health recommendations in this area.

Methods

For the purpose of this study, reports summarising the investigation of all IMD cases reported in 2003-2006 were screened for information on prophylaxis of close contacts and detection of disease clusters. In Poland, physicians are legally obliged to report all newly diagnosed cases of IMD to the local sanitary-epidemiological stations (SES). Public health officers at SES carry out the epidemiological investigation of cases, administer prophylactic measures to their closest contacts and complete standardised surveillance reports. Completed surveillance reports containing demographic, clinical, epidemiological and laboratory data on each case are sent to the National Institute of Hygiene. Case-based information for meningococcal meningitis has been available since 1994, and for all-spectrum IMD since 2005 [2].

An additional survey on cluster surveillance of IMD was collected from public health departments to supplement information on routinely collected case reports from 2003-2006. Some information was collected specifically for the purpose of this survey, e.g. the length of the follow-up period in each case.

The following definitions were used in the present study: a primary case was defined as the first case of IMD in a household setting; a household contact was a person living in the same household or household type situation, as the primary case, during the seven days before onset of illness; a co-primary household case was defined as a case of IMD in a household contact of a primary case with onset within 24 hours after the onset in the index case; a secondary household case was defined as a case of IMD in a household contact of a primary case with onset >24 hours after

onset in the index case; follow-up period was defined as the time between the notification of the case and the end of the investigation of cases and their close contacts.

Results

The number of primary cases reported in 2003-2006 was 635, including 293 cases of meningitis only, 156 cases of septicaemia only, and 186 cases of meningitis with septicaemia. The number of cases with symptoms of meningitis ranged from 76 in 2003 (incidence of 0.2 per 100,000 population) to 148 in 2006 (incidence of 0.4 per 100,000), and the number of cases with symptoms of septicaemia ranged from 23 in 2003 (incidence of 0.06 per 100,000) to 147 in 2006 (incidence of 0.4 per 100,000). Chemoprophylaxis was administered to close contacts in the average of 33.2% cases, the proportion increasing from 3.9% in 2003 to 43.8% in 2006, with marked variations between regions (Figure).

In 2003-2006, five IMD household clusters were reported, involving a total of 10 cases (average household size = 5 persons; mean attack rate = 38.5%) (Table).

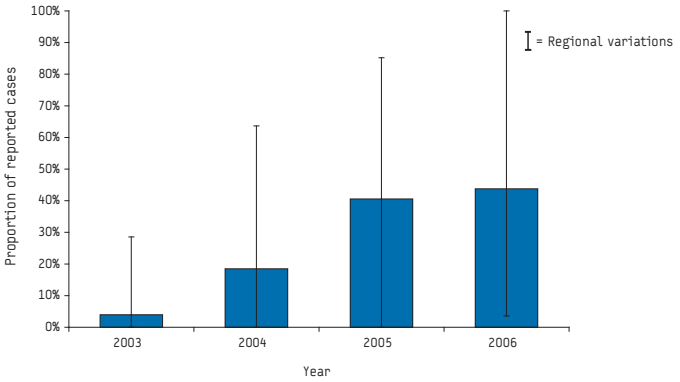
In one cluster, the cases occurred within 24 hours in two household members (co-primary cases), and in four clusters secondary cases were detected (mean time interval between primary and secondary cases = 15.7 days; mean attack rate in contacts = 18.2%). Four of the five clusters were microbiologically confirmed. The serogroup was established for at least one case in two clusters (one C, one B). Chemoprophylaxis was administered to close contacts in two clusters. In one cluster, it was given correctly to all household members after the diagnosis of the primary case, and a further case was recorded 42 days after the onset of disease in the primary case. In the second cluster, chemoprophylaxis was only administered after the onset of illness in the second case. Vaccination of contacts was not performed during the studied period. No deaths or serious disease sequelae were observed in the course of described household clusters.

Discussion

The epidemiological surveillance of IMD should result in applying prophylactic measures to prevent subsequent cases in households and in monitoring their effectiveness. Administering antibiotics

Figure

Proportion of cases of invasive meningococcal disease in which chemoprophylaxis was administered to close contacts, Poland, 2003-2006



eradicating meningococcal carriage was confirmed to be a cost-effective method of preventing subsequent cases [6]. One of the primary aims of the case investigation should be the follow-up of close contacts and the administration of chemoprophylaxis. Despite clear recommendations, chemoprophylaxis was not widely used in 2003-2006. This highlights the urgency of extensively educating public health officers and physicians and discussing the possibility of providing chemoprophylaxis to close contacts free of charge.

During 2006, no household clusters of IMD were identified, which could be related to the higher proportion of contacts given prophylaxis. In contrast, two large institution-based and two community-based outbreaks caused by group C meningococci occurred in 2006-2007, which required the undertaking of considerable control measures. In case of two outbreaks in army barracks massive chemoprophylaxis was undertaken [3,5] and the decision was adopted to routinely vaccinate all military personnel in Poland. In case of the two community outbreaks local immunisation campaigns were undertaken with conjugate meningococcal group C vaccine to reduce the carriage of hyperinvasive strains amongst teenagers [4,7].

Table

Selected characteristics of household clusters of invasive meningococcal disease, Poland, 2003-2006

Year	Follow up period (months)	House-hold size	Number of primary cases	Number of co-primary cases	Number of secon-dary cases	Time interval between primary and secondary cases (days)	Chemo-prophy-laxis of close contacts	Type of microbio-logical confir-mation	Sero-group	Number of fatal cases
2003	2	8	1	-	1	42	Yes	Isolation	C	0
2004	1.5	4	1	-	1	8	No	Latex	-	0
2005	0.5	4	-	2	-	-	No	Isolation	-	0
2005	0.25	6	1	-	1	6	No	Isolation	B	0
2005	1	4	1	-	1	7	Yes*	Isolation	-	0

* Chemoprophylaxis administered to close contacts after the secondary case occurred.

The studied period was selected based on availability of data on chemoprophylaxis administered. During this period, in 2005, the IMD surveillance system has changed, with its extension to all-spectrum IMD, and implementation of case definitions [2]. The exclusion of non-meningitis cases from surveillance before 2005 probably resulted in the underascertainment of clusters, especially if cases of septicaemia were involved. Additionally, the occurrence of group C outbreaks in 2006-2007 has led to increased sensitivity of IMD surveillance. The preliminary data for 2007 indicate that the proportion of cases in which chemoprophylaxis was administered to close contacts was higher than in 2006. A recent review of public health policies for managing cases of meningococcal disease in European countries helped identify several areas in which clear recommendations were missing in Poland, including the lack of guidelines for administering chemoprophylaxis to contacts in institutional settings and to fellow passengers in buses, trains and aeroplanes [8]. Based on these considerations, further work needs to be performed to update national recommendations for chemoprophylaxis and improve their implementation.

Acknowledgment

The authors wish to thank Dr James Stuart for his valuable comments.

References

1. Skoczynska A, Kadlubowski M, Hryniewicz W. [Principles of management of central nervous system infections caused by Neisseria meningitidis and other pathogens – guidelines for healthcare personnel]. Bielsko-Biala: Alfa-medica press; 2004. p. 46-48. Polish. Available from: http://www.gis.gov.pl/pdf/meningokoki/wytyczne.pdf
2. Gryniewicz O, Kolbusz J, Rosinska M, Zielinski A, Stefanoff P. Epidemiology of meningococcal meningitis and changes in the surveillance system in Poland, 1970-2006. Euro Surveill 2007;12(5). Available from: http://www.eurosurveillance.org/em/v12n05/1205-224.asp
3. Kadlubowski M, Wasko I, Klarowicz A, Hryniewicz W. Invasive meningococcal disease at a military base in Warsaw, January 2007. Euro Surveill 2007;12(3):E070301.2. Available from: http://www.eurosurveillance.org/ew/2007/070301.asp#2
4. Stefanoff P. Vaccination campaign with meningococcal serogroup C conjugate vaccine in response to ongoing community outbreak. ECDC Newsletter on Vaccines and Immunization number 20 (11 April 2007). Available from: http://www.ecdc.eu.int/documents/pdf/070411_VI_number_20.pdf
5. Grecki M, Bienias M. Outbreak of invasive meningococcal disease among soldiers in Skwierzyna, Poland, March 2006. Euro Surveill 2006;11(7):E060706.4. Available from: http://www.eurosurveillance.org/ew/2006/060706.asp#4
6. Purcell B, Samuelsson S, Hahné SJ, Ehrhard I, Heuberger S, Camaroni I, et al. Effectiveness of antibiotics in preventing meningococcal disease after a case: systematic review. BMJ. 2004;328(7452):1339-42.
7. Maiden, MCJ, Stuart JM for the UK Meningococcal Carriage Group. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. Lancet. 2002;359(9320):1829-31.
8. Hoek M, Hanquet G, Heuberger S, Stefanoff P, Zucs P, Ramsay M, et al. European survey on public health policies for managing cases of meningococcal disease and their contacts. Euro Surveill 2008;13(10). Available from: http://www.eurosurveillance.org/edition/v13n10/080306_4.asp

This article was published on 6 March 2008.

Citation style for this article: Stefanoff P, Rosinska M, Karczewski G, Zielinski A. The detection of meningococcal household clusters and their prophylaxis in the changing epidemiological situation of invasive meningococcal disease in Poland, 2003-2006. Euro Surveill. 2008;13(10):pii=8059. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8059

The first report on *Campylobacter coli* family outbreak detected in Poland in 2006

S Wardak (swardak@pzh.gov.pl)[1], J Szych[1], M Sadkowska-Todys[2]
1. Department of Bacteriology, National Institute of Public Health - National Institute of Hygiene, Warsaw, Poland
2. Department of Epidemiology, National Institute of Public Health - National Institute of Hygiene, Warsaw, Poland

A family outbreak of gastroenteritis caused by *Campylobacter coli* occurred in May 2006 in Bielsko-Biala, in the south of Poland. Four members of a family had non-bloody diarrhea and abdominal cramps. *C. coli* were isolated in three of the four patients. PFGE and PCR-RFLP-flaA patterns confirmed the link between cases, showing the usefulness of these methods in outbreak investigation. At the same time, the epidemiological and environmental investigations of this outbreak were very limited and did not provide enough evidence to identify the source of infection, and thus to support the hypothesis formulated by the local epidemiologist. It is necessary to improve surveillance of campylobacteriosis mainly by multidisciplinary training of epidemiologists, microbiologists and general practitioners.

Introduction

Thermotolerant species of *Campylobacter* (mainly *C. jejuni* and *C. coli*) are among the most frequently isolated bacterial agents of human gastroenteritis in many developed countries [1]. Globally, more than 90% of *Campylobacter* spp. infections are caused by *C. jejuni*, followed by *C. coli* with 5-10% [1]. In an earlier study we showed that in Poland *C. jejuni* was the species most frequently isolated from humans with diarrhea (94.5%) followed by *C. coli* (5.5%) [2].

C. jejuni are found mostly in poultry, whereas *C. coli* are usually isolated from pigs but may also be found in poultry and cattle [3]. Most *Campylobacter* infections occur as sporadic cases; outbreaks are uncommon [1,4] and are mostly caused by *C. jejuni*, whereas *C. coli* outbreaks are extremely rare [3].

Since 2003, the reporting of campylobacteriosis has been mandatory in Poland; the European Union case definition was introduced in 2005. The surveillance system relies on general practitioners (GPs) and hospitals sending notifications to the local sanitary-epidemiological stations (SES). After the notification of a case/outbreak, the local epidemiologists conduct an investigation and report it through the regional sanitary-epidemiological station to the national level. The information is gathered at the national level, and verified and analysed by the Department of Epidemiology of the National Institute of Public Health – National Institute of Hygiene (NIZP-PZH).

Despite the national surveillance system, data about *Campylobacter* infections are restricted to some regions of the country. This is mostly due to the limited number of laboratories performing the diagnosis of *Campylobacter*, which is based on isolation of the organisms from stool samples using selective media. In Poland, there are no more than 10 laboratories routinely performing culture of *Campylobacter*.

In this report, we describe an outbreak caused by *C. coli* and discuss the epidemiological situation regarding campylobacteriosis in Poland.

Outbreak description

In May 2006, four cases of gastroenteritis in a single family were notified to the SES in Bielsko-Biala, a city with around 180,000 inhabitants in southern Poland. The patients included a woman and a man in their forties, a nine-year old boy and a teenage girl. All of them presented with non-bloody diarrhea and abdominal cramps; in addition, the father and the son had also emesis. No fever or other clinical symptoms were observed. Upon notification to SES, the local epidemiologists launched an investigation, which included laboratory testing of stool samples taken from the affected patients.

Methods

The epidemiological investigation was limited to routine interviews of the patients by the local epidemiologists. The questionnaire used included demographic data, clinical symptoms and the date of onset of symptoms, treatment and diagnostic tests, and epidemiological data on housing conditions, travel history, animal exposure and food consumption in the past 72 hours.

The investigation was limited only to the affected family. No active case finding was conducted and no case control study was performed.

The stool samples from patients were examined for the presence of *Campylobacter* as well as *Salmonella*, *Shigella*, *Yersinia*, enteropathogenic (EPEC) and verotoxic (VTEC) Escherichia coli in the SES laboratory in Bielsko-Biala. Isolates of *C. coli* were sent to the Department of Bacteriology in NIZP – PZH for confirmation and further investigation. Species-level identification of *Campylobacter* isolates was based upon hippurate and indoxyl acetate hydrolysis tests and polymerase chain reaction (PCR) [5]. The *C. coli* ATCC 33559 and *C. jejuni* ATCC 33560 strains were used as controls. To determine differences or similarities between *C. coli* isolates, PFGE using SmaI, PCR-RFLP-flaA and antimicrobial susceptibility studies were performed. To test the value of the genotypic methods,

the molecular fingerprints of the outbreak-related isolates were compared with the patterns of three additional epidemiologically unrelated control isolates of *C. coli* obtained from patients with diarrhea from the Bielsko-Biala region. These *C. coli* control isolates were obtained in the same laboratory between March and September 2006. PFGE and flaA-RFLP analysis was carried out as described on the Campynet website (http://campynet.vetinst.dk/PFGE.html). The minimum inhibitory levels (MIC) of tetracycline, ciprofloxacin, nalidixic acid, ampicillin, erythromycin and gentamycin for *C. coli* isolates were determined by the E-test method (AB Biodisc, Solna, Sweden) with Mueller-Hinton agar with 5% sheep blood (bio Mérieux, France) according to the CLSI standard (formerly NCLLS) [2,6] and technical guidelines provided by the manufacturer.

As a result of the outbreak investigation, a standard inspection of food items and kitchen area of the restaurant that was implicated in the course of the investigation was also performed by inspectors from food safety unit of SES. This routine inspection, however, did not include testing food and environmental samples for *Campylobacter*.

Results

The investigation revealed that the only meal common to all family members was chicken shoarma with vegetable salad they had consumed a day before the onset of symptoms in a restaurant in town. This prompted the local epidemiologist to suspect the identified food items as a possible source of infection and undertake routine inspection of the restaurant and investigation of incriminated food. The quantitative results of swabs taken from the restaurant's kitchen utensils and chopping boards showed that they were microbiologically contaminated, but particular pathogens were not identified. This indicated poor hygienic practices in the restaurant, which could have contributed to this outbreak.

Laboratory analysis revealed the presence of *C. coli* in stool samples taken from three out of four members of the family (the mother and two children). No other causative agent has been identified in stool samples taken from the patients.

The outbreak-related isolates had the same pattern according to PFGE (pulsed-field gel electrophoresis) and PCR-RFLP (polymerase chain reaction - restriction fragment length polymorphism) of flaA methods. This pattern, however, was different from those observed in epidemiologically unrelated control isolates obtained from patients with diarrhea from the same region.

The outbreak-related isolates had identical patterns of antimicrobial susceptibility. They were resistant to ciprofloxacin (MIC >32 µg/ml), nalidixic acid (MIC > 256 µg/ml), ampicillin (MIC > 256 µg/ml), and were susceptible to erythromycin (MIC 0.5 µg/ml) and gentamicin (MIC 1 µg/ml). These findings support the assumption of a common source of the outbreak.

Discussion

In 2006, a total of 175,561 cases of campylobacteriosis were reported from 21 European Union Member States. Specifically, countries neighbouring with Poland, Germany, Czech Republic, Slovakia and Lithuania reported 52,035; 22,571; 2,718 and 624 confirmed cases, respectively [7]. In 2006, in Poland, only 156 *Campylobacter* infections were notified, with incidence of 0.4 per 100 000 population. For comparison, in the same period, 12,502 confirmed cases of *Salmonella* infection were reported in Poland, with incidence of 32.8 per 100,000. Despite the fact that we observed an increase in the number of reported *Campylobacter* cases between 2005 and 2006 – from 47 to 156 – we are very far from estimating the true number of cases and incidence of campylobacteriosis in our country.

The main reason of the underreporting of campylobacteriosis in Poland is the limited laboratory capacity for *Campylobacter* detection, available only in some regions of the country. For example, in 2005-2006 in the region of Bielsko-Biala, *Campylobacter* was the second after *Salmonella* most frequently isolated pathogen, and accounted for 41% (n=70) of all cases of bacterial gastroenteritis [8].

In 2006, 22 countries of the European Union reported 5,710 food-borne outbreaks, involving 53,568 people; 2,709 were considered family outbreaks. *Salmonella* was the most common cause of food-borne outbreaks (53.9% of all reported outbreaks). *Campylobacter* was the third most common cause associated with 6.9% of all food-borne outbreaks. In Poland, in the same year, a total of 561 food-borne outbreaks were reported (378 family outbreaks), affecting 6,974 people. The predominant causative agent was *Salmonella* spp. accounting for 292 (52%) of these outbreaks. In about 28% of reported outbreaks, the etiological agent was not identified.

In 2005, no outbreak of campylobacteriosis was reported in Poland, in 2006 only three outbreaks were notified, all were considered family outbreaks. Two of these were caused by *C. jejuni* (involving eight people) and one by *C. coli*. According to our knowledge this is the first report of a *C. coli* outbreak in Poland.

Our study shows that genotyping methods such as PFGE and PCR-RFLP flaA may be useful in investigating outbreaks due to *Campylobacter*. The results of these tests allow to link cases and thus identify outbreaks and look for their sources. The outbreak-related *C. coli* isolates were highly resistant to ciprofloxacin (MIC >32 µg/ml). The high prevalence of *Campylobacter* isolates resistant to fluoroquinolones is an emerging problem in Poland. In our previous study conducted between 2003 and 2005 we showed that 55.9% of *C. jejuni* and four out of six *C. coli* isolates were resistant to ciprofloxacin. This situation may reflect the broad use of this group of antibiotics in veterinary medicine in our country.

The outbreak described here provides more evidence of the importance of *C. coli* as a food-borne pathogen and underlines the need to strengthen surveillance of campylobacteriosis in Poland. It also reveals limitations of the epidemiological investigation conducted in relation to this outbreak. Not enough information was collected on food consumed by the affected patients to formulate the hypothesis that the source of infection was a meal containing chicken consumed at a particular restaurant in town. As the incubation period of campylobacteriosis is 3-4 days (range of 1 to 7), other common meals within the family before the visit to the restaurant should have been considered as a possible source of infection at the beginning of the investigation. In particular, information on the consumption of pork should have been gathered as, apart from poultry, *C. coli* are most frequently found in this kind of meat. In addition, once the hypothesis was formulated, there was no attempt at active case-finding, which could have confirmed the restaurant meal as a source of infection.

In Poland a lot of effort is still needed to improve the surveillance of campylobacteriosis. The NIZP-PZH provides training and education programmes that include both practical and theoretical courses on the diagnosis, treatment and epidemiology of campylobacteriosis. In recent years, on average about 80% of recorded *Campylobacter* isolates in Poland have been sent voluntarily by microbiology laboratories to NIZP-PZH where the diagnosis is confirmed by biochemical and PCR tests and isolates undergo antimicrobial resistance testing. This allows us to evaluate the quality of particular laboratories performing the diagnosis of campylobacteriosis. However, these actions would be enhanced if *Campylobacter* was included in the set of enteric pathogens (*Salmonella*, *Shigella*, *Yersinia*, VTEC, EPEC) routinely tested for in cases of diarrhea.

Acknowledgments

This study was supported by a grant from the Polish Ministry of Science and Higher Education N404 2532 33. We thank U. Duda and J. Klimczak for kindly providing *C. coli* isolates. We also wish to thank R. Gierczynski for useful advice.

References

1. Friedman, CR, Neimann J, Wegener HC, Tauxe RV. Epidemiology of Campylobacter jejuni infections in the United States and other industrialized nations, In: Nachamkin I, Blaser MJ, editors. Campylobacter. 2ed. Washington DC: ASM Press; 2000. p. 121-38.
2. Wardak S, Szych J, Zasada AA, Gierczynski R. Antibiotic resistance of Campylobacter jejuni and Campylobacter coli clinical isolates from Poland. Antimicrob Agents Chemother 2007;51(3):1123-5.
3. Miller WG, Mandrell RE. Prevalence of Campylobacter in the food and water supply: incidence, outbreaks, isolation and detection, In: Ketley JM, Konkel ME, editors. Campylobacter. Molecular and cellularbiology. Wymondham UK: Horizon Bioscience; 2005. p. 101-163.
4. Rautelin H, Hänninen ML. Campylobacters: the most common bacterial enteropathogens in the Nordic countries. Ann Med. 2000;32(7):440-45.
5. Vandamme P, Van Doorn LJ, al Rashid ST, Quint WG, van der Plas J, Chan VL, et al. Campylobacter hyoilei Alderton et al. 1995 and Campylobacter coli Véron and Chatelain 1973 are subjective synonyms. Int J Syst Bacteriol. 1997;47(4):1055-60.
6. Clinical and Laboratory Standards Institute. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline M45-A., Clinical and Laboratory Standards Institute, Wayne, Pa; 2006.
7. The Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents, Antimicrobial resistance and Foodborne outbreaks in the European Union in 2006. Available from: http://www.efsa.europa.eu/EFSA/DocumentSet/Zoon_report_2006_en.pdf
8. Wardak S, Duda U, Szych J. Epidemiological analysis of campylobacteriosis reported by Sanitary Epidemiological Station in Bielsko-Biala, Silesia, in Poland. Przegl Epidemiol. 2007;61:417-24. (in Polish).

This article was published on 28 February 2008.

Citation style for this article: Wardak S, Szych J, Sadkowska-Todys M. The first report on Campylobacter coli family outbreak detected in Poland in 2006. Euro Surveill. 2008;13(9):pii=8052. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8052

The introduction of the SENTINEL influenza surveillance system in Poland - experiences and lessons learned from the first three epidemic seasons

M Romanowska (nic@pzh.gov.pl)[1], I Nowak[1], K Rybicka[2], L B Brydak[1,2]
1. National Institute of Public Health – National Institute of Hygiene, National Influenza Centre, Warsaw, Poland
2. Chair and Department of Family Medicine, Medical University of Warsaw, Warsaw, Poland

Influenza surveillance provides information on virus activity and is necessary for the selection of vaccine strains and early warning in the case of the threat of an epidemic or pandemic. To improve this surveillance in Poland, a sentinel surveillance system was introduced in 2004-5 ("SENTINEL"). This paper presents results from SENTINEL during three seasons of its existence. Voivodship Sanitary-Epidemiological Stations (VSESs), physicians and the National Influenza Center (NIC) participate in SENTINEL. Laboratory course was performed by the NIC for VSESs. Stations were provided with procedures, report forms, etc. Physicians register number of influenza-like illnesses (ILI) and collect swabs. VSESs perform diagnostic tests. On the basis of information from VSESs, the NIC prepares weekly reports for the entire country. In 2004-5 epidemiological reports were received from 50% of VSESs, while in 2005-6 and 2006-7 from all VSESs. Virological reports were obtained from 37.5% of VSESs (2004-5), 75% (2005-6) and 94% (2006-7). Weekly number of reporting physicians ranged in three consecutive seasons from 165 to 219, 98 to 949 and 696 to 1,054. A total of 399 specimens were tested during the 2004-5 winter; 63 (16%) were positive for influenza and 21 (5%) for other respiratory viruses. In 2005-6, 949 specimens were tested. Influenza infections were confirmed in 47 cases (5%) and infections with other respiratory viruses in 36 cases (4%). A total of 1,195 specimens were tested during the 2006-7 winter; 37 (3%) were positive for influenza and 26 (2%) for other respiratory viruses. SENTINEL provided improvement of influenza surveillance when compared with seasons before 2004. Nevertheless, due to decreasing rate of positive specimens, virological surveillance is the most important part to improve in the next years.

Introduction

Influenza surveillance provides useful information on current influenza activity, including two types of data, i.e. epidemiological information, such as influenza incidence, mortality rates, hospitalization rates and virological information as types/subtypes of circulating influenza viruses and their antigenic and/or genetic characteristics. The above knowledge is necessary for the appropriate selection of vaccine strains, the development of new effective antivirals and new diagnostic reagents as well as for early warning in the case of epidemic, pandemic or avian flu in a human population, including the introduction of appropriate measures to reduce the number of influenza illnesses, complications and deaths, and consequently to reduce the high social and economic costs of influenza [1-3].

At the European level, virological and epidemiological information on influenza has been collected and analyzed by the European Influenza Surveillance Scheme (EISS), since 1996 [4]. The general aim of EISS is to contribute to a reduction in influenza morbidity and mortality, and the main objectives are: the collection and exchange of timely information on influenza activity in Europe; the aggregation, interpretation and making available of epidemiological and virological data regarding influenza in Europe; the strengthening and harmonizing of the methods used for the assessment of influenza activity; the contribution to the selection of influenza vaccine strains; the monitoring of influenza prevention and control policies in Europe; the contribution to pandemic preparedness planning; the promotion of research; and the operation of a Community Network of National Reference Laboratories for Human Influenza in Europe [4].

To become a full member of EISS requires the following criteria to be met: (1) The network is nationally or regionally representative; (2) The authority of the network is recognised by the national or regional health authority; (3) Epidemiological surveillance and virological surveillance are integrated in the same population; (4) The network has functioned successfully for at least two years; and (5) The network can deliver data on the weekly basis [4]. At present, EISS is a network of reference laboratories located in all European Union Member States, and also in Norway, Serbia, Switzerland and Ukraine. Poland, represented by the National Influenza Center (NIC) at the National Institute of Public Health – National Institute of Hygiene (NIPH-NIH), became an associate member of EISS in 2001 [5]. There were three reasons that made Poland impossible to be a full member of EISS: virological surveillance was not nationally/regionally representative (EISS membership criterion no. 1); epidemiological surveillance was not integrated with virological surveillance (criterion no. 3); and data were not delivered on a weekly basis (criterion no. 5) [4].

Until the epidemic season 2004-05, epidemiological and virological influenza surveillance were two separate systems in Poland [6]. Epidemiological surveillance was nationally and regionally representative, but virological surveillance was not. Laboratories of 16 Voivodship Sanitary-Epidemiological Stations (VSESs) in 16 administrative regions (voivodships) very sporadically participated in virological surveillance. Influenza isolates and other laboratory confirmations were obtained almost exclusively from Warsaw and

the NIC. Epidemiological influenza surveillance was nationally and regionally representative, because it was and still is a part of the national surveillance of infectious diseases, which includes influenza. Nevertheless, the significance of epidemiological data was limited due to the lack of appropriate laboratory confirmations and integration with virological influenza surveillance.

Another difficulty concerned entering epidemiological information into the EISS database, which requires weekly data according to the calendar numbering of weeks and separate data for age groups: 0-4, 5-14, 15-64 and >=65 years [7,8]. At that time, epidemiological data were obtained from the national surveillance existing for a wide range of different diseases. According to this surveillance, all physicians should collect data on the number of ILI and send to the local stations, including VSESs. Then, VSESs forward data to the Department of Epidemiolog at the NIPH-NIH, which prepares reports for periods: 1st-7th, 8th-15th, 16th-22nd and 23rd-30th/31st day of a month. This means that the reporting periods do not always agree with the calendar weeks. The last problem was data collection for the specific four age groups. In Poland, epidemiological data were collected in two age groups: under 14 years and >=15 years.

As a result of the above, the NIC, together with the Chief Sanitary Inspectorate, took action to establish a sentinel system that integrated virological and epidemiological influenza surveillance (called SENTINEL), similar to other countries and consistent with EISS requirements [7,9-11]. A sentinel system enables active surveillance to be performed by the collection of data from the selected active sentinel sites, such as outpatient clinics, health centres, hospitals or from individual participants, such as family physicians [12]. In this way, information received from the selected sentinel sites that cover only certain parts of the population is used to assess the situation in the entire population [12,13]. In Poland, the idea was to create the conditions to enable the inclusion of VSESs and a representative number of family physicians in the system, with the NIC as coordinator. This paper describes how this sentinel influenza surveillance system was developed in Poland in order to fulfill EISS requirements and presents how it has operated during the first three influenza epidemic seasons.

Methods

To establish SENTINEL, the NIC developed guidelines for participants to have system collecting on time-credible information of a high enough quality to become an integral part of the European data on influenza activity in different periods of the epidemic season.

In 2003, the Chief Sanitary Inspector and the NIC prepared a set of documents to provide VSESs with information on SENTINEL, including its general principles and information on the tasks of VSESs and physicians. The Chief Sanitary Inspectorate played a significant role in including VSESs into SENTINEL, as the NIC has no appropriate entitlements with reference to VSESs.

VSESs received guidelines regarding reporting epidemiological and virological data as well as swabbing instructions, specimen forms and reporting forms. These forms were updated in 2005 and 2006 to make them optimal for collecting valuable information in the easiest way.

Between November 2003 and April 2004, the NIC ran a practical laboratory course for VSESs on virus isolation (cell line, chicken embryos), the detection of virus antigens by immunofluorescence (IF), virus titration by hemagglutination test and serology by hemagglutination inhibition test. VSESs received laboratory procedures with the list of reagents and equipment to make their start in SENTINEL easier. In the case of technical problems, the NIC advised VSESs by telephone or e-mail. The Chief Sanitary Inspectorate financially assisted VSESs to equip and obliged them to join SENTINEL, establish cooperation with physicians and coordinate surveillance on the voivodship level.

Physicians participating in SENTINEL are family doctors as well as pediatricians and internists with or without specialization in family medicine, working in public or private outpatient heath care units. They practice in 16 administrative regions (voivodships) and were recruited by VSESs. None are paid for SENTINEL activities, due to a lack of funds for such aim. Therefore, the only criteria for selecting sentinel physicians were: to obtain their interest to participate in SENTINEL on the voluntary basis according to principles established by the NIC. Physicians in SENTINEL register number of ILI cases on the weekly basis and collect swabs from patients with influenza symptoms according to the instructions prepared by the NIC. These instructions describe the aim of specimen collection; the conditions of storage and transport of the specimens; include guidelines on who should be swabbed and when, as well as including technical instructions on how to collect throat and nasal swabs. Clinical criteria presenting a basis for physicians to collect specimens are the following: symptoms of influenza/ILI, i.e. at least one respiratory tract symptom (e.g. cough, sore throat, rhinitis) and at least one systemic symptom (e.g. sudden onset of disease, fever >38°C, perspiration, chills, muscular/joint pain, headache, malaise/fatigue, nausea). Epidemiological data and swabs are sent with the specimen form to an appropriate VSES.

In the first version of the specimen form used in the first season, 2004-5, physicians listed individual symptoms in a given patient. Nevertheless, the NIC decided to simplify this form and deleted the clinical picture of disease. In the 2005-6 season, the following information were to be provided by sentinel physicians in the specimen form: age of the patient, sex, date onset of illness, date of specimen collection, date of sending of the specimen to laboratory, information on whether the patient had been vaccinated against influenza in a given epidemic season, information on whether the patient had been exposed to the specific antivirals and physician's contact details. In the specimen form used in the 2006-7 season, the date of sending of the specimen to laboratory was changed to the date of the receipt of the specimen by the laboratory and an additional space was given for the results of diagnostic tests performed by laboratories. VSESs perform tests to confirm or exclude influenza infection. Depending on the capacity, they isolate virus and/or perform IF assay for influenza and sometimes, but not routinely, for other viruses (RSV, adenovirus, parainfluenza) [14,15]. The results are forwarded to the physician who collected the specimen. Weekly epidemiological and virological reports are then prepared and sent by VSESs to the NIC.

In the epidemiological reports, the following information is included: the calendar week number; the number of ILI cases registered in the specific age groups (0-4, 5-14, 15-64, >=65, unknown age) in each week; the number of all patients in the specific age groups attributed to the healthcare units in which

sentinel physicians work; and the number of reporting sentinel physicians in a given week. In the case of virological reports, data collected in the season 2004-5 included: the calendar week number; the number of specimens received and tested by a given method in each week; the number of positive specimens and the results of testing; the number of negative specimens; and the number of specimens/isolates sent to the NIC for confirmation. In the 2005-6 season, the latter was deleted, but two other items were added: the number of specimens during laboratory testing (when the result is not available within the same reporting period as in the case of virus isolation) and a table for overdue results of tests performed with specimens collected in the previous weeks. Influenza isolates are sent to the NIC, where antigenic characteristics is made. VSESs are informed of the results of such analysis. The NIC then sends isolates to the World Health Organization (WHO) Collaborating Centre in London, the United Kingdom, for detailed analysis. After verification of information received from VSESs, the NIC prepares weekly epidemiological and virological reports and sends the data to EISS and the WHO (FluNet).

Results presented in this paper for each epidemic season include periods between week no. 36 of a given year and week no. 16 of the next year, inclusive.

Results

Characteristics of data reporting by VSESs and information on the number of physicians in SENTINEL are presented in Table 1.

SENTINEL covered 1.3%, 4.7% and 5.0% of the total population of Poland in the 2004-5, 2005-6 and 2006-7 seasons, respectively. The population covered by SENTINEL in each of 16 voivodships ranged from 0.4% to 9.4% (season 2004-5), from 0.8% to 14.4% (season 2005-6) and from 1.3% to 16.9% (season 2006-7) of the total population of a given voivodship. Representativeness of the specific age groups covered by SENTINEL differed between voivodships. In 2004-5, SENTINEL covered, depending on the voivodship, between 0.2% and 9.1% of the population aged 0-4; 0.2% to 8.6% of the population aged 5-14; 0.2% to 9.2% of the population aged 15-64 and 0.2% to 10.6% of the population aged >=65. In 2005-6 these parameters were between 0.8% and 12.7% (0-4 years), 0.7% and 14.4% (5-14 years), 0.7% and 14.5% (15-64 years), 1.4% and 14.7% (=65 years). In 2006-7 these values ranged from 1.3% to 15.4% (0-4 years), 1.1% to 17.1% (5-14 years), 1.3% to 16.1% (15-64 years) and from 1.7% to 22.2% (>=65 years). In contrast to the above data, there were no significant differences in the representativeness of different age groups in SENTINEL within individual voivodships.

In 2004-5, the total number of SENTINEL swabs amounted to 399 and this is 91.1% of the total number of specimens in this season (remaining 8.9% were received from non-sentinel system as hospitals). Percentage of specimens positive for respiratory viruses (influenza, RSV, parainfluenza or adenovirus) amounted to 21.1%, while positive only for influenza - 15.8%. Weekly percentage of specimens positive for influenza ranged from 0% to 31.8% (Table 2).

Among influenza infections 52.4% were caused by type A (13 cases of influenza A not subtyped, one case of influenza A subtype H1, 19 cases of influenza A subtype H3) and 47.6% by type B (30 cases). The total number of influenza isolates amounted to 48, including 41 strains obtained within SENTINEL (85.4%). Twenty three of 41 isolates were identified as type B (56.1%), 17 strains as subtype A/H3N2 (41.5%) and one strain as subtype A/H1N1 (2.4%). The highest influenza activity was observed between week 8/2005 and 11/2005 with the highest weekly incidence of 641.7/100,000 (Figure 1).

In the 2005-6 season, 949 SENTINEL specimens were tested (98.1% of the total number of samples). Infections with respiratory viruses including influenza were confirmed in 83 cases (8.7%), while infections with influenza in 47 cases (5%). Weekly rate of influenza-positive specimens was between 0% and 26.3% (Table 2). Among influenza infections 25.5% were caused by type A (six cases of influenza A not subtyped, four cases of influenza A subtype A/H1, two cases of influenza A subtype H3) and 74.5% by type B (35 cases). Thirty-five influenza strains were isolated and all of them were obtained within SENTINEL. There were 27 strains of influenza B (77.1%), six strains of A/H1N1 (17,1%) and two strains of A/H3N2 (5.7%). The highest influenza activity was between week 10/2006 and 13/2006 with the highest weekly incidence of 229.7/100,000 (Figure 2).

Table 1

Weekly reporting of epidemiological and virological data by the voivodship Sanitary-Epidemiological Stations (VSESs) to the National Influenza Center (NIC) and the number of physicians in the influenza sentinel surveillance system (SENTINEL) in Poland, epidemic seasons 2004-5 to 2006-7

	epidemic season[a]		
	2004-5	2005-6	2006-7
number of VSESs sending epidemiological reports	6 (38%) – 10 (63%) (median: 8)	8 (50%) – 16 (100%)[b] (median: 16)	8 (50%) – 16 (100%)[d] (median: 16)
number of VSESs sending virological reports	1 (6%) – 9 (56%) (median: 6)	6 (38%) – 15 (94%)[c] (median: 12)	10 (63%) – 16 (100%)[e] (median: 15)
number of physicians in SENTINEL	165 – 219	98 - 949 (median: 868)	696 - 1054 (median: 1,017)

[a] periods between week 36 of a given year and week 16 of the following year, inclusive, according to the calendar numbering of weeks
[b] since week 45/2005 reports received from all 16 VSESs
[c] one VSES did not send reports due to laboratory conversion
[d] between week 41/2006 and week 15/2007 reports received from all 16 VSESs
[e] one VSES did not send reports until week 13/2007 due to laboratory conversion

In the 2006-7 season, 1,195 specimens (97.5% of the total number of swabs) were tested. Percentage of specimens positive for respiratory viruses including influenza amounted to 5.3%, while positive only for influenza - 3.1%. Weekly percentage of specimens positive for influenza ranged from 0% to 11.1% (Table 2). Among influenza infections 94.6% were caused by type A (25 cases of

TABLE 2

Weekly percentage of influenza-positive specimens collected and tested within the influenza sentinel surveillance system (SENTINEL) in Poland, epidemic seasons 2004-5 to 2006-7

week number (according to calendar)	epidemic season		
	2004-5	2005-6	2006-7
36	*	*	*
37	*	*	0.0
38	*	0.0	0.0
39	*	0.0	0.0
40	*	0.0	0.0
41	*	0.0	4.0
42	0.0	14.3	0.0
43	0.0	0.0	0.0
44	*	*	0.0
45	0.0	0.0	0.0
46	0.0	0.0	0.0
47	*	0.0	2.9
48	0.0	5.9	0.0
49	0.0	0.0	0.0
50	0.0	0.0	0.0
51	0.0	11.1	0.0
52	*	0.0	0.0
53	0.0	n.a.	n.a.
01	0.0	0.0	10.0
02	*	0.0	0.0
03	0.0	0.0	3.6
04	31.8	0.0	1.9
05	21.7	2.6	6.3
06	17.6	0.0	4.8
07	22.0	12.7	4.5
08	19.6	8.6	2.1
09	13.0	10.6	7.8
10	24.5	5.6	5.3
11	15.1	5.5	0.0
12	3.3	3.8	2.3
13	0.0	4.2	0.0
14	20.0	26.3	0.0
15	0.0	4.5	0.0
16	0.0	0.0	11.1

* no specimens collected in the given week
n.a. – not applicable

FIGURE 1

Influenza-like illness (ILI)* incidence and number of laboratory-confirmed influenza cases in the epidemic season 2004-5 according to the influenza sentinel surveillance system (SENTINEL) in Poland

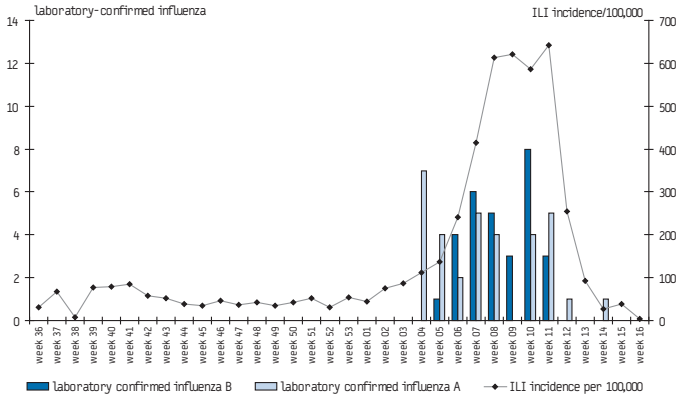


FIGURE 2

Influenza-like illness (ILI)* incidence and number of laboratory-confirmed influenza cases in the epidemic season 2005-6 according to the influenza sentinel surveillance system (SENTINEL) in Poland

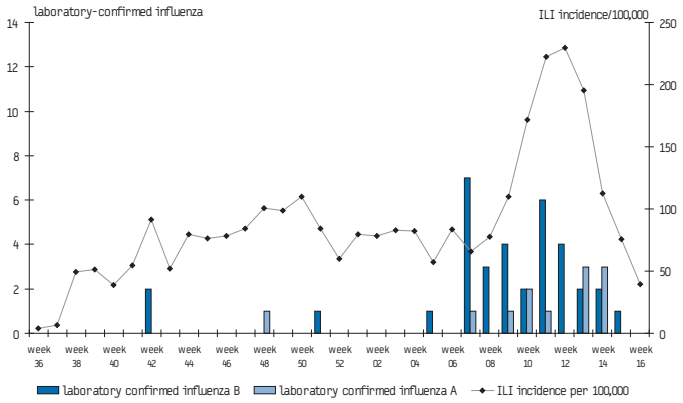
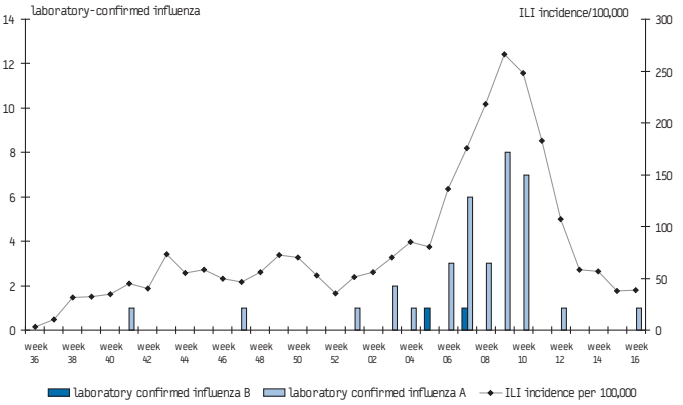


FIGURE 3

Influenza-like illness (ILI)* incidence and number of laboratory-confirmed influenza cases in the epidemic season 2006-7 according to the influenza surveillance system (SENTINEL) in Poland



influenza A not subtyped, five cases of influenza A subtype H1, five cases of influenza A subtype H3) and 5.4% by type B (two cases). Seventeen influenza strains were isolated, including 10 strains (five A/H1N1 and five A/H3N2) obtained within SENTINEL and seven strains (A/H1N1) isolated from hospital specimens. The highest influenza activity was between week 08/2007 and 11/2007 with the highest weekly incidence of 265.8/100,000 (Figure 3).

In all epidemic seasons, the highest ILI incidence was observed in children under 14 years (Table 3). Other indicators of influenza activity summarizing data for three epidemic seasons are presented in Table 3.

Discussion

Epidemiological influenza surveillance is performed in Poland since 1936, and virological surveillance since 1953 [18-20]. Although this surveillance has a long history, its effectiveness was various. The major problem regarded virological part and a small number of specimens collected for laboratory processing. As it is indicated in the Introduction section, epidemiological data on ILI cases without simultaneous laboratory confirmations is not sufficient to have credible information on influenza activity. The reason is that symptoms similar to influenza illness may be caused by influenza virus as well as many other pathogens [20]. Therefore, improvement of virological surveillance through the establishment of SENTINEL influenza surveillance system within which sentinel physicians collect swabs from patients with ILI symptoms was necessary to validate clinical reports on ILI as well as to obtain community-based respiratory specimens for virological testing. Limited and not nationally representative virological information became especially disturbing since when one of the most important global priorities is influenza pandemic preparedness and surveillance is one of the fundamental components of preparedness plans [3,20,21]. Therefore, the NIC and the Chief Sanitary Inspectorate decided to improve surveillance by creating SENTINEL to provide nationally representative, integrated virological and epidemiological influenza surveillance and to have uniform system with other European countries according to EISS recommendations [4,5,7].

The first seasons of SENTINEL in Poland showed that the system works well, although is not perfect as yet. There was a major improvement, especially in the virological surveillance, in comparison with the previous seasons. There was observed a significant increase in the number of specimens: almost three-fold in 2004-5, over six-fold in 2005-6 and almost eigh-fold increase in 2006-7 when compared with 2003-4. Moreover, the specimens were obtained from different regions of the country.

Nevertheless, there were still some difficulties. One of the most important issues is to maintain the integration of epidemiological surveillance with virological surveillance [7,10]. The number of physicians increased, even up to over 1,000 in one week. Nevertheless, this increase was not always connected with participation of physicians in virological surveillance, and consequently with the increased number of specimens. Every week the number of specimens was below 1.0 per physician. The question, therefore, is how to encourage physicians to contribute to SENTINEL and to ensure an appropriate and sustained quality of their work in this surveillance. The number of physicians significantly varied between seasons as well as during individual seasons. These

Table 3

Summary of data on influenza activity in Poland in the epidemic seasons from 2004-5 to 2006-7 according to the influenza sentinel surveillance system (SENTINEL)

indicators of influenza activity	epidemic season[a]		
	2004-5	2005-6	2006-7
weeks of peak ILI* incidence	08/2005 – 11/2005	10/2006 – 13/2006	08/2007 – 11/2007
most affected age groups according to ILI* incidence	0-4 5-14	0-4 5-14	0-4 5-14
peak level of intensity[b]	high	medium	medium
peak level of geographical spread[c]	regional	sporadic	sporadic
week of peak laboratory confirmations of influenza infection	10/2005	07/2006	09/2007
week of peak percentage of influenza-positive specimens	04/2005	14/2006	16/2007
predominant[d] type/subtype of influenza virus	co-circulation of influenza A (mainly subtype H3) and B	B	influenza A (subtype H1 and H3, but most cases not subtyped)

* ILI = influenza-like illness

[a] periods between week 36 of a given year and week 16 of the following year, inclusive, according to the calendar numbering of weeks

[b] according to European Influenza Surveillance Scheme (EISS): low = no influenza activity or influenza activity at baseline level; medium = level of influenza activity usually seen when virus is circulating in the country based on historical data; high = higher than usual influenza activity compared to historical data; very high = particularly severe influenza activity compared to historical data [7, 16, 17]

[c] according to EISS: no activity = clinical activity at baseline levels and infections are not laboratory confirmed; sporadic = isolated cases of laboratory-confirmed influenza in a region, or an outbreak in a single institution with clinical activity remaining at or below baseline levels; local outbreak = increased ILI* activity in local areas within a region, or outbreaks in two or more institutions within a region, with laboratory-confirmed cases, levels of activity in the rest of the region and other regions remain at or below baseline levels; regional activity = ILI* activity above baseline levels in one or more regions with a population comprising less than 50% of the country's total population, with laboratory confirmed infections in the affected region(s), levels of activity in other regions remain at or below baseline levels; widespread activity = ILI* activity above baseline levels in one or more regions with a population comprising 50% or more of the country's population, with laboratory confirmed influenza infections [7, 16, 17]

[d] all laboratory confirmations were taken into account (virus isolations, detections by IF and RT-PCR)

differences were probably due to not all of the sentinel physicians performing their work in accordance with the principles established by the NIC and VSESs. On the one hand, some of them did not send reports to VSESs every reporting week while on the other hand other "new" physicians became interested in SENTINEL and decided to participate in this system. The problem is that sentinel physicians work as volunteers. Sometimes a feedback information on the result of testing is a sufficient incentive for them. Cooperation with possibly the same physicians season by season would also be a favorable situation to ensure better and better experienced participants.

The same requirement applies to VSESs to ensure the highest and sustained quality of specimen processing. The percentage of influenza-positive specimens consistently decreased since 2004-5 (15.8%) through 2005-6 (8.7%) until 2006-7 (3.1%). Moreover, there were significant differences in the percentages of influenza-positive specimens week by week within the same epidemic season (sudden increases and decreases). There are two possible explanations: negative results were in fact negative, or the conditions essential for proper specimen collection and processing were not fulfilled. Therefore, the awareness of laboratory staff and physicians of factors affecting a result of testing (specimen collection, storage, transport) should be increased [15]. Each epidemic season, the NIC provides VSESs with the updated reporting forms, but also with detailed instructions for physicians how to collect different types of specimens, who can be swabbed and when, how to store and transport the specimens, etc. Nevertheless, the results presented in this paper show that practical courses for the sentinel physicians would be organized and swabbing instructions should be supplemented with the specific requirements regarding minimal number of swabs to collect each week by every sentinel physician taking into account laboratory capacity of individual VSESs. Besides, it is important to ensure access to rapid, sensitive (e.g. RT-PCR) and new laboratory techniques (real-time RT-PCR). It should also be worth assessing the quality of laboratory work in VSESs.

Another important aspect is the communication between VSESs, physicians and the NIC. Channels of rapid communication should include sending reports and results of laboratory tests on time, transport of specimens and isolates and exchange of any other information regarding surveillance. Differences between the number of epidemiological reports and number of virological reports were probably caused by lack of effective communication and exchange of clear information between individual participants of SENTINEL. For example, some VSESs were not aware of the necessity to send epidemiological and virological reports to the NIC even if no ILI cases were registered or no specimens were collected in a given week. Considering the above aspects, special questionnaires will be sent to VSESs and physicians to identify any problems, suggestions, strong and weak elements of SENTINEL.

At present, influenza surveillance is performed during the epidemic season. Nevertheless, VSESs and physicians should be prepared for all-year-round surveillance, according to EISS' plans. The NIC would also like to use influenza SENTINEL to perform virological surveillance for other respiratory infections as RSV [22-24]. Another objective will be for the NIC to prepare national reports similar to EISS annual reports [4,5,7].

The first seasons of SENTINEL were a success. Poland has been a full member of EISS since May 2006 and participates effectively in Europe's influenza surveillance. Nevertheless, SENTINEL should be continuously improved in coming years, especially in the area of specimen collection by physicians, laboratory testing and its quality. Before new tasks will be introduced (such as the introduction of new laboratory techniques, and all-year-round surveillance), a more important goal is to maintain the correct and reliable completion of basic principles of SENTINEL. Further improvement of SENTINEL should lead to:

- sustained integration of epidemiological and virological surveillance;
- effective encouragement of physicians to participate in SENTINEL despite the system's volunteer basis;
- possible cooperation with the same family physicians from season to season;
- assurance of appropriate and sustained quality of physicians' work in SENTINEL during the entire epidemic season, even under the risk of decrease of the number of sentinel physicians;
- increased number of specimens collected by individual physicians every week;
- improved quality of the collection, storage and transport of the specimen;
- improved quality of laboratory processing of the collected specimens;
- better qualified and experienced laboratory staff to ensure the highest quality of laboratory processing;
- decreased discrepancies between voivodships in the population size covered by SENTINEL, including population size of the specific age groups;
- better control and coordination of the surveillance in the individual regions (voivodships);
- improved communication between all participants of SENTINEL to ensure the effective exchange of any information and to guarantee that all principles of this system is clear for all participants;
- year-round influenza surveillance according to the EISS plans;
- introduction of respiratory viruses other than influenza and causing ILI into SENTINEL;
- publishing detailed national reports similar to EISS' annual reports on influenza activity in a given epidemic season.

Acknowledgements

The authors are grateful to all VSESs and physicians who actively participated in the SENTINEL influenza surveillance system in the 2004-5 and 2006-7 seasons.

References

1. World Health Organization, Dept. of Communicable Disease Surveillance and Response. Terms of Reference for National Influenza Centres. Available from: http://www.who.int/csr/disease/influenza/en/TORNICs.pdf
2. World Health Organization: The role of National Influenza Centres (NICs) during interpandemic, pandemic alert and pandemic periods. 2007 May:1-13. Available from: http://www.who.int/csr/disease/avian_influenza/guidelines/RoleNICsMayf.pdf
3. World Health Organization, Department of Communicable Disease Surveillance and Response. WHO global influenza preparedness plan. The role of WHO and recommendations for national measures before and during pandemics. WHO/CDS/CSR/GIP/2005.5, Global Influenza Programme, WHO, Geneva, Switzerland, 2005:1-50. Available from: http://www.who.int/csr/resources/publications/influenza/GIP_2005_5Eweb.pdf

4. European Influenza Surveillance Scheme. Annual Report 2005-2006 influenza season. Utrecht, the Netherlands, NIVEL, 2007:1-38. Available from: http://www.eiss.org/documents/eiss_annual_report_2005-2006.pdf
5. European Influenza Surveillance Scheme. Annual Report 2001-2002 influenza season. Utrecht, the Netherlands, NIVEL, 2002:1-34. Available from: http://www.eiss.org/documents/eiss_annual_report_01-02.pdf
6. Brydak LB, Machala MK. Role of a family physician in the European integrated influenza surveillance SENTINEL. Family Medicine & Primary Care Review 2006;8(3):848-853 [in Polish].
7. European Influenza Surveillance Scheme. Annual Report 2004-2005 influenza season. Utrecht, the Netherlands, NIVEL, 2006:1-60. Available from: http://www.eiss.org/documents/eiss_annual_report_2004-2005_+_cover.pdf
8. EISS Weekly Electronic Bulletin. Available from: http://www.eiss.org/cgi-files/bulletin_v2.cgi
9. Turner J, Kelly H. A medical locum service as a site for sentinel influenza surveillance. Euro Surveill 2005;10(4):96-8. Available from: http://www.eurosurveillance.org/em/v10n04/1004-222.asp
10. Fleming DM, van der Velden J, Paget WJ. The evolution of influenza surveillance in Europe and prospects for the next 10 years. Vaccine. 2003;21(16):1749-53.
11. Centers for Disease Control and Prevention. Weekly report: influenza summary update. Available from: http://www.cdc.gov/ncidod/diseases/flu/weekly.htm
12. Losos JZ. Routine and sentinel surveillance methods. East Mediterr Health J. 1996;2(1):46-50.
13. Deckers JGM, Paget WJ, Schellevis FG, Fleming DG. European primary care surveillance networks: their structure and operation. Fam Pract. 2006;23(2):151-158.
14. Centers for Disease Control and Prevention. WHO Collaborating Center for the Surveillance, Epidemiology and Control of Influenza. Concepts and procedures for laboratory-based influenza surveillance. U.S. Department of Health and Human Services, Public Health Service, July 1982.
15. Manuguerra J-C, Hannoun C. Influenza and other viral respiratory diseases. Surveillance and laboratory diagnosis. Paris: Institut Pasteur; 1999.
16. European Influenza Surveillance Scheme. Indicators of influenza activity: 2005-2006 influenza season. Available from: http://www.eiss.org/cgi-files/bulletin_v2.cgi?season=2005
17. European Influenza Surveillance Scheme. Indicators of influenza activity: 2006-2007 influenza season. Available from: http://www.eiss.org/cgi-files/bulletin_v2.cgi?season=2006
18. Brydak LB, Kuszewski K. Influenza. In: Kostrzewski J, Magdzik W, Naruszewicz-Lesiuk D, editors. Choroby zakazne i ich zwalczanie na ziemiach polskich w XX wieku. Warszawa: Wydawnictwo Lekarskie PZWL; 2001. p. 233-242 [in Polish].
19. Kantoch M. Medical virology (Wirusologia lekarska). Warszawa: Wydawnictwo Lekarskie PZWL; 1998 [in Polish].
20. Brydak LB. Influenza and its prophylaxis (Grypa i jej profilaktyka). 2nd ed. Poznan: Wydawnictwo Termedia; 2004 [in Polish].
21. The National Influenza Pandemic Preparedness Plan for Poland. Prepared by the National Influenza Pandemic Committee on the basis of the project prepared by the National Influenza Center (Brydak Lidia B., Machala Magdalena), 10 August 2005. Available from: http://www.gis.gov.pl/pdf/grypa/plan.pdf
22. Druce J, Tran T, Kelly H, et al. Laboratory diagnosis and surveillance of human respiratory viruses by PCR in Victoria, Australia, 2002-2003. J Med Virol. 2005;75(1):122-9.
23. Meerhoff T, Fleming D, Smith A, Mosnier A, van Gageldonk-Lafeber AB, Paget WJ; EISS RSV Task group. Surveillance recommendations based on an exploratory analysis of respiratory syncytial virus reports derived from the European Influenza Surveillance System. BMC Infect Dis. 2006;6:128.
24. Meerhoff TJ, Paget WJ, Aguilera JF, van der Velden J. Harmonising the virological surveillance of influenza in Europe: results of 18-country survey. Virus Res. 2004;103(1-2):31-3.

This article was published on 21 February 2008.

Citation style for this article: Romanowska M, Nowak I, Rybicka K, Brydak LB. The introduction of the SENTINEL influenza surveillance system in Poland - experiences and lessons learned from the first three epidemic seasons. Euro Surveill. 2008;13(8):pii=8046. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8046

An outbreak of measles in an ultra-orthodox Jewish community in Jerusalem, Israel, 2007 - an in-depth report

C Stein-Zamir (chen@lbjer.health.gov.il)[1], N Abramson[1], H Shoob[1], G Zentner[1]
1. Jerusalem District Health Office, Ministry of Health, Israel

Measles elimination in Europe is hindered by recurrent outbreaks, typically in non-immunised specific sub-populations. In 2003 and 2004, two measles outbreaks occurred in Jewish ultra-orthodox communities in Jerusalem, Israel. In 2007, another measles outbreak emerged in Jerusalem. Epidemiological investigation and control activities were initiated. Three measles cases (15 years old, 22 years old and an infant; all unvaccinated) were diagnosed in Jerusalem in August 2007. All three belonged to Jewish ultra-orthodox communities in London, United Kingdom, and had had contact with patients in London. The epidemiological investigation did not reveal any connection between these cases other than their place of origin. The disease spread rapidly in extremely ultra-orthodox sub-groups in Jerusalem. Until 8 January 2008, 491 cases were reported. Most patients (70%) were young children (0-14 years old), 96% unimmunised. Frequently, all the children in a large family were infected; two thirds of the cases belonged to family clusters of more than two patients per family (in part due to non-compliance with post-exposure prophylaxis recommendations). The high age-specific incidence among infants 0-1-year- (408.5/100,000) and 1-4-year-olds (264.1/100,000) is a cause for concern. The hospitalisation rate was 15% (71/491), mainly due to fever, vomiting and dehydration. The median age of hospitalised patients was 3.6 years; 19 patients (26.7%) presented with pneumonitis or pneumonia and two patients presented with encephalitis. There have not been any deaths to date.
The outbreak was apparently caused by measles importation into unprotected groups. Despite a high national immunisation coverage (94-95%), programmes to increase and maintain immunisation coverage are essential, with special focus on specific sub-populations.

Introduction

Measles presents a major global disease burden and is still the number one killer among vaccine-preventable diseases, causing almost half a million deaths a year [1-3].

Measles elimination in Europe is hindered by recurrent outbreaks, typically in non-immunised sub-populations. In 1999 and 2000, such an outbreak was reported in the Netherlands, with three measles-related deaths and 68 hospitalisations among 2,961 cases; 84 percent of the cases (2,317 people) were eligible for vaccination, but were not vaccinated for religious reasons [4]. Under-vaccination was also reported in Bavaria, Germany [5] and in the United Kingdom (UK) and Ireland, where the coverage declined due to fears of side-effects such as autism and inflammatory bowel disease [6,7]. In recent years, the nomad Roma/Sinti population has been associated with the spread of measles in several regions of Europe [8,9].

Kremer et al. described the measles virus genotypes in Europe during 2005 and 2006 as being mainly D4, D6 and B3 [9]; the largest outbreaks considered in that paper happened in the Ukraine, Romania, Germany and the Russian Federation.

In 2003 and 2004, two measles outbreaks occurred in ultra-orthodox Jewish communities in Jerusalem, Israel [10]. The index case of the outbreak in 2003 was a two-year-old unvaccinated child from Switzerland. Within five months, 107 people in Jerusalem had become infected. The outbreak in 2004 started in a different ultra-orthodox community and saw a total of 117 cases within five months. The first cases were three girls aged four to five years who attended the same kindergarten. The virus genotypes were D8 in 2003 and D4 in 2004. Altogether, these two outbreaks affected 96 households, with 79% of the cases belonging to family clusters of more than two patients per family. Most cases (91.5%) were unvaccinated, and 87% were children under 14 years of age. The immunisation coverage in the neighbourhoods affected by the outbreaks was lower than in the district overall. An intervention programme subsequently increased the coverage with the first dose of the measles/mumps/rubella (MMR) vaccine to an average of 95.2% in Jerusalem and of 94.2% in ultra-orthodox neighbourhoods.

Despite these efforts, non-compliant communities still exist. We are currently in the throes of another, even larger measles outbreak that started in August 2007 among extremely ultra-orthodox groups in Jerusalem. A preliminary report was published in Eurosurveillance in September 2007 [11,12]. The first cases in this outbreak came from London, United Kingdom (UK), and, as in 2004, the genotype involved (in Israel and in the UK) was D4. In November 2007, clusters of measles cases linked to the UK were also reported in Jewish orthodox communities in Antwerp [13].

Methods

In Israel, the notification of measles is mandatory by law. The case investigation includes demographic characteristics, clinical and laboratory data and vaccination status in terms of the national MMR vaccine routine schedule (first dose at one year of age, second dose at six years or in the first school year). Household, school/kindergarten, and community contacts are also investigated. A clinical case is defined as having a generalised rash for more than three days, temperature of over 38.3°C and cough, coryza or conjunctivitis. A confirmed case is a clinical case with either laboratory confirmation (positive measles IgM antibody test) or an epidemiological link to another case (two epidemiologically-linked clinical cases are considered confirmed). Serological tests

are performed at the laboratories of the health maintenance organisations. Serology validation, virus isolation, RT-PCR and genotyping are carried out at the Ministry of Health's central national virology laboratory using methods described previously [10].

Routine measles immunisation in Israel started in 1967. In 1990, concerns of under-immunisation and primary vaccine failure (in circa 5%) led to the introduction of a two-dose regime. Since 1994, two doses of MMR are provided at the ages of 12 months and six years.

Results

The population in the Jerusalem district in late 2007 was 860,700. Children aged 0 to 14 years made up 31% of the population.

In August 2007, three measles cases (15 years, 22 years, and an infant; all unvaccinated) were diagnosed in Jerusalem. They had arrived from Jewish ultra-orthodox communities in London, where they reported having had contact with measles patients. The epidemiological investigation did not reveal any connection between these cases other than their place of origin. On 31 August 2007, six secondary cases were reported in Jerusalem. By the end of the year, 491 cases (61% males, 39% females) – almost exclusively in the ultra-orthodox population – had been reported to the Jerusalem District Health Office.

Most cases were confirmed, either serologically (78 cases, 15.9%) or by clinical-epidemiological association (361 cases, 73.5%). The weekly distribution of reported cases is shown in Figure 1.

The age distribution is shown in Figure 2. Most of the patients were children, with a median age of 5.8 years and an average age of 9.6±10.2 years (range: two weeks to 54.6 years). It should be noted that 70% of the cases occurred in children under the age of 14 years, while children in the group of one- to four year-olds accounted for a third (31%) of the patients.

Those children should have been immunised against measles as part of the routine paediatric immunisation schedule in Israel. However, 96% were not vaccinated. Frequently, all the children in a large family were infected; two thirds of the cases belonged to family clusters of more than two patients per family. This was at least partly due to the fact that patients did not comply with the recommendations of timely post-exposure prophylaxis.

A striking feature of the current outbreak has been the very high incidence of measles in infants under one year of age (Figure 3).

The age-specific measles incidence among children under one year of age was 408.5 per 100,000. This is much higher than the incidence in any other age group, and significantly higher than that of the next age group, the one- to four-year-olds, who had an incidence of 264.1/100,000 (relative risk=1.55, 95% confidence interval 1.32-1.80, p=0.0001).

Seventy-one patients (15%) required hospitalisation, most of them due to fever, vomiting or dehydration. The median age of hospitalised patients was 3.6 years, their average age 12±13.8 years. Nineteen (26.7%) patients presented with pneumonitis or pneumonia, and two patients presented with encephalitis. A

Figure 1

Weekly epidemiological curve of measles cases reported in the Jerusalem district from 3 August 2007 to 8 January 2008 (n=491).

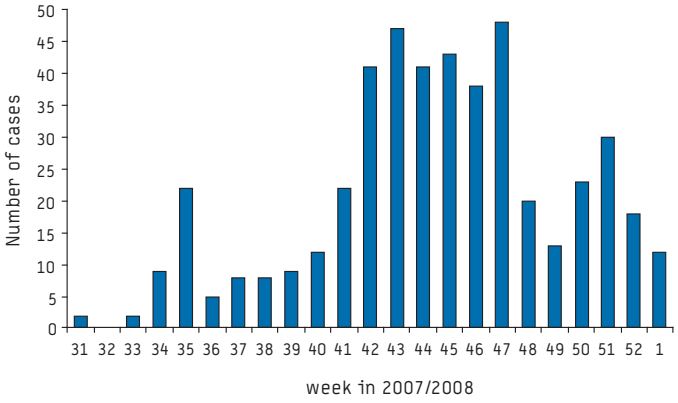


Figure 2

Age groups of reported measles cases in the Jerusalem district from 3 August 2007 to 8 January 2008 (n=491)

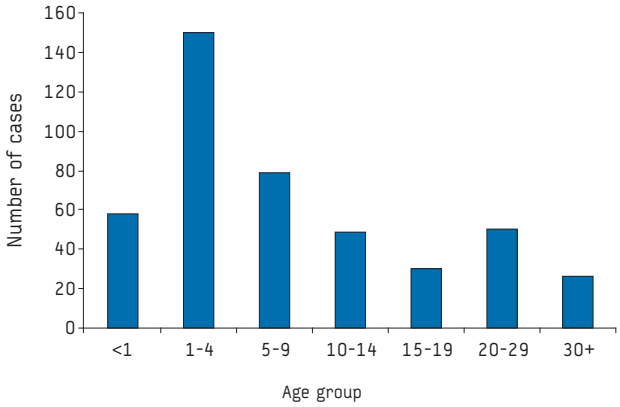
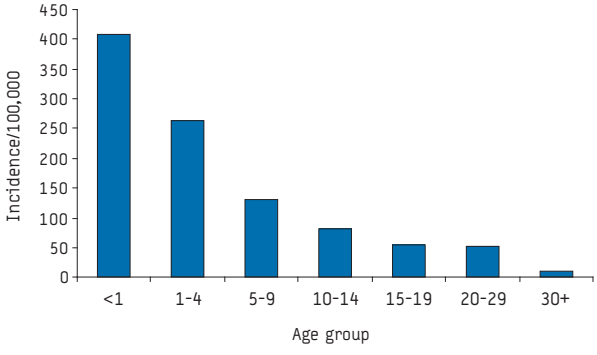


Figure 3

Age-specific incidence per 100,000 population of reported measles cases, Jerusalem district from 3 August 2007 to 8 January 2008 (n=491)



13-year-old girl, one of nine children in a single household who were all clinically diagnosed with measles, was hospitalised due to severe respiratory distress. In the past she had been diagnosed with bronchial asthma and atrial septal defect. She was put on mechanical ventilation, and as her condition did not improve transferred to extra-corporeal membrane oxygenation (ECMO). She recovered, and was released within two weeks.

To date, there have not been any deaths.

Five cases involved pregnant women. Four delivered healthy, full-term infants, and one delivered a premature infant at 29 weeks of gestation, who survived. There were no reports of intra-uterine foetal death (IUFD).

Outbreak control policy included the administration of the MMR vaccine to those aged between six and 12 months within three days of their exposure to a case, and to susceptibles aged one year and older at any time following exposure. From August to December 2007, circa 5,000 doses of vaccine were administered in the Jerusalem district – three times the average in the same period in the 2006, a year without an outbreak. We interpret these numbers as suggesting that two thirds of the doses (circa 3,300) were used for post-exposure prophylaxis.

Children younger than six months were given immunoglobulin (IG) within six days of exposure to a case. IG was also given to children aged six to 11 months within four to six days of exposure to a case. In addition, individuals with contraindications to MMR vaccine (immunocompromised vaccinees and pregnant women) received IG.

Since most of the cases were children and had mild disease, with very few becoming ill following post-exposure immunisation, our data did not allow an assessment of the effect of post-exposure vaccination on the clinical course of the disease.

To date, measles cases are almost exclusively confined to the ultra-orthodox groups in Jerusalem and to several similar communities of ultra-orthodox Jews in other towns in the country. Several sporadic cases were reported in non-orthodox communities. The source of infection for some of them was exposure to measles cases, but remains unclear for others.

Discussion

The past five years have seen a plethora of reports on measles outbreaks from different countries and geographic regions throughout Europe. In the past two to three years, clusters of measles were reported in the Bavaria region of Germany [5], Puglia in Italy [14], the Geneva region in Switzerland [15], and London in the UK [6,12]. In addition, there have been reports of morbidity among the ethnic group of Irish Travellers in the UK and Norway [16,17].

The member states of the World Health Organization European Region (WHO EURO) reported approximately 90,000 measles cases during 2005 and 2006 [9], with large outbreaks in the Ukraine, Romania, Germany and the Russian federation accounting for over half the cases. The most frequent scenario is importation of measles virus from an unimmunised community that has cultural, religious or family ties with communities in other regions.

Globalisation has resulted in increasing mobility of people, which facilitates the spread of the virus between countries and continents. As a consequence, epidemiological investigation is rendered much more difficult, as is the investigation and prevention of further cases, be it by post-exposure immunisation of contacts, or by outbreak control measures such as mass immunisation.

Not infrequently, these difficulties are compounded by lack of cooperation from communities who are recalcitrant in the first place. There is often implicit or explicit stigmatisation of such populations, who are judged as being difficult to treat and obstructive to the ingress of public health personnel. As we have described previously [10], these communities do not take kindly to what they perceive as "intervention in their internal affairs".

Recently, voices have been heard in Israel calling for the introduction of legislation or governmental directives requiring proof of immunisation as a precondition to school entry, as is the case for example in the United States, some European countries (e.g. Italy) and most Australian jurisdictions. It should be noted, however, that in Israel, the communities in question are allowed to conduct independent educational systems, based on religious and ideological principles, and it is possible that even if legislation requiring proof of immunisation were to be introduced, those institutions would not necessarily fully comply with such requirements. Incentives to encourage immunisation are more likely to bear fruit than sanctions.

The goal set by the World Health Organization (WHO) for the eradication of measles by 2010-2015 [18] is likely to be extremely difficult to achieve. It has recently been suggested that elimination, or perhaps merely control of the disease is a more realistic target. Since the measles virus is one of the most contagious viruses known, prevention of spread requires maximal herd immunity. As long as homogeneous groups who are unimmunised remain, we can expect to see repeated penetration of the virus, in spite of high immunisation coverage (of the order of 95% in many countries). In those regions in London where the disease occurs, vaccine coverage is assessed as 77% for the first dose and 52% for the second dose [12]; during the large measles outbreak in 2000 in Dublin, the coverage was estimated as 76% [7].

It is important to continue to maintain herd immunity, targeting first those populations that cooperate and comply with immunisation requirements, and to minimise as much as possible "missed opportunities" for immunisation in young children. As can be seen from Figure 2 and 3, infants and young children were the major victims of the recent outbreak in Jerusalem. The high incidence (408.5/100,000) in infants under one year of age is worrying. As opposed to the previous outbreaks, in which young infants did not figure prominently (five infants (4.7%) in 2003, and six (5.1%) in 2004), 58 infants have been reported to the District Health Office to date in the current outbreak, representing 12.1% of all the patients. In addition, there have been several instances of the disease in pregnant women.

Among young adult females and women of childbearing age (particularly among populations with high fecundity, as are the ultra-orthodox Jews), MMR vaccination should be encouraged as part of the policy of prevention of congenital rubella. The protection of pregnant woman is crucial in view of the recent report from Japan of *in utero* foetal demise (IUFD) [19]. The vaccination policy in Europe has recently been re-evaluated in view of the evidence of low passive antibody levels due to waning maternal immunity [20].

Children contracting measles at a young age are at increased risk for subacute sclerosing panencephalitis (SSPE) [21]. This is not a notifiable disease in Israel and perhaps a special follow-up programme should be instituted for those children.

The outbreaks we witnessed among the ultra-orthodox population of Jerusalem were imported in 2003 from Switzerland and in 2007 from London. These outbreaks were apparently caused by separate importations of measles virus into unprotected groups and to date have not extended to the general population, but remained confined to these communities. This may be attributable to adequate overall herd immunity in the general population. Outbreaks in Israel reflecting a similar pattern have been reported among unvaccinated Bedouins in southern Israel during the 1990s [22] and among the military [23]; in those cases, successful immunisation campaigns were implemented.

Outbreak control necessitates a culture-sensitive approach and appropriate outreach activities. Despite high national immunisation coverage (94-95%), programmes to increase and maintain immunisation coverage are essential, with special attention to specific sub-populations. The great writer of sententiae in the first century BC, Publilius Syrus, wrote: *"He is most free from danger who, even when safe, is on his guard"* – he could well have been referring to the challenges facing public health authorities in the 21st century.

Acknowledgements

The authors express their deep gratitude to the public health nurses and doctors in the Jerusalem District Health Office and the Jerusalem municipality Well Baby Clinics for their unflagging dedication and exceptional efforts in dealing with the outbreaks described. The cooperation of doctors in community medical centres, private and health fund clinics, and hospitals enabled prompt and effective public health measures to be instituted. The authors acknowledge the invaluable service provided by the ministry of health central national virology laboratory.

References

1. Richard JL, Masserey-Spicher V. Ongoing measles outbreak in Switzerland: results from November 2006 to July 2007. Euro Surveill. 2007;12(7):E070726.1. Available from: http://www.eurosurveillance.org/ew/2007/070726.asp#1
2. van den Hof S, Conyn-van Spaendonck MA, Van Steenbergen JE. Measles epidemic in the Netherlands, 1999-2000. J Infect Dis. 2002;186(10):1483-6.
3. Ciofi Degli Atti ML, Salmaso S. New measles epidemic in southern Italy. Eurosurveillance weekly 2003;7:E030703.1. Available from: http://www.eurosurveillance.org/ew/2003/030703.asp#1
4. Bolker BM, Grenfell BT. Impact of vaccination on the spatial correlation and persistence of measles dynamics. Proc Natl Acad Sci U S A. 1996;93(22):12648-53.
5. Papania MJ, Seward JF, Redd SB, Lievano F, Harpaz R, Wharton ME. Epidemiology of measles in the United States, 1997-2001. J Infect Dis. 2004;189 Suppl 1:S61-8.
6. Peltola H, Heinonen OP, Valle M, Paunio M, Virtanen M, Karanko V, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. N Engl J Med. 1994;331(21):1397-402.
7. Fine PE, Clarkson JA. Measles in England and Wales--I: An analysis of factors underlying seasonal patterns. Int J Epidemiol. 1982;11(1):5-14.
8. Grassly NC, Fraser C. Seasonal infectious disease epidemiology. Proc Biol Sci. 2006;273(1600):2541-50.
9. World Health Organization.Regional Office for Europe. Strategic plan for measles and congenital rubella infection in the European region of WHO. 2003;43.
10. World Health Organization. Regional Office for Europe. Strengthening national immunization systems through measles and rubella elimination and prevention of congenital rubella infection in WHO's European Region. 2005; EUR/RC55/R7. Available from: http://www.euro.who.int/Governance/resolutions/2005/20050920_3
11. Bernard H, Santibanez S, Siedler A, Ludwig MS, Fischer R, Hautmann W. An outbreak of measles in Lower Bavaria, Germany, January-June 2007. Euro Surveill 2007;12:E071004.1. Available from: http://www.eurosurveillance.org/ew/2007/071004.asp#1
12. Cheryl Clark. Measles cases now total 11 in monthlong outbreak. SignOnSanDiego.com. February 15, 2008. Available from: http://www.signonsandiego.com/news/metro/20080215-1745-bn15outbreak.html

This article was published on 21 February 2008.

Citation style for this article: Stein-Zamir C, Abramson N, Shoob H, Zentner G. An outbreak of measles in an ultra-orthodox Jewish community in Jerusalem, Israel, 2007 - an in-depth report. Euro Surveill. 2008;13(8):pii=8045. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8045

Outbreak of verocytotoxin-producing *E. coli* O145 and O26 infections associated with the consumption of ice cream produced at a farm, Belgium, 2007

K De Schrijver (koen.deschrijver@wvg.vlaanderen.be)[1,2], G Buvens[3], B Possé[4], D Van den Branden[1], O Oosterlynck[5], L De Zutter[4], K Eilers[1], D Piérard[3], K Dierick[6], R Van Damme-Lombaerts[5], C Lauwers[7], R Jacobs[7]

1. Department of Control of Infectious Diseases, Antwerp, Belgium
2. Department of Epidemiology and Social Medicine, University of Antwerp, Belgium
3. Belgian Reference Laboratory for E. coli Department of Microbiology, University of Brussels, Belgium
4. Laboratory for Food Microbiology, Department of Veterinary Public Health and Food Safety University of Ghent, Ghent, Belgium
5. Department of Paediatric Nephrology, Catholic University of Leuven, Leuven, Belgium
6. Department of Microbiology, Institute of Public Health, Brussels, Belgium
7. Federal Agency for the Safety of the Food Chain, Antwerp, Belgium

In October 2007, an outbreak of verocytotoxin-producing *Escherichia coli* (VTEC) O145 and *E. coli* O26 occurred among consumers of ice cream produced and sold in September 2007 at a farm in the province of Antwerp (Belgium). The ice cream was consumed at two birthday parties and also eaten at the farm. Five children, aged between two and 11 years, developed haemolytic uraemic syndrome (HUS), and seven other co-exposed persons contracted severe diarrhoea. In three of the five HUS cases VTEC O145 infections were laboratory confirmed, one in association with VTEC O26. Identical isolates of *E. coli* O145 and O26 were detected with PCR and PFGE in faecal samples of patients and in ice cream leftovers from one of the birthday parties, in faecal samples taken from calves, and in samples of soiled straw from the farm at which the ice cream was produced. Ice cream was made from pasteurised milk and most likely contaminated by one of food handlers.

Introduction

Verocytotoxin-producing *Escherichia coli* (VTEC), including *E. coli* O157:H7, O26, O145 and other *E. coli* serotypes, are important causes of gastrointestinal illness and haemolytic uraemic syndrome (HUS) in young children. This syndrome is characterised by haemolytic anaemia, thrombocytopenia and acute renal failure, a complication occurring in 5-14% of VTEC infections [1,2]. HUS is a potential life-threatening disease and can induce hypertension, proteinuria and chronic renal failure in 5% of affected patients. The age group primarily affected are children under five years. VTEC O157:H7 is considered as the most clinical significant serotype, and is often associated with severe bloody diarrhoea and HUS. The prevalence of VTEC serotype O145 in human infections is relatively low, accounting for 5%-7% of all non O157 strains in prevalence studies [3]. The range of products associated with VTEC infections is wide: hamburger, ground beef, cider, spinach, unpasteurised ice cream, milk and cheese, and others. Infections have also been linked to municipal water supplies [4,5].

VTEC infections in Europe and the United States have increased in the last decade causing several large epidemics of food poisoning in industrialised countries [4,5,6]. In Belgium, however, it has been a sporadic disease [7,8]. In 2005, the incidence of VTEC in Belgium was 0.5 cases per 100,000 population, compared to a mean incidence in Europe of 1.2 cases per 100,000 population [7,8,9]. However, this is probably an underestimation, as most of the country's clinical laboratories do not test for these micro-organisms in routine gastroenteritis samples [8].

We report on five children with HUS of which three had a laboratory confirmed VTEC O145 infection. All patients consumed ice cream produced and sold at a farm.

Methods

The outbreak

On 2 October 2007, the detection of three isolates of VTEC O145, one of which was associated with *E. coli* O26, was reported by Belgium's Federal Reference Laboratory for *E. coli* to the Antwerp department of Infectious Diseases Control. The strains were obtained from patients hospitalised with HUS and living in the northern part of Antwerp province. On 3 October, investigators instituted active case finding and interviewed the parents of the different patients. All patients had eaten ice cream produced and sold at the same farm within eight days of developing gastrointestinal symptoms. The ice cream was consumed at two birthday parties or consumed on the farm.

The farm was a traditional dairy farm with a limited number of cows, young cows and calves. The farm that made the ice cream was well known in the region and, depending on season and weather, up to 160 litres of ice cream were sold daily.

On 3 October, the Antwerp Department of Control of Infectious Diseases invited the Antwerp Department of the Federal Agency for the Safety of the Food Chain, the Laboratory of Food Microbiology of the University of Ghent, and the Reference Laboratory for *E. coli* of the University of Brussels to assist in the investigation. The study was carried out to determine the impact of the outbreak, to identify risk factors, and to interrupt transmission. On 5 October, investigators were informed of the existence of leftovers of ice cream consumed at one of the birthday parties.

Epidemiologic investigation

In order to develop hypotheses regarding possible sources of *E. coli* O145 infections investigators interviewed the parents of the patients who contracted HUS on 3 October using an adapted standard questionnaire for HUS' investigation generated by the Netherlands' Landelijke Coördinatiestructuur Infectieziektebestrijding (Coordination Structure for Combating Infectious Diseases) [10]. They were asked about consumption of food and drinks, contact with animals (domestic, farm, zoo), and travel history in the 10 days before onset of diarrhoea.

Hypothesis – generating interviews suggested that the outbreak occurred among participants in two birthday parties with eight and 11 participants respectively, respectively on 14 and 16 September. A third group of consumers was an undefined group of individuals who consumed ice cream at the farm. Consequently a retrospective cohort study was conducted among the participants in the birthday parties.

For case-ascertainment purposes, a probable case of HUS was defined as a patient who developed acute diarrhoea (three or more loose stools in a 24-hour period) complicated with HUS (acute haemolytic anaemia, thrombocytopenia, and signs of renal failure) occurring within 10 days of consumption of ice cream produced at a farm in Mol in September 2007. A confirmed case with HUS was defined as a patient meeting the criteria of a probable case and accompanied by isolation of *E. coli* O145 and/or *E. coli* O26 in stools or a positive serology for *E. coli* O145 and/or O26. A patient with a probable VTEC diarrhoea infection without HUS was defined as a patient who developed acute diarrhoea (three or more loose stools in a 24-hour period) in the 10 days following consumption of the farm-made ice cream and the patient belonged to a group in which a confirmed case has been detected. A patient with only a confirmed VTEC infection was a patient meeting the criteria of a probable VTEC diarrhoea infection accompanied by *E. coli* O145 and/or *E. coli* O26 in stools or a positive serology for *E. coli* O145 and/or O26.

A retrospective cohort study was established among the participants in the birthday parties. Relative risks and P-values (Fisher exact) were calculated using Epi Info, version 3.3.2 [11].

Environmental investigation

The farm's layout, ice cream production process and staff activities were determined. Different environmental samples were obtained: faecal samples from animals (calves, young animals and cows), and samples from each pen floor, dust and feed. To identify the source of the infection, raw milk, fresh ice cream produced at the farm and leftover portions of the ice cream from the birthday party on 16 September 2007 were sampled.

Microbiological examination and molecular analysis

Stools and urine samples of HUS patients were collected, and sent to the Belgian reference laboratory for *E. coli* for microbiological analysis. The stools were cultured using SMAC/SMAC+CT medium. On the basis of biochemical tests, PCR, and agglutination assay VTEC of serogroup O145 and O26 were identified. Additional PCR tests were performed to identify specific virulence genes carried by these VTEC strains. Serum samples of the fifth HUS patient were collected and tested for presence of anti-VTEC antibodies using agglutination assay.

Pulsed Field Gel Electrophoresis (PFGE) was used to examine and to compare the genetic profiles of the VTEC isolates.

Results

Clinical information and epidemiologic information

By 5 October, five cases of HUS had been identified among consumers of ice cream sold at the farm between September 12 and 16, 2007 (Figure I). All patients with HUS were girls aged between two and 11 years. Three cases met the criteria of a confirmed case. VTEC of serogroups O145 and O26 were isolated from faeces and urine in a two-year-old girl and serogroup O145 was isolated from the faeces of an eight-year-old girl. In a third case, serology was

FIGURE 1

Cases of haemolytic uraemic syndrome (HUS) and VTEC diarrhoea by onset of symptoms, Mol, Belgium, 2007

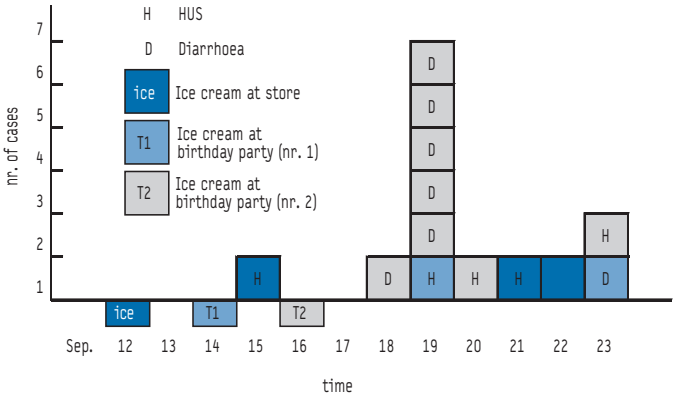
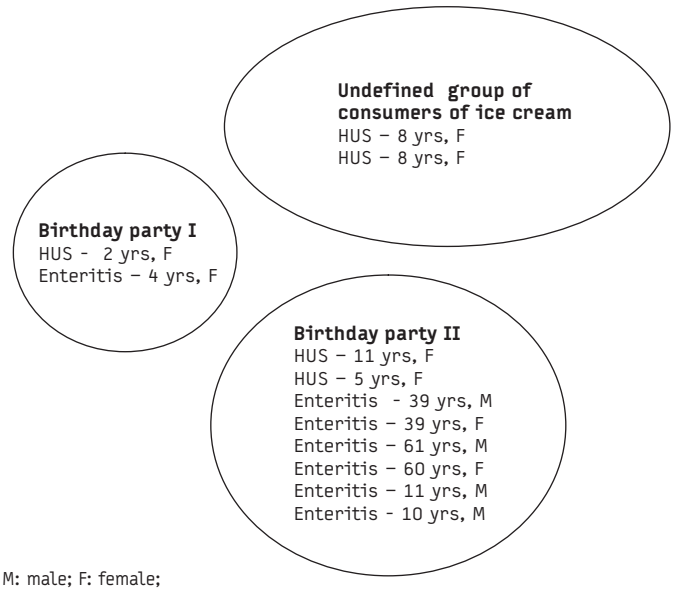


FIGURE 2

Cases by place of consumption of ice cream, VTEC outbreak, Mol, Belgium, September 2007



M: male; F: female;
HUS: haemolytic uraemic syndrome

positive for O145 antigen. All HUS patients were admitted to the hospital, two requiring haemodialysis and three transfusion. No deaths have occurred among the identified patients

Two of the cases had eaten ice cream at the farm and three cases during birthday parties. Seven cases of acute diarrhoea were identified among persons co-exposed at the same birthday parties. The age of the diarrhoea patients ranged from four to 61 years.

The distribution of the HUS cases and the VTEC diarrhoea by time and place of consumption of the ice cream is shown in Figures 1 and 2. The mean incubation period between infection and onset of diarrhoea was five days. The mean interval between onset of diarrhoea and HUS was 5.6 days.

Of all the VTEC cases, only two patients had visited the farm but had had no contact with the stables or animals. No cases of VTEC diarrhoea could be identified among the consumers of ice cream at the farm.

The attack rate for patients with HUS among the participants in Birthday Party 1 on 14 September was 12.5% (1/8) and 18% (2/11) in Birthday Party 2 on 16 September. The attack rate for the probable VTEC infections was 25% (2/8) in Birthday Party 1 and 73% (8/11) in Birthday Party 2. No diarrhoeal illness was reported among the farm workers and the staff involved in the ice cream preparation. Relative risks were undefined in Birthday Party 1 and 2. P-values calculated with Fisher exact one tailed test were p=0.75 in Birthday Party 1 and p=0.20 in Birthday Party 2.

Environmental study and microbiologic data

Evaluation of the ice cream production process did not reveal major processing errors. pasteurised milk was used for the production of the ice cream. One person who was normally not involved in the production process of ice cream and who also worked at the farm participated only in the production of ice cream in the week of 12 September. Fresh milk stored at the farm and prepared ice cream samples collected on 4 October 2007 were negative for VTEC O145 and O26 pathogenic bacteria, but faecal samples of calves and dust samples of the calves' stables were positive for VTEC O145 and O26. Leftovers of the ice cream consumed at Birthday Party 2 on 16 September were also positive for VTEC O145 and O26.

Molecular analysis

Sorbitol-fermenting VTEC O145 strains were identified in stools of two HUS patients, one in association with serogroup O26 which was isolated in both stool and urine samples. PCR analysis revealed that the VTEC O145 and O26 isolates were positive for, respectively, verocytotoxin type 2 and type 1 (VT2 and VT1). Both serogroups were positive for additional virulence genes *eaeA* and *ehxA*. Agglutination assay performed on the serum samples of the fifth HUS patient revealed the presence of anti-VTEC O145 antibodies.

PFGE was performed on the VTEC strains isolated from patients, ice cream, and the farm environment. These results confirmed that the VTEC O145 strains, isolated from the two female patients were undistinguishable from isolates from ice cream and samples collected on the farm (Figure 3.A, lanes 3, 4, 6, 7, 8, and 9). The VTEC O26, isolated from faeces and urine of a two-year-old female patient, were undistinguishable from VTEC O26 isolated from the environment of the farm and the ice cream (Figure 3.B lanes 3, 4, 6, and 7).

Discussion

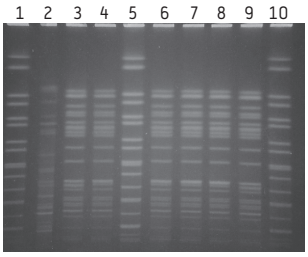
We have described an outbreak of VTEC infections among individuals who had eaten ice cream produced and sold at a farm in the northern part of the province of Antwerp. The infections were transmitted from animals and their environment to people.

There is strong epidemiological evidence to assume that the incriminated vehicle was contaminated ice cream. All patients had eaten ice cream sold at the farm in the week before onset of the diarrhoea and HUS. Individuals participating in the birthday parties where the ice cream was eaten and who had never been at the farm, developed the disease. Most likely due to the small number of participants in the parties, a significant association among the ice cream eaters and the disease could not be identified. The leftovers of the ice cream and the stools of the two patients with positive cultures had identical PFGE profiles for VTEC O145 and O26 respectively. Taking into account that pasteurised milk was used in the production of the ice cream, cross-contamination is the most likely explanation for the contamination. One of the most likely explanations might be the participation in the production process of an individual who was not trained, properly instructed and had contact with the animals.

FIGURE 3

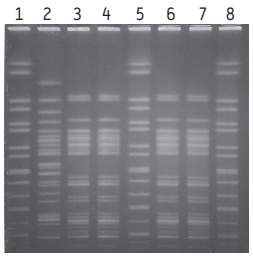
Molecular typing of VTEC isolates, Mol, Belgium, September 2007

(A) PFGE analysis of VTEC O145 isolates



Lane 1: *Salmonella Braenderup* H9812 (molecular size standard), lane 2: unrelated VTEC O145 isolate, lane 3: VTEC O145 isolate in stool of a female patient aged 8 years, lane 4: VTEC O145 isolate in stool of a female patient aged 2 years, lane 5: *S. Braenderup*, lane 6: VTEC O145 isolate from hay sample of the farm, lane 7: VTEC O145 isolate from dust sample of the barn, lane 8: VTEC O145 isolate from faeces of calf, lane 9: VTEC O145 isolate from ice cream cake, lane 10: *S. Braenderup*.

(B) PFGE analysis of VTEC O26 isolates



Lane 1: *S. Braenderup*, lane 2: unrelated VTEC O26 isolate, lane 3: VTEC O26 isolate in stool of a female patient aged 2 years, lane 4: VTEC O26 isolate in urine of female patient aged 2 years, lane 5: *S. Braenderup*, lane 6: VTEC O26 isolate from ice cream cake, lane 7: VTEC O26 isolate from environment of calf stable, lane 8: *S. Braenderup*.

Only the five HUS cases were tested for non-O157 VTEC and of these only three were confirmed as VTEC infections. The VTEC diarrhoea cases were not confirmed by laboratory testing. Testing of faecal samples of patients with diarrhoea for the presence of VTEC is not regularly undertaken in Belgium. One of the reasons might be that testing for E coli is not reimbursed by social security in Belgium. The delay between acute diarrhoea and the onset of HUS, late diagnosis and the intake of antibiotics before diagnosis might also explain the absence of VTEC confirmation in two of the HUS patients.

To our knowledge, this is the first outbreak of HUS and VTEC caused by O145 and O26 in Belgium associated with the consumption of ice cream made from pasteurised milk. Outbreaks associated with VTEC O157 among visitors to a dairy farm were recently described in Belgium [12], with consumption of unpasteurised milk as a source of the VTEC, as described by Allerberger *et al*. [13].

There is significant morbidity and mortality associated with diarrhoea-associated HUS in children due to the devastating microvascular thrombotic angiopathia [1,2]. A Canadian prospective study showed an annual incidence of 1.11 case of diarrhoea associated HUS per 100,000 children under the age of 16 years [14]. The disease occurred most frequently in children younger than five years old [15]. However, in this outbreak, only one out of five patients belonged to this age group. This probably underscores the underdetection of HUS in the population.

Faecal samples of calves and dust of the barn were positive for VTEC O145 and O26. Studies on prevalence of *E. coli* O157 in cattle in Belgium show percentages ranging from 0 to 85% according to age of animals, specific farms, herds, and time of sampling. Young animals in particular have higher carriage. The prevalence of *E. coli* O157:H7 in beef carcasses was 1.1% (N=2,554) in 2005, while no VTEC were detected in 175 samples of raw milk in 2005 [7]. No data are yet available regarding the prevalence of other serogroups in Belgian cattle.

This outbreak underscores the need to consider zoonotic transmission and to highlight the prevention measures in facilities where there is easy contact with farm animals and their environment. Moreover, in our case the presence of VTEC in cattle at the farm and the shared activities of food-handling are problematic, as these pathogens can survive for months on surfaces [3].

The association between ice cream made with pasteurised milk and VTEC is very unusual [13,14]. However as shown in this outbreak, cross-contamination is a significant risk. Our data underline the need to reinforce hygienic measures for food-handlers working at farms where food products are prepared.

This study illustrates the usefulness of appropriate source tracing in VTEC infections and possibilities of good collaboration among the clinicians, microbiologists, and public health officials.

Control measures

To control the outbreak GPs, paediatricians, hospitals and health authorities were alerted and asked to look for cases. The food-preparing process and the quality of the ice cream and milk were checked and identified as free of VTEC. The food handlers were informed about the risk of contamination and prevention. Finally, the Safety in the Food Chain Agency is considering launching a prevention campaign targeted at this kind of facility.

Acknowledgements

We would like to thank all the physicians, microbiologists and staff of the following participating institutions: Department of Control of Infectious Diseases in Antwerp, Belgian reference laboratory for *E. coli* of the Free University of Brussels, the laboratory for Food Microbiology of the department of Veterinary Public Health and Food Safety of the University of Ghent, the Federal Agency for the Safety of the Food Chain, and the different hospitals where the patients were admitted. Namely: G. Buvens, S. M. De Ceuninck, De Raedt, L. De Zutter, K. Dierick, K. Eilers, L. Geyskens, L. Goderis, P. Maes, C. Oosterlynck, L. Peeters, B. Possé, D. Piérard, R. Van Damme - Lombaerts, D. Van den Branden, K. Van Hoeck, I. Venken, A. Wijnants, W. Wilms, and the patients and their parents for their collaboration in providing data.

References

1. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin-producing Escherichia coli and haemolytic uraemic syndrome. Lancet. 2005;365(9464):1073-86.
2. Boyce TG, Swerdlow DL, Griffin PM. Escherichia coli O157:H7 and the haemolytic-uremic syndrome. N Engl J Med. 1995:333(6):364-8.
3. Busch U, Hörmansdorfer S, Schranner S, Huber I, Bogner KH, Sing A. Enterohemorrhagic Escherichia coli Excretion by Child and her Cat. Emerg Infect Dis. 2007;13(2):348-9.
4. European centre for disease control and prevention. Annual epidemiological report on communicable diseases in Europe. December 2007:34-9. Available from: http://www.ecdc.europa.eu/pdf/ECDC_epi_report_2007.pdf
5. Maki DG. Don't Eat Spinach – Controlling Foodborne Infections. N Engl J Med. 2006;355(19):1952-5.
6. Crump JA, Sulka AC, Langer AJ, Schaben C, Crielly AS, Gage R, et al. An outbreak of Escherichia coli O157:H7 infections among visitors to a dairy farm. N Engl J Med. 2002;347(8):555-60.
7. Working group on Foodborne Infections and Intoxications. Verotoxin producing Escherichia coli. In: Trends and sources report on zoonotic agents in Belgium in 2005. Eds: FAVV-AFSCA. Brussels: Federal Agency for the safety of the food chain 2007: 61-5.
8. Piérard D, De Zutter L, Cobbaut K, Lauwers S. Enterohemorrhagische Escherichia coli O157 en andere serotypes: voorkomen in België bij mens, dier en levensmiddelen. In: 22e Seminarie: Diagnose en surveillance van infectieuze aandoeningen 2006. Ed: Wetenschappelijk instituut Volksgezondheid. Brussels: ISP 2006:7-13.
9. De Valk H. Epidemie van infecties met Escherichia coli O157:H7 veroorzaakt door de consumptie van rundergehakt, Frankrijk 2005. In: Diagnose en surveillance van infectieuze aandoeningen 2006. Eds.: Wetenschappelijk instituut Volksgezondheid. Brussels: ISP 2006:17-20.
10. Steenbergen J, Timen A. E.coli infectie. In: Guidelines Infectious Disease Control for the Netherlands 2006. Bilthoven: RIVM 2006: 111-6.
11. Centers for Disease Control and Prevention. Epi Info Version 3.3.2, 2005.
12. Van den Branden D, De Schrijver K, Evens K, Jeurissen A, Vanbroekhoven J, Jacobs R, et al. Een cluster van E. coli O157:H7 infecties met een hemolytisch uremisch syndroom na een verblijf op een vakantiehoeve. Vlaams Infectieziektebulletin 2007;60:3-10.
13. Allerberger F, Wagner M, Schweiger P, Rammer H, Resch A, Dierich M, and al. Escherichia coli O157 infections and unpasteurised milk. Euro Surveill. 2001;6(10):147-151. Available from: http://www.eurosurveillance.org/em/v06n10/0610-222.asp
14. Proulx F, Sockett P. Prospective surveillance of Canadian children with the haemolytic uraemic syndrome. Pediatr Nephrol. 2005;20(6):786-90.
15. Haeghebaert S, Vaillant V, Decludt B, Grimont PAD. Surveillance of haemolytic uraemic syndrome in children under 15 years of age in France in 1998. Euro Surveill. 2000;5(6):68-73. Available from: http://www.eurosurveillance.org/em/v05n06/0506-222.asp

This article was published on 14 February 2008.

Citation style for this article: De Schrijver K, Buvens G, Possé B, Van den Branden D, Oosterlynck O, De Zutter L, Eilers K, Piérard D, Dierick K, Van Damme-Lombaerts R, Lauwers C, Jacobs R. Outbreak of verocytotoxin-producing E. coli O145 and O26 infections associated with the consumption of ice cream produced at a farm, Belgium, 2007. Euro Surveill. 2008;13(7):pii=8041. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8041

Mumps outbreak in young adults following a festival in Austria, 2006

D Schmid[1], H Holzmann[2], C Alfery[1], H Wallenko[3], T H Popow-Kraupp[2], F Allerberger (franz.allerberger@ages.at)[1]
1. Austrian Agency of Health and Food Safety (AGES), Vienna, Austria
2. Institute of Virology, University of Vienna, Vienna, Austria
3. Provincial Health Authority, Carinthia, Austria

Mumps is not a mandatorily notifiable disease in Austria. However, in the first week of May 2006, a sudden increase in serologically confirmed cases of mumps, confined to three public health districts of the southern Austrian province of Carinthia, was identified by the Austrian Reference laboratory for MMR. An epidemiological investigation of this cluster of mumps cases was performed. A total of 214 cases fulfilled the outbreak case definition; 143 cases were laboratory confirmed and 71 cases were epidemiologically linked and fulfilled the clinical picture of the case definition. The vaccination status was known for 169 patients. Nearly half of the cases for whom the vaccination status was known occurred in non-vaccinated persons, another 40% were vaccinated with one dose of the vaccine and 11% had received two doses. Only four mumps cases occurred in children aged 14 years or younger, indicating that the vaccination coverage and the acceptance of the recommended childhood vaccinations have strongly improved within the past 15 years. Vaccination scheme failure but not vaccine failure is primarily to blame for this mumps outbreak.

Introduction

Mumps is an acute viral infection characterised by fever and non-suppurative swelling of the salivary glands; an estimated 20-30% of cases are asymptomatic. Complications may include inflammation of the testicles or ovaries, and of the central nervous system manifesting as meningitis and meningo-encephalitis, which can lead to deafness. During the pre-vaccine aera, nearly everyone experienced mumps, and 90% of cases occurred among children aged under 15 years.

In Austria, mumps is not a mandatorily notifiable disease. Data on disease occurrence in Austria are mainly based on data of serologically confirmed cases provided by the Institute of Virology of the Medical University of Vienna, the Austrian reference laboratory for mumps, measles and rubella (MMR). Between 2001 and 2005, the median number of annual serologically confirmed mumps cases was 20, with a range from 9 to 30 cases. Furthermore, data can be gathered from hospital discharge statistics. Based on the World Health Organization's (WHO) International Classification of Diseases - ICD-10 code 10th Revision (coding numbers B26.0, B26.1, B26.2, B26.3, B26.8, B26.9) [1], the annual number of hospitalisations due to mumps between 2003 and 2005 ranged from 18 to 27 with a median of 27. Both figures are only a tip of the iceberg as most cases might not be detected via these two sources, nevertheless they are helpful to detect outbreaks.

Vaccination against mumps was introduced into the childhood vaccination schedule in Austria in 1974. Table 1 illustrates the mumps immunisation policy in Austria since 1974 until present. For controlling a mumps outbreak, a post-exposure vaccination is recommended for susceptible contact persons - unvaccinated or not sufficiently vaccinated persons - within three days post-exposure [2]. In case of an ongoing outbreak the susceptible persons of the region where the outbreak takes place are offered vaccination (mass vaccination).

The outbreak

In the first week of May 2006, a sudden increase in serologically confirmed cases of mumps, confined to three public health districts

Table 1

Active mumps immunisation in Austria between 1974 and 2008

Year of introduction	1974	1994	2001	Since 2003
Type of vaccine	bivalent; mumps, measles (MMII)	trivalent; mumps, measles, rubella (MMR)	trivalent; mumps, measles, rubella (MMR)	
Produced by	Merck Sharp & Dohme	Pasteur Merieux Connaught	Glaxo Smith Kline	
Dosage	**1 dose scheme:** dose: at age 15 months	**2 doses scheme:** dose 1: at age 15 months dose 2: at age 6 years	**2 doses scheme:** dose 1: at age 15 months dose 2: at age 6 years	**2 doses scheme:** dose 1: in 2nd year of life dose 2: at least 4 weeks later
Vaccine strain	Jeryl Lynn strain	Jeryl Lynn strain	RIT 4385 mumps strain derived from the Jeryl Lynn strain	

of the southern Austrian province of Carinthia, was identified by the Austrian Reference laboratory for MMR. Sixteen cases of laboratory-confirmed mumps were observed in the first week of May 2006; no cases had been identified in these three public health districts in the previous months of 2006. Comparing with data from all of Austria for the same period one case of laboratory confirmed mumps had been detected in May 2001, whereas no cases of mumps had been recognized in the same period in the years 2002 to 2005. The regional health authorities mandated the Austrian Agency for Health and Food Safety (AGES) to perform an epidemiological investigation of this cluster of mumps cases. An initial case series investigation implicated the attendance at an Easter youth festival on 16 April in one of the three affected public health districts as the common link among the index cases from Carinthia. The following report is a follow-up of a previously published preliminary report after the completion of the investigation [3,4].

Methods

Case definition

In this outbreak a confirmed case was defined (1) as a patient with self-limited swelling of the parotid without another apparent cause, or with meningitis or orchitis, (2) and a clinical onset of at least 10 days after 16 April 2006, (3) with a serological confirmation of mumps infection or virus isolation from a saliva sample or a throat swab AND (4) any epidemiological link to the Easter festival such as contact with a person having attended the festival or contact with a contact person of an infected individual related to the outbreak.

A probable case of the outbreak was defined (1) as a patient with self-limiting swelling of the parotid gland without another apparent cause, or with meningitis or orchitis (2) and a clinical onset of at least 10 days after 16 April 2006 AND (3) any epidemiological link to the Easter festival.

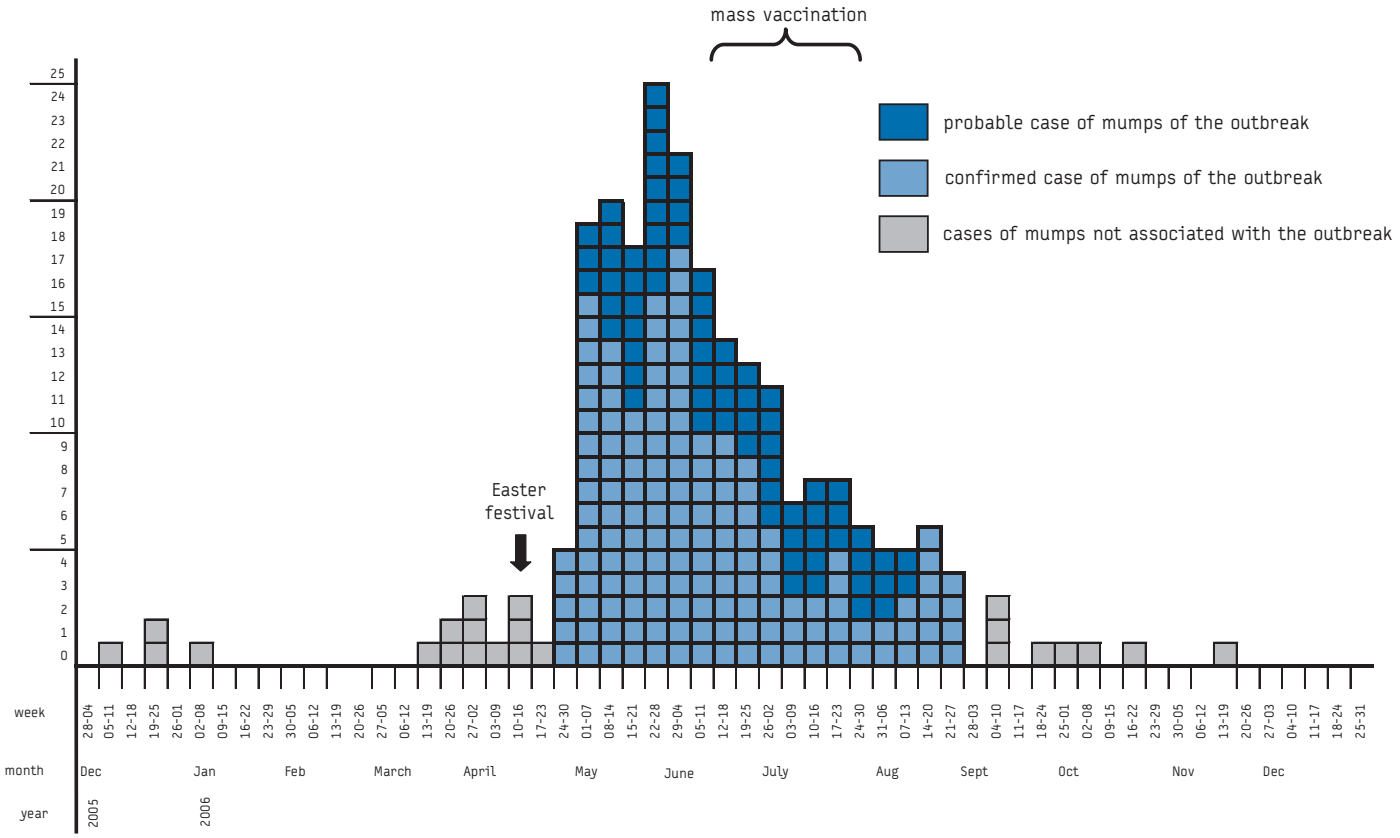
Case finding

The outbreak investigation team acquired data on serologically confirmed cases of mumps from the Austrian reference laboratory. In addition active case finding was performed by asking general practitioners and clinicians of hospitals of the three affected provinces to notify all clinical cases of mumps having occurred since the beginning of May to the local public health authorities. Physicians were also asked to collect blood samples from all incident cases of parotitis and orchitis for serological examination.

A telephone interview of mumps cases was performed to obtain information on vaccination status including the number of doses received, based on the vaccination certificate and clinical manifestation such as parotitis, orchitis or meningitis, hospitalisation, history of exposure such as attendance of the Easter festival, contact to a case of mumps having attended the festival and, on demographic data.

Figure 1

Mumps cases in Austria by week of onset of clinical symptoms, December 2005 to December 2006 (n = 237; outbreak cases = 214, including 143 laboratory-confirmed and 71 probable cases)



Results

A total of 214 cases fulfilled the outbreak case definition including 143 confirmed and 71 probable cases. The epidemic curve of the outbreak illustrates a sudden increase in the number of cases within the first week of May 2006, two weeks after an Easter festival attended mainly by adolescents in a small village in Carinthia. The number of cases peaked in the fourth week of May and returned to the endemic level at the end of August. Eight cases of laboratory confirmed mumps recognized in the months September to December 2006 had no relation to the outbreak.

Between the end of May and the end of July, the MMR vaccine was offered to all residents of Carinthia (population approximately 550,000) free of charge by local health authorities, physicians and hospitals. Approximately 2,000 people were vaccinated (Figure 1).

Geographical distribution

Five of Austria's nine provinces were affected by the outbreak (Figure 2): Carinthia had 134 cases, 76 (57%) of these were serologically confirmed, Vienna had 36 cases, 32 (89%) serologically confirmed, Lower Austria had 35 cases (30 cases, 86% serologically confirmed), Salzburg had eight cases (five serologically confirmed), and one additional serologically confirmed case was from Styria. The latter was in a 31 year old male patient who had had direct contact with an outbreak case in Carinthia.

Demographic features and complications

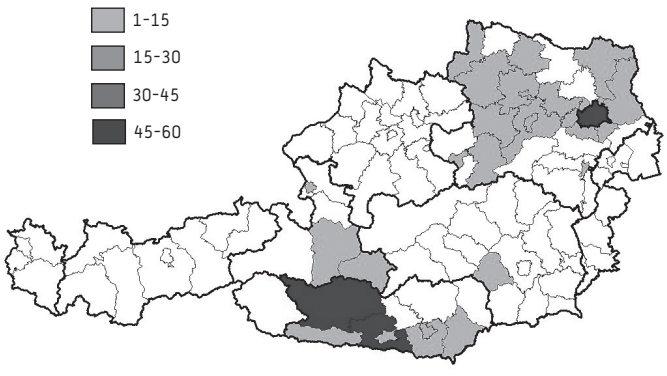
In total 91% of all cases (195/214) were younger than 36 years (median: 24; range 6 to 69 years). The majority of cases (80%) occurred in persons between 16 and 30 years of age with a peak in the age group of 21 to 25 years (42%). There was no case in children under six years; two cases were in the age group six to 10 years. The female to male ratio was 1:1.74; in the age group 16 to 30 years female and male cases were almost equally distributed. In total there were complications in 36 (17%) patients, eight of those suffered from meningitis (Table 2).

Vaccination status

The vaccination status was known for 169 patients (Table 2). Nearly half of the cases for whom the vaccination status was known occurred in non-vaccinated persons, another 40% were vaccinated with one dose of the vaccine and 11% had received two doses.

Figure 2

Mumps cases by public health districts in the affected provinces Vienna, Lower Austria, Carynthia, Salzburg and Styria, outbreak in Austria, May 2006 to end of August 2006, (n= 214)



Discussion

The described mumps outbreak involving 214 cases is the largest reported in Austria to date. However, as mumps is not a mandatorily notifiable disease in Austria, the number of cases may underestimate the true number of cases in the outbreak. In the past years, mumps virus activity observed in Austria was very low, and it has to be considered that the number of laboratory confirmed endemic, outbreak-unrelated cases may include healthy persons who have been tested for mumps antibodies following mumps vaccination.

Considering the minimum incubation period of 10-14 days, the mumps outbreak probably originated with virus transmissions to susceptible individuals at a village festival. Traditional festivals provide opportunities for sharing cutlery, glasses, plates, and for a variety of close personal contacts allowing for possible transmission of mumps virus to susceptible persons. Gerstel et al. recently reported on an outbreak involving 19 cases originating from a village festival in Spain [5]. As in this outbreak, we were unable to perform an analytical study for identifying risk factors for virus transmission.

Although mumps vaccination has been part of the Austrian national immunisation schedule since 1974, 83 of 169 (49%) cases interviewed were unvaccinated. Whether the absence of sufficient antibody titers despite vaccination (non-responder), or the absence of neutralizing antibodies specific for this mumps outbreak's causative viral strain was responsible for the susceptibility to infection in the remaining 86 vaccinated cases cannot be answered conclusively [6]. We hypothesize that susceptibility to mumps infection in those vaccinated is due to the lack of compliance with the recommended two-dosage scheme, i.e. administration of only one vaccine dose is documented for 68 vaccinated cases. However, in this context it has to be considered that until the mid 1990s only one dose of the measles mumps vaccine was recommended in Austria. The fact that 18 of 169 cases had received two doses accounts for a vaccine efficacy of 89.3% for the Jeryl-Lynn strain with a two-dose scheme, which should be sufficient to induce herd immunity [7]. An epidemiological investigation of seven institutional outbreaks of mumps in Singapore found a vaccine efficacy of 80.7% for the Jeryl-Lynn strain, 54.4% for the Urabe strain, and 55.3% for the Rubini strain mumps vaccine; Rubini strain mumps vaccine conferred no protection and has since been deregistered in Singapore [8].

Only four mumps cases occurred in children aged 14 years or younger, indicating that the vaccination coverage and the acceptance of the recommended childhood vaccinations have strongly improved within the past 15 years. The fact that the majority of cases occurred in non- or only once vaccinated young adults – 75% out of the unvaccinated cases (62/83) were between 16 and 30 years old – suggests susceptibility to mumps virus infection in this age group of the Austrian population.

The belief that mumps is only a harmless disease and the risk of vaccine side effects are the leading arguments of groups opposing the MMR vaccination program. Therefore it is important to inform the public about the safety of the vaccine and possible complications of mumps. Orchitis, the most common complication, occurs in 20-30% of affected post-pubertal males [2]. In the current

Table 2

Mumps cases by demographic features, complications, vaccination status and provincial residence outbreak in Austria, May 2006 to end of August 2006, (n= 214)

Variables under study	Carinthia n=134	Lower Austria n=35	Vienna n=36	Salzburg n=8	Styria n=1	Total n_{total}=214
Age (median; min, max)	**24** (9-69)	**22** (15-57)	**25** (6-59)	**22** (21-29)	**31** (31-31)	**24 (6-69)**
Sex **m** (%)/f	**80** (59.7)/ 54	**23** (65.7)/12	**26** (72.2)/10	**6** (75)/2	**1** (100)/0	**136 (63.6)/78**
Hospitalization (%)	**20** (14.9)	**16** (45.7)	**8** (22.2)	**4** (50)	**0** (0)	**48 (22.4)**
Duration of hospitalisaton (median, range)	5 (4-7)	6 (3.5-9)	7 (3-8)	3 (2-4)	-	**5 (4-8.5)**
Serologically confirmed (%)	**76** (56.7)	**30** (85.7)	**32** (88.9)	**5** (62.5)	**0** (0)	**143 (66.8)**
Complication (%)	**14** (10.4)	**11** (31.4)	**9** (25)	**2** (25)	**0** (0)	**36 (16.8)**
Orchitis	7	5	8	1	0	**21**
Meningitis	4	3	0	0	0	**7**
Pancreatitis	2	2	1	1	0	**6**
Meningitis+Orchitis	1	0	0	0	0	**1**
Pancreatitis+Orchitis	0	1	0	0	0	**1**
Vaccination status known	**n=107**	**n=27**	**n=26**	**n=8**	**n=1**	n_{total}=169
	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
No vaccination	53 (49.5)	13 (48.1)	14 (53.8)	3 (37.5)	0	**83 (49.1)**
1 vaccine dose	45 (42.1)	8 (29.6)	10 (38.5)	4 (50)	1	**68 (40.2)**
2 vaccine doses	9 (8.4)	6 (22.2)	2 (7.7)	1 (12.5)	0	**18 (10.7)**

mumps outbreak, 23 of 136 (17%) male patients suffered from orchitis. Symptomatic aseptic meningitis occurs in up to 10% of mumps cases; patients usually recover without sequelae [2]. Eight of the 214 (3.7%) patients developed meningitis. Pancreatitis, usually mild, occurs in 4% of cases [2]. Seven of the 214 (3.3%) cases had pancreatitis.

Conclusions

Our data indicate that the one-dose scheme failed to generate sufficient mumps immunity in the Austrian population. This mumps outbreak clearly demonstrates that additional MMR vaccination campaigns are necessary, especially targeting the age group of adolescents and young adults in order to avoid mumps and measles outbreaks in the future and for achieving the vaccine coverage required for herd immunity. In contrast to some other recent European outbreaks, vaccination scheme failure but not vaccine failure is primarily to blame for this mumps outbreak [9,10,11]. Future seroprevalence studies or the implementation of a notification system for vaccination data are required to identify susceptible groups to prevent future outbreaks of measles, mumps or rubella in Austria [12,13]. Similar to the situation of food-borne outbreaks, there should also be a clear legal basis requiring the epidemiological investigation of clusters of vaccine-preventable diseases not presently reportable under the Austrian Public Health Act. Otherwise, data protection laws can be used as a false pretence for hampering investigation of such outbreaks.

Acknowledgements

We would like to thank Jutta Hutecek for her excellent technical assistance in the data collection process.

References

1. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision – ICD-10. 2nd ed. World Health Organization, Geneva, 2000.
2. Heymann DL. Control of Communicable Diseases Manual. 18th ed. American Public Health Association, Washington D.C., 2004
3. Schmid D, Pichler A-M, Wallenko H, Holzmann H, Allerberger F. Mumps outbreak affecting adolescents and young adults in Austria, 2006. Euro Surveill. 2006;11(6):E060615.1. Available from: http://www.eurosurveillance.org/ew/2006/060615.asp#1
4. Schmid D, Pichler A-M, Wallenko H, Holzmann H, Popow-Kraupp Th, Allerberger F. Mumps outbreak affecting adolescents and young adults in Austria, 2006: update. Euro Surveill. 2006;11(7):E060706.2. Available from: http://www.eurosurveillance.org/ew/2006/060706.asp#2
5. Gerstel L, Lenglet A, García Cenoz M. Mumps outbreak in young adults following a village festival in the Navarra region, Spain, August 2006. Euro Surveill. 2006;11(11):E061109.4. Available from: http://www.eurosurveillance.org/ew/2006/061109.asp#4
6. Schmid D, Holzmann H, Popow-Kraupp Th, Wallenko H, Allerberger F. Mumps vaccine failure or vaccination scheme failure? Clin Microbiol Infect. 2007;13(11):1138-9.
7. Fine P. Herd immunity: history, theory, practice. Epidemiol Rev. 1993;15(2):265-302.
8. Ong G, Goh KT, Ma S, Chew SK. Comparative efficacy of Rubini, Jeryl-Lynn and Urabe mumps vaccine in an Asian population. J Infect. 2005;51(4):294-8. Epub 2004 Nov 5.

9. Germann D, Strohle A, Eggenberger K, Steiner CA, Matter L. An outbreak of mumps in a population partially vaccinated with the Rubini strain. Scand J Infect Dis. 1996;28(3):235-8.

10. Pons C, Pelayo T, Pachon I, Galmes A, Gonzalez L, Sanchez C et al. Two outbreaks of mumps in children vaccinated with the Rubini strain in Spain indicate low vaccine efficacy. Euro Surveill. 2000;5(7):80-84. Available from: http://www.eurosurveillance.org/em/v05n07/0507-223.asp

11. Goncalves G, De Araujo A, Monteiro Cardoso ML. Outbreak of mumps associated with poor vaccine efficacy - Oporto Portugal 1996. Euro Surveill. 1998;3(12):119-121. Available from: http://www.eurosurveillance.org/em/v01n04/0104-222.asp

12. Task Force on Community Preventive Services. Recommendations to improve targeted vaccination coverage among high-risk adults. Am J Prev Med. 2005;28(5 Suppl):231-7.

13. Germann D, Matter L. Die Erhöhung der Immunitätsrate von Medizinstudentinnen und -studenten gegen Masern, Mumps und Röteln an der Universität Bern. Schweiz Med Wochenschr 1999;129:499–507.

This article was published on 14 February 2008.

Citation style for this article: Schmid D, Holzmann H, Alfery C, Wallenko H, Popow-Kraupp TH, Allerberger F. Mumps outbreak in young adults following a festival in Austria, 2006. Euro Surveill. 2008;13(7):pii=8042. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8042

Trends in hepatitis B incidence in Romania, 1989-2005

D Pitigoi[1], A Rafila (arafila@yahoo.com)[1], A Pistol[2], V Arama[3], V Molagic[3], A Streinu-Cercel[3]
1. Department of Microbiology and Epidemiology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
2. National Centre of Communicable Diseases Prevention and Control, Institute of Public Health, Bucharest, Romania
3. Prof Dr Matei Bals National Institute of Infectious Diseases, Bucharest, Romania

In the early 1990s, Romania had a high incidence of hepatitis B, with over 30 cases per 100,000 population annually. The disease represented a serious public health problem, especially for children. As a result, public health measures were introduced during the 1990s such as the enforcement of the use of single-use needles and a routine vaccination programme for children and health workers. This paper describes the change in incidence of HBV infection in Romania from the late 1980s until 2005, and demonstrates the impact of those measures. They have lead to a dramatic decrease in hepatitis B incidence across the country: overall, the incidence has decreased from 43 per 100,000 in 1989 to 8.5 per 100,000 in 2004. The decrease has been most prominent in children under 15, dropping from 81 to 11 per 100,000 population and year during that period.

Introduction

Despite the availability of safe and effective vaccines, hepatitis B virus (HBV) infection remains a serious global public health problem, with an estimated two billion people infected and more than 350 million chronic carriers [1].

HBV infection can be either self-limiting or chronic. People with acute, self-limiting infection clear the infection spontaneously and develop protective immunity to the virus. Children are less likely than adults to clear the infection. The risk of developing a chronic infection is inversely related to the age at infection and ranges from over 90% in those infected as newborns to under 5% in immunocompetent adults [2]. Around 15 to 25% of chronic carriers develop cirrhosis or hepatocellular carcinoma [3].

HBV surface antigen (HBsAg) is the first detectable viral antigen to appear during infection, and the one most frequently used to screen for the presence of HBV infection. HBsAg disappears with clearance of the infection. Instead, IgG antibodies against the surface and core antigens (anti-HBs and anti-HBc) become detectable. A sample negative for HBsAg but positive for anti-HBs indicates either a past infection or vaccination. Chronic HBV infections are characterised by persistence of HBV surface antigen (HBsAg) in the serum for at least six months [2].

Romania has a history of high incidence of hepatitis B, especially in children. Between 1990 and 2002, it reported a yearly incidence of 10-50 HBV infections per 100,000 population [4]. According to two comparative studies on morbidity rates conducted in 1990 in several European countries, hepatitis B was endemic in Romania [5,6]. In a study conducted in Bucharest (April-July 1990), the prevalence was high in all age groups, with 47% of adults and 40% of children aged 0-16 years positive for at least one HBV marker (HBsAg and/or anti-HBc). Among infants (children under three years of age) living in orphanages, the prevalence of at least one HBV marker (HBsAg and/or anti-HBc) was 55%. In the same study, almost 8% of pregnant women were found to be HBsAg-positive [5].

A different study performed in 1990 reported a prevalence of current HBV infection (determined as HBsAg positivity) of 3.8% among pregnant women in northwestern Romania [7]. The most effective route of infection is transmission from infected mothers to newborns, both perinatal and during early childhood [7]. Other possible forms of transmission include contaminated blood products and tissues, child-to-child transmission, re-use of contaminated needles and syringes, and unprotected sexual contact [1].

Another study from 1995 showed that 32% of pregnant women admitted to give birth in southern Romania had evidence of past or current HBV infection (determined by presence of either anti-HBc or HBsAg) [8]

The following preventive measures have since been taken in Romania to control the high incidence and prevalence of HBV infection:

1991 After reports on HIV infections associated with the possible re-use of syringes and needles among children in Romanian orphanages, single-use syringes were introduced for immunisation programmes and in all healthcare settings in Romania. By the late 1990s, single-use syringes and needles were reported to be the standard for all injections [9].

1992 The generalised use of modern immunoenzymatic assays (ELISA for HBsAg and anti-HBc) was introduced for blood donations and viral hepatitis diagnostics.

1995 The HBV vaccine was introduced into the routine immunisation schedule for newborns (first dose at birth) and health care workers.

1999 HBV vaccination was expanded to include nine-year-old children (born before vaccine introduction in the Extended Programme of Immunisation (EPI)) and medical students.

2004 HBV vaccination was expanded to include to 18-year-olds (born before vaccine introduction in the EPI).

Since 1995, Romania has used the following he HBV vaccination schedules:

- For newborns, the first dose of HBV vaccine is given 24 hours after birth, with second and third doses at two and six months of age (0-2-6). Since 2002, a combined vaccine against HBV and diphtheria, tetanus, and pertussis (DTP-HBV) has been used for the second and third doses.

- For schoolchildren, teenagers and health care workers, a standard vaccination schedule of three doses, with the first after birth, and the other two at one and six months of age (0-1-6), has been used.

This study was conducted in order to assess the impact of these public health measures and to describe the incidence of HBV infection in Romania over a period of over 15 years, from 1989 until 2005.

Methods

Surveillance data on hepatitis B incidence in Romania was obtained from the following two reporting systems and used to describe the change in hepatitis B epidemiology from 1989 to 2005:

1. The mandatory reporting of acute viral hepatitis (in place since 1978). The reports are sent on a monthly basis. Data for acute hepatitis A, B, and C are collected in an aggregated format by type of hepatitis, district, age groups, and type of residence (urban or rural). The primary data are reported by infectious diseases hospitals and general practitioners to the local (district) public health authorities, and from there to the National Health Statistics Centre.
2. A case-based passive surveillance system for acute viral hepatitis, in place since 1997 in order to provide additional data regarding risk factors, vaccination status and laboratory results. The case classification is based on standard case definitions (European Union case definitions since 2004), a standard investigation form is filled in by the epidemiologist from the local public authorities and sent quarterly to the four regional public health institutes. The data are analysed on the regional level and transferred to the National Centre of Communicable Diseases Prevention and Control.

Results

Overall trend in HBV incidence

Based on the mandatory reporting of acute infections, the trend in hepatitis B incidence in Romania was followed over a period of almost 20 years, from 1986 to 2004. Since 1989, the incidence has decreased significantly, from 43 per 100,000 population in 1989 to 25 per 100,000 in 1995 and 8.5 per 100,000 in 2004 (Figure 1) [10]. The numbers show a steady decrease, with the exception of a slight increase around 1995.

Trend according to age group

Two main age groups, 0-14 year-olds and over 14 year-olds, were analysed separately in order to assess the effect of the new vaccination policy. The data clearly show that the trend in hepatitis B incidence is decreasing for both age groups (Figure 2).

Both curves show a relapse around 1993-1995. This temporary increase is stronger for the group of 0-14-year-olds, but is followed by a sharp decline in the number of acute infections. As of 2005, there were almost no reports of hepatitis B in this age group.

Impact of immunisation programmes

Since 1995, Romania's vaccination policy has focused primarily on children. By the end of the period between 1995 and 2004, over 95% of the 0-18-year-olds had been immunised, according to data from the Centre for Prevention and Surveillance of Communicable Diseases at the Institute of Public Health in Bucharest. Routine immunisation coverage of children is estimated based on the WHO methodology (EPI cluster) [11] at 18-24 month of age.

Figure 1

Hepatitis B virus acute infection incidence in Romania, 1989-2005

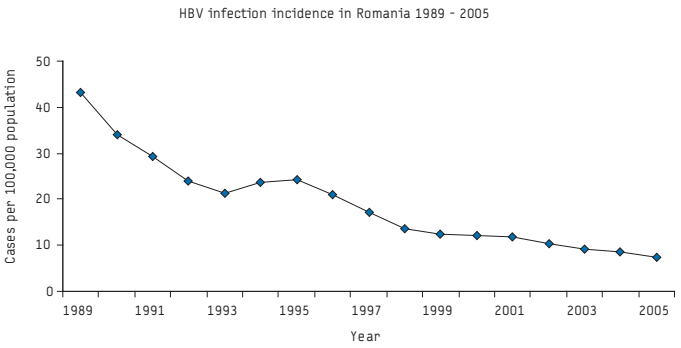


Figure 2

Hepatitis B virus acute infection incidence trends by age groups, compared with vaccination coverage, Romania, 1989-2005

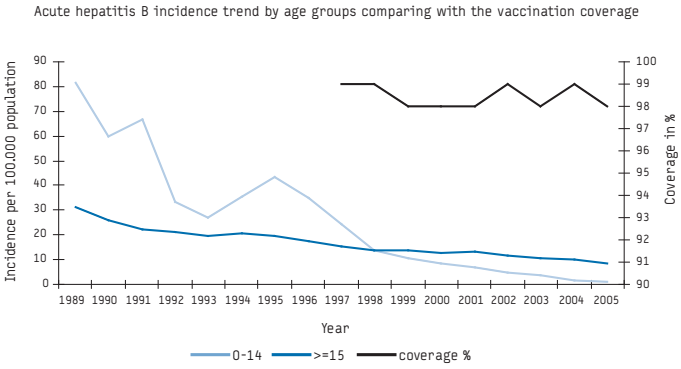
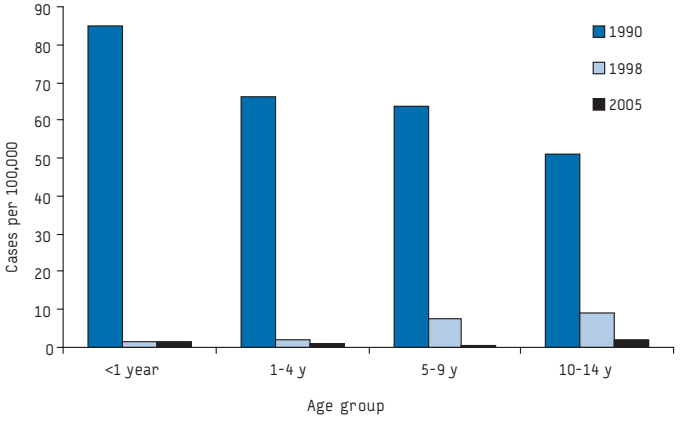


Figure 3

Hepatitis B virus acute infection incidence in children up to 14 years of age, Romania, 1990, 1998 and 2005



The vaccine coverage for health care workers was 63% (data from the Centre for Prevention and Surveillance of Communicable Diseases). In addition, other people can be vaccinated on a voluntary basis as a result of health promotion campaigns between 2001 and 2004, but the cost of the vaccine has to be paid by the vaccinees themselves.

In order to assess in a comprehensive manner the impact of the vaccination programme on the hepatitis B incidence in children, data for children at different ages were compared. Figure 3 shows the numbers reported in the years 1990 (before the introduction of routine HBV vaccination), 1998 (three years after the introduction of routine HBV vaccination of newborns) and 2005 (10 years after the introduction of routine HBV vaccination).

Three years after the introduction of routine vaccination of newborn children, a dramatic reduction in HBV infections was observed in all children under the age of 14. By 1998, the danger of infection had almost disappeared in children under the age of four years who had received the vaccine at birth. But even in the group of 5-14 year-olds, a dramatic effect was already apparent in 1998. There was a further reduction in incidence in these age groups by 2005, when routine immunisation covered children up to the age of 10 years.

Geographical differences

To assess possible geographical differences within Romania, we compared the hepatitis B incidence in 1995 and 2004 based on districts. As shown in Figure 4, there was significant heterogeneity throughout the country in 1995, with some districts reporting an incidence of under 11.7 per 100,000 population, compared to over 36.7 per 100,000 in others. In 2004, all districts had reduced their HBV incidence to be under 11.7 per 100,000.

Discussion

According to HBV serology data published in the final report of the European Sero-Epidemiology Network 2 (ESEN2) [12], 28% of serum samples from Romania in 2002 were positive for anti-HBc and 8% for HBsAg. The number of new cases has further decreased since then, especially in children, indicating the overall success of the public health measures adopted during the 1990s that is due to the introduction of single- use syringes, blood testing and more general precautions.

Since 2003, Romania has had a hepatitis B incidence in the range of 0-10 cases per 100,000 [4]. It is currently an intermediate prevalence country for chronic HBV infection with 2 to 7% of the population HBsAg-positive [3].

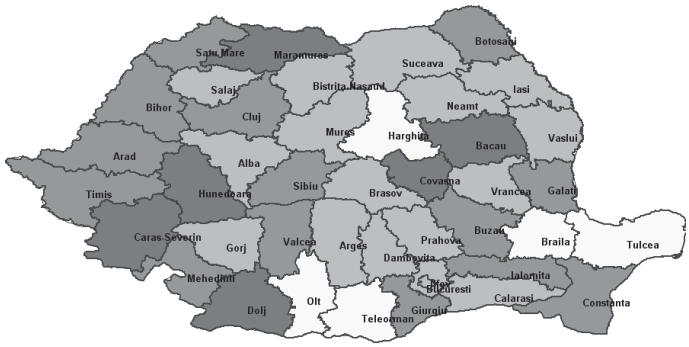
When HBV vaccination was introduced, it aimed at reaching a high coverage for different age groups of children and teenagers in a reasonable period of time through a programme compatible with human and financial resources. By 2005, a vaccination coverage of over 95% had been reached and was reflected in an almost complete disappearance of new hepatitis B cases registered in children. However, it needs to be noted that hepatitis B infection in children is often asymptomatic and therefore may be underreported.

Already by 1998, three years after the introduction of routine vaccination, almost no new hepatitis B infections were reported from the age group of 0-4-year-olds, and the incidence was dramatically reduced even in older children. This is probably due to the fact that vaccination of their younger siblings has reduced the risk of child-to-child transmission, while immunisation of health workers has reduced the risk of infection of children in health care institutions.

FIGURE 4

Hepatitis B virus acute infection incidence in Romania by district (data from the National Statistic Centre – CCSS)

A. 1995



B. 2004

Analysis of the development by district indicates that the immunisation programme has been implemented effectively in all parts of Romania, with all districts having reduced the hepatitis B incidence to below 11.7 per 100,000 population by 2004. Despite this encouraging development regarding HBV infection control in Romania, many actions should still be taken, in particular a more efficient approach to increase the vaccination coverage in hard-to-reach groups of population (e.g. Roma) who often suffer from new hepatitis B cases [13]. A study performed in Bucharest in 2001 suggested that the transmission of acute viral hepatitis B and also C was more frequently associated with individuals' behaviour (in 19% of hepatitis B and 20% of hepatitis C cases) than with iatrogenic transmission. In the case of hepatitis B, sexual contacts with more than one partner are the most common route of transmission (16%) [14].

References

1. World Health Organization. Hepatitis B. World Health Organization Fact Sheet 204 (Revised October 2000). Available from: http://who.int/inf-fs/en/fact204.html
2. Kerkar N. Hepatitis B in children: complexities in management. Pediatric transplantation 2005;9(5):685–91.
3. CDC Travelers' Health: Yellow Book Chapter 4 – Prevention of Specific Infectious Diseases: Hepatitis, Viral, Type B. CDC Health Information for International Travel 2008.
4. WHO regional Office for Europe. Centralized information system for infectious diseases. Hepatitis B. HepB incidence euroregion 1990-2004. Available from: http://data.euro.who.int/CISID/DOC/HepB/HepB_incidence_euroregion_1990-2004.pps
5. Paquet C, Babes VT, Drucker J, Senemaud B, Dobrescu A. Viral hepatitis in Bucharest. Bull World Health Organ. 1993;71(6):781-6.
6. Bonanni P. Report on Working Group 1: Albania, Andorra, Canada, France, Italy, Moldova, Portugal, Poland, Romania and Spain. Vaccine. 1998 Nov;16 Suppl:S58-60.
7. Molnar GB, Leentvaar-Kuijpers A, Hausman BA Prevalence of HBsAg among parturient pregnant women in northwestern Romania. Eur J Public Health.1995; 5: 223-225.
8. Balan A, Beldescu N, Popa R.The prevalence of viral hepatitis B in pregnant women in an area of southern Romania. Bacteriol Virusol Parazitol Epidemiol. 1998 Oct-Dec;43(4):254-60. [In Romanian].
9. CDC. Injection practices among nurses – Valcea, Romania, 1998. MMWR Morb Mortal Wkly Rep. 2001 Feb 2;50(4):59-61. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5004a3.htm
10. Aurel Ivan, Epidemiology of Infectious diseases: pp. 272-273., Ed Polirom, Iasi 2002
11. WHO. The EPI coverage survey, Geneva, 1991. (WHO/EPI/MLM/91.10)
12. National Centre of Communicable Diseases Prevention and Control, Institute of Public Health, Bucharest, Romania. ESEN2- report (2001-2005)-pp.32. Available from: www.eurohep.net/files/presentations/MALS51Nardoneweb.pdf
13. U.N.D.P., C.H.P.S. Social Assessment of Roma and HIV/AIDS in Central East Europe 2003-2004. National Report-Romania, pp. 85.
14. Ion-Nedelcu N, Velea L, Ulmeanu V, Dragomirescu C, Dumitrache-Marian R, Gherasim P, et al. Nature and prevalence of risk factors associated to type B and C acute viral hepatitis cases in Bucharest, 1998-2000. Roum Arch Microbiol Immunol. 2001 Jan-Mar;60(1):55-67.

This article was published on 10 January 2008.

Citation style for this article: Pitigoi D, Rafila A, Pistol A, Arama V, Molagic V, Streinu-Cercel A. Trends in hepatitis B incidence in Romania, 1989-2005. Euro Surveill. 2008;13(2):pii=8012. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8012

The value of ProMED-mail for the Early Warning Committee in the Netherlands: more specific approach recommended

M E Zeldenrust[1], J C Rahamat-Langendoen (janette.rahamat@rivm.nl)[2], M J Postma[3], J A van Vliet[2]
1. University of Groningen, Groningen, the Netherlands
2. Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
3. Groningen Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, the Netherlands

This article describes a retrospective and descriptive study into the added value of ProMED-mail – the global electronic reporting system for outbreaks of emerging infectious diseases and toxins maintained by the International Society for Infectious Diseases – as an early warning system for the Netherlands Early Warning Committee (NEWC). Information about infectious disease events in foreign countries originating from ProMED-mail was retrieved from the reports of the NEWC between May 2006 and June 2007. Each event was analysed in depth in order to determine if it could have been a possible threat to public health in the Netherlands. It was determined whether these events were mentioned in other sources of information used by the NEWC besides ProMED-mail. In addition, we assessed the possible consequences of missing an event when not reading ProMED-mail or of being informed of the event with a time delay. Semi-structured interviews with stakeholders were conducted to explore other functions of ProMED-mail besides early warning. Five out of 25 events reported in ProMED-mail were assessed as a potential threat to the Netherlands, mainly because of the known vulnerability of the Netherlands for vaccine preventable diseases: an outbreak of measles in the United Kingdom and Japan, a case of poliomyelitis in Kenya, and two events concerning Highly Pathogenic Avian Influenza (HPAI) H5N1. The outbreak of measles in Japan and one case of HPAI H5N1 infection in a bird in Germany were only reported by ProMED-mail; the other potential threats were mentioned in other sources with a time delay.
ProMED-mail has a limited but real added value over other sources in the early warning of threats. A more specific approach of using ProMED-mail by defining vulnerabilities of a country would be useful and efficient. ProMED-mail is appreciated for providing background and preliminary outbreak information.

Introduction

ProMED-mail, the Program for Monitoring Emerging Diseases, is an internet-based system, set up in 1994, which provides a mechanism to share alerts on emerging diseases involving humans, animals and plants around the world. Sources of information include media reports, official reports, online summaries, local observers, and others. Between seven and 10 signals are distributed every day to more than 30,000 people in over 180 countries [1,2].

The Netherlands' Early Warning Committee (NEWC) was established in order to recognise threats to public health caused by infectious diseases in the Netherlands in a timely and complete fashion [3]. The committee has a weekly meeting, in which possible threats to public health are discussed. Before the meeting, several

Table 1

Foreign sources of information regularly used by the Early Warning Committee

Organisation	Bulletin/report	Website
World Health Organisation (WHO)	Weekly Epidemiological Record	http://www.who.int/wer/en/
	Disease Outbreak News	http://www.who.int/csr/don/en/
	Outbreak Verification List	confidential
European Union (EU)	Eurosurveillance (European Centre for Disease Prevention and Control, ECDC)	http://www.eurosurveillance.org/
	Communicable Disease Threats Report (CDTR) (ECDC)	http://www.ecdc.europa.eu/Activities/CDTR.html (confidential)
	Early Warning and Response System (Health and Consumer Protection Directorate General, DG-SANCO)*	https://webgate.cec.europa.eu/ewrs/ (confidential)
Centers for Disease Control and Prevention (CDC)	Morbidity and Mortality Weekly Report (MMWR)	http://www.cdc.gov/mmwr/
International Society for Infectious Diseases (ISID)	ProMED-mail	http://www.promedmail.org/
Other sources of information, like the Medical Information System (MedISys), the Healthcare Effectiveness Data and Information Set (HEDIS), and the Global Polio Eradication Website are used incidentally following certain events.		

* Since December 2007, the EWRS system is coordinated by ECDC

Box

Interview questions

	Questions
1.	How often and for what purpose do you use ProMED-mail?
2.	What aspects do you like of ProMED-mail?
3.	What is less useful about the system?
4.	Any further remarks or questions on this topic.

sources of domestic and foreign information are scanned in order to pick up relevant signals (Table 1) [3]. As well as being a possible threat to public health, signals can also be picked up because of high media attention or out of general interest. After each meeting a report is made with all relevant signals; this is sent to over 500 people involved in infectious disease control in the Netherlands [3-5]. If necessary, further outbreak management is undertaken.

In recent years, there have been some important developments in the field of infectious disease surveillance. The need to strengthen disease surveillance and response systems is recognised globally and was expressed in the revised International Health Regulations, adopted by the Word Health Assembly in 2005 [6,7,10,11]. The establishment of the European Centre for Disease Prevention and Control (ECDC) in 2005 and its role in identifying, assessing and communicating current and emerging threats also has implications for the surveillance of infectious diseases on a national and European level [8,9].

These developments led to the question of whether precise reading of all ProMED-mail postings and subsequent assessment of the events is worth the effort (an average time investment of about four hours a week, and for a less experienced person even more). We wanted to investigate whether a more specific approach to the information distributed through ProMED-mail would be possible and whether ProMED-mail fulfilled other functions than early warning for the members of the Netherlands' EWC.

Methods

For a period of 13 months (May 2006 until June 2007), foreign events mentioned in the reports of the NEWC and originating from ProMED-mail were listed. An in depth-analysis was made of each event in order to assess if the event could have been a possible threat for public health in the Netherlands. Two questions were used to define whether an event could have been a threat:

1 Was there an increased chance of importation and further dissemination in the Netherlands of the micro-organism mentioned?
and/or
2 Was there a possibility that the (potential) source of the infection mentioned was present in the Netherlands?

For a further assessment of each of the events, experts' opinions and scientific literature were consulted [12-16]. The events were classified either as threats requiring immediate outbreak management, or as alerts, for which it would be sufficient to inform people involved in infectious disease control in the Netherlands via the report sent out after the meeting.

Other official foreign sources of information used by the NEWC were searched for the same events mentioned in ProMED-mail (Table 1). The time lag between the two, if applicable, was established. We further determined the possible consequences of missing an event when not reading ProMED-mail. If an event was reported by other sources with a time delay, the possible consequences of noticing the event later than published on ProMed were determined as well.

Other functions of ProMED-mail besides early warning were explored through semi-structured interviews with members of the NEWC (n=13). The questions posed during the interviews are shown in Box 1.

Results

Between 1 May 2006 and 1 June 2007, 27 events originating from ProMED-mail were reported by the NEWC. Verification of the source of the information led to the exclusion of two events.

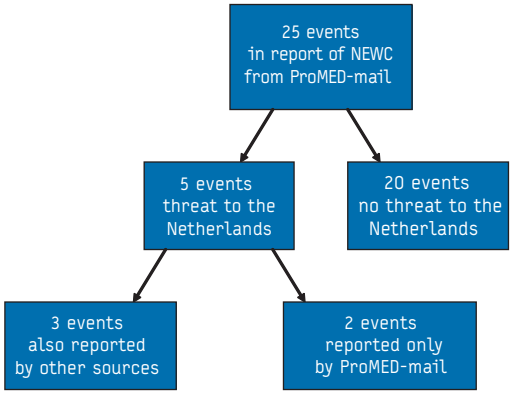
After assessment of the remaining 25 events, five of them (20%) were identified as possible threats for the Netherlands (Figure). The remaining 20 events were mentioned in the report of the NEWC because they were thought at the time to be a possible threat, but after evaluation turned out not to be, or were included in the report for other reasons (for example, general interest or media attention).

The characteristics of the events are shown in Table 2. None of the five events identified as possible threats required immediate outbreak management; they could all be classified as "alerts".

Three of the five alerts concerned vaccine-preventable diseases (VPDs): outbreaks of measles in the United Kingdom (UK) and Japan, and a case of poliomyelitis in Kenya. The Netherlands have an increased susceptibility to outbreaks of VPDs due to a large group of unvaccinated people living in the so-called 'Bible Belt' [17]. The Communicable Disease Threats Report (CDTR) mentioned the measles outbreak in the UK seven days after its posting on ProMED-mail. The delay in notification this would have caused had the ProMED-mail not been read would probably not

Figure 1

Flow chart of events originating from ProMED-mail that were included in the report of the Netherlands Early Warning Committee (NEWC) between 1 May 2006 and 1 June 2007



have had consequences for public health in the Netherlands. The case of poliomyelitis in Kenya was reported by the World Health Organization (WHO) three days after the event was distributed by ProMED-mail; this delay in notification is not regarded as important. The outbreak of measles in Japan was not mentioned by any other source than ProMED-mail. This outbreak would have been missed by the NEWC without reading ProMED-mail, with possible consequences for public health in the Netherlands.

Two of the five alerts considered Highly Pathogenic Avian Influenza (HPAI) H5N1 infection in birds. The outbreaks among poultry in Romania were seen as a threat because commercially sold infected poultry could have been transported to the Netherlands. This event was reported in the CDTR and Eurosurveillance Weekly within two and three days, respectively, after the ProMED-mail posting. This delay would probably not have had major consequences. The HPAI H5N1 infection in a bird in Germany was seen as a threat because it was unclear at the time whether the disease had spread to the Netherlands, Germany being a neighbouring country. This event was not mentioned by other sources used by the NEWC, and therefore would have been missed without ProMED-mail. The event was reported by the Office International des Epizooties (World Organisation for Animal Health, OIE) before it was distributed by ProMED-mail. However, the OIE is not an official source of information of the NEWC. Missing the event could have had consequences for animal health in the Netherlands, although probably not for human health.

Thus, for two out of five alerts, measles in Japan and HPAI H5N1 in Germany, information provided by ProMED-mail was essential.

All members of the NEWC participated in the semi-structured interviews to assess other functions of ProMED-mail. The interviewees looked at ProMED-mail with varying frequency, from daily to weekly. Most people received ProMED-mail digests and scanned them for relevant items, which they then read more thoroughly. Among the reasons for reading ProMED-mail, the ones most frequently mentioned were: to find relevant background

Table 2

Events in the report of the Early Warning Committee originating from ProMED-mail, 1 May 2006 - 1 June 2007

Micro-organism/ disease	Country	Also reported by	Time lag (days)	Threat to NL	Reason for threat
Measles	United Kingdom	CDTR	7	minor	susceptible population
Bacillus anthracis	Scotland	Eurosurveillance	1	no	
Human bocavirus	China			no	
Angiostrongylus canonensis.	China			no	
Poliomyelitis	Kenya	DON/CDTR/WER	3 / 4 / 11	minor	susceptible population
Hepatitis E	Congo			no	
West Nile Virus	Argentina			no	
Mumps	Spain	Eurosurveillance	35	no	
Avian influenza H9N2	Hong Kong			no	
Chikungunya virus	Gabon			no	
Measles	Japan			minor	susceptible population
Syphilis/*Treponema pallidum*	Australia			no	
HPAI H5N1, migratory birds	Africa	Eurosurveillance	42	no	
HPAI H5N1, poultry	Romania	CDTR/Eurosurveillance/OIE	2 / 3 / 10	minor	infected poultry sold commercially
HPAI H5N1, migratory birds	China	OIE	10	no	
HPAI H5N1, poultry	Russia	CDTR/Eurosurveillance	21 / 27	no	
HPAI H5N1, wild birds	Germany	OIE	-2	minor	neighbouring country, import possible
HPAI H5N1,human, asymptomatic	South Korea			no	
HPAI H5N1, poultry	South Korea	OIE	15	no	
HPAI H5N1, wild birds	Hong Kong			no	
HPAI H5N1, poultry	Pakistan	OIE	0	no	
HPAI H5N1, poultry	Russia	OIE	4	no	
HPAI H5N1, poultry	Bangladesh	OIE	8	no	
HPAI H5N1, poultry	Saudi Arabia	OIE	9	no	
HPAI H5N1, poultry	Ghana	OIE	1	no	

HPAI: Highly pathogenic avian influenza; CDTR: Communicable Diseases Threats Report; DON: Disease Outbreak News; WER: Weekly Epidemiological Record; OIE: World Organisation for Animal Health.

information, to stay up to date, to be informed about threats at an early stage, and to discover exiting news. The fact that alerts concerning animals and humans are combined in ProMed-mail was seen as an advantage compared to other sources. The perceived disadvantages of ProMED-mail that were mentioned most often were the large number of postings, sometimes originating from doubtful sources, and the lack of scientific language. Observations during the NEWC meeting showed that, postings from ProMED-mail, which are often drawn from general media sources, were not always taken seriously and confirmation from other sources was often awaited.

Discussion

Our study shows that ProMED-mail has a certain, albeit limited, value in the early warning of threats posed by infectious diseases in the Netherlands.,ProMED-mail is appreciated for providing background and preliminary outbreak information.

This research has some limitations. Events were analysed over a relatively short period of time, and a large proportion of the events covered in this period were reports on HPAI H5N1. However, we think that this has no major consequences for the outcome of this study. The inclusion of more events over a longer time period would probably have led to the same conclusions, although it might have resulted in defining more vulnerabilities for the Netherlands besides those regarding VPDs. For the monitoring of HPAI H5H1, the early warning committee could consider to start using the OIE as an official source of information, in order not to miss any outbreak of avian influenza in birds.

ProMED-mail is a sensitive but not very specific system, which is reflected in the large number of postings (about five to 10 postings per day, requiring at least 15-20 minutes' reading time), of which only a small fraction made it into the report of the NEWC. Reading ProMED-mail for the purpose of detecting threats could therefore be regarded as rather inefficient. However, the members of the NEWC often waited for confirmation of events by other information sources, and this probably also accounted for the small proportion of postings mentioned in the report. In those cases, only the second, confirmed source is cited in the EWC report.

Most threats defined in this study are related to the increased susceptibility for outbreaks of VPDs in the Netherlands in the so-called 'Bible Belt' [17]. In this socially and geographically clustered group, the vaccination coverage is low, making the group highly susceptible for VPDs, especially measles, rubella and poliomyelitis. This group has strong bonds to the same religious group in Canada [18]. As infectious diseases have no boundaries, this emphasises the importance of international surveillance of infectious diseases. The Netherlands are expected to remain vulnerable for VPDs, and outbreaks of measles or polio in the near future are considered realistic [19]. According to this study, ProMED-mail is in some cases the only source of information regarding an outbreak of a VPD. Even though this might change in the future, with the WHO currently enhancing its role in surveillance with implementation of the International Health Regulations (IHR), looking at ProMED-mail specifically for these VPDs can be recommended for the Netherlands in order to avoid missing an outbreak. Compared to the current unspecific way of screening, this would be less time consuming, as only 68 postings during the entire study period were related to measles, poliomyelitis and rubella.

Thus, defining the vulnerabilities of a country arising from country-specific aspects like strong ties with other countries (ex-colonies), vaccination coverage, agricultural habits, etc. allows a more specific approach of using ProMED-mail, focussing on events related to these particular vulnerabilities.

References

1. Madoff LC, Woodall JP. The internet and the global monitoring of emerging diseases: lessons from the first 10 years of ProMED-mail. Arch Med Res. 2005;36(6):724-30.
2. Madoff LC. ProMED-mail: an early warning system for emerging diseases. Clin Infect Dis. 2004;39(2):227-32.
3. Rahamat-Langendoen JC, van Vliet JA, Suijkerbuijk AW. Recognition of threats caused by infectious diseases in the Netherlands: the early warning committee. Euro Surveill. 2006;11(12):242-5. Available from: http://www.eurosurveillance.org/em/v11n12/1112-230.asp
4. Helsloot I, van Steenbergen JE. [Control of Infectious Diseases. Studies into organisation and practices]. Den Haag: Boom; 2005. In Dutch.
5. van Steenbergen JE, Timen A. [The control of infectious diseases in The Netherlands]. Ned Tijdschr Geneeskd. 2005;149(4):177-81. In Dutch.
6. WHO. Communicable disease surveillance and response systems. A guide to planning. 2006. Available from: http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_LYO_2006_1.pdf
7. Kaiser R, Coulombier D, Baldari M, Morgan D, Paquet C. What is epidemic intelligence, and how is it being improved in Europe? Euro Surveill 2006;11(2):E060202.4. Available from: http://www.eurosurveillance.org/ew/2006/060202.asp#4
8. ECDC. The First European Communicable Disease Epidemiological Report. 2007. Available from: http://www.ecdc.europa.eu/pdf/ECDC_epi_report_2007.pdf
9. Rodier G, Hardiman M, Plotkin B, Ganter B. Implementing the International Health Regulations (2005) in Europe. Euro Surveill. 2006;11(12):208-11. Available from: http://www.eurosurveillance.org/em/v11n12/1112-222.asp
10. Heymann DL, Rodier GR. Hot spots in a wired world: WHO surveillance of emerging and re-emerging infectious diseases. Lancet Infect Dis. 2001;1(5):345-53.
11. Grein TW, Kamara KB, Rodier G, Plant AJ, Bovier P, Ryan MJ, et al. Rumors of disease in the global village: outbreak verification. Emerg Infect Dis. 2000;6(2):97-102. Available from: http://www.cdc.gov/ncidod/eid/vol6no2/grein.htm
12. Avian influenza fact sheet (April 2006). Wkly Epidemiol Rec. 2006;81(14):129-36. Available from: http://www.who.int/wer/2006/wer8114/en/index.html
13. Monteny M, Niesters HG, Moll HA, Berger MY. Human bocavirus in febrile children, The Netherlands. Emerg Infect Dis. 2007;13(1):180-2. Available from: http://www.cdc.gov/ncidod/eid/13/1/180.htm
14. Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, et al. Avian influenza A (H5N1) infection in humans. N Engl J Med. 2005;353(13):1374-85. Available from: http://content.nejm.org/cgi/content/full/353/13/1374
15. Mandell GL, Bennet JE, Dolin R. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Churchill Livingstone; 2005.
16. Heymann, DL. Control of Communicable Diseases Manual. 18th ed. Washington: American Public Health Association; 2004.
17. Oostvogel PM, van Wijngaarden JK, van der Avoort HG, Mulders MN, Conyn-van Spaendonck MA, Rumke HC, et al. Poliomyelitis outbreak in an unvaccinated community in The Netherlands, 1992-93. Lancet. 1994;344(8923):665-70.
18. Hahné S, Macey J, Tipples G, Varughese P, King A, van Binnendijk R, et al. Rubella outbreak in an unvaccinated religious community in the Netherlands spreads to Canada. Euro Surveill 2005;10(5):E050519.1. Available from: http://www.eurosurveillance.org/ew/2005/050519.asp#1
19. Rahamat-Langendoen JC, van Vliet JA. [Recent changes in the epidemiology of infectious diseases in the Netherlands: the report 'Status of infectious diseases in the Netherlands, 2000-2005']. Ned Tijdschr Geneeskd. 2007;151(24):1333-8. In Dutch.

This article was published on 7 February 2008.

Citation style for this article: Zeldenrust ME, Rahamat-Langendoen JC, Postma MJ, van Vliet JA. The value of ProMED-mail for the Early Warning Committee in the Netherlands: more specific approach recommended. Euro Surveill. 2008;13(6):pii=8033. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8033

A European survey on public health policies for managing cases of meningococcal disease and their contacts

M Hoek[1,2], G Hanquet[3], S Heuberger[4], P Stefanoff[5], P Zucs[6], M Ramsay[2], J Stuart (james.stuart@hpa.org.uk)[2], on behalf of the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS)[7]

1. European Programme for Intervention Epidemiology Training
2. Health Protection Agency, London, United Kingdom
3. Scientific Institute of Public Health, Brussels, Belgium
4. Austrian Agency for Food and Health Safety, Graz, Austria
5. National Institute of Hygiene, Warsaw, Poland
6. Federal Office of Public Health, Berne, Switzerland
7. European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS)

In 2007, a European survey was conducted to compare national policies on public health management of cases of meningococcal disease and their contacts. An electronic questionnaire was sent to 27 national public health institutes; 22 countries responded (response rate 81%). The results of the survey revealed differences in definitions of close contacts and prophylactic regimens between countries. These differences can be attributed to a lack of evidence on optimal prevention and treatment strategies. The development of guidance for best practice in priority areas, based on evidence or consensus, is therefore recommended.

Introduction

Meningococcal disease is a severe illness with high morbidity and mortality. The relatively high risk of further cases among close contacts of a primary case is well established [1,2]. Close contacts may be the source of the organism that caused disease in the index case, or may have recently acquired the organism from another contact or from the index case [3]. Applying antibiotic treatment to close contact persons to eliminate meningococcal carriage reduces the risk of further cases [3], but evidence is lacking in many other areas of policy, leading to difficulties in adopting a consistent approach [4,5]. We conducted a survey to map the variations in public health management policies for meningococcal disease across Europe.

Methods

We prepared a questionnaire to collect information on case and contact definitions, the use of chemoprophylaxis and vaccination, and communication about changes in the guidelines. In April 2007, the questionnaires were sent by email to public health representatives of the European Union Invasive Bacterial Infection Surveillance network (EU-IBIS, http://www.euibis.org) and the European Meningococcal Disease Society (EMGM, http://www.emgm.eu) in 27 countries in Europe. The responses were analysed using Microsoft Excel.

Results

Of the 27 countries represented in EU-IBIS and EMGM, the questionnaires were completed and returned by 22 (81%): Austria, Belgium, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Lithuania, Malta, the Netherlands, Norway, Poland, Romania, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom. Two questionnaires were returned from Belgium and six from Austria, reflecting sub-national political structures. For analysis, the two questionnaires from Belgium were included separately, but only the questionnaire returned from the national reference laboratory was taken as representing Austrian national policy, bringing the denominator to 23.

Definition of close contacts

All countries recommended chemoprophylaxis for close contacts of a case. However, we found differences in the definitions of cases and close contacts in use for applying control measures (Tables 1 and 2). The trace-back period for close contacts varied from seven days (14/23) to 10 days (7/23) or no particular period at all (2/23). There was also variation in the criteria of duration and proximity of exposure to a case used to define a close contact, especially evident in contacts on public transport (Table 3).

Chemoprophylaxis

Ciprofloxacin, rifampicin and ceftriaxone were the antibiotics most frequently recommended in adults (aged 18 years or older). In those under 18 years, the most commonly recommended antibiotics were rifampicin and ciprofloxacin. The recommended age for prescribing ciprofloxacin varied widely. In some countries ciprofloxacin was prescribed for newborns, while in others the use of ciprofloxacin under the age of 18 years was not recommended. Three countries recommended the use of azithromycin in children, and one in adults (Table 4). Giving antibiotics to a patient with suspected meningococcal disease prior to hospitalisation was not a common practice. Nine countries (39%) recommended an injection of penicillin as soon as a meningococcal infection was suspected. Chemoprophylaxis in a case before discharge from hospital to eradicate carriage was recommended by 11 countries unless the case had been treated with a cephalosporin (third generation). Four of these countries specifically mentioned ceftriaxone. Twelve countries did not specifically recommend the use of antibiotics to eradicate carriage in a case prior to discharge from hospital.

Vaccination

Seventeen countries (74%) recommended vaccination in addition to chemoprophylaxis for close contacts if illness in the case was due to a vaccine-preventable serogroup. Nine countries had defined epidemiological thresholds to commence local or regional vaccination campaigns during outbreaks of meningococcal disease. The most commonly used thresholds were 10 or 40 cases per 100,000 population, or three or more cases of the same serogroup within three months in a defined age group of the population of a defined region. Eight countries included serogroup C conjugate vaccine in the national childhood vaccination programme.

Communication issues

Changes and amendments in the national or sub-national guidelines case definitions, treatment, and prevention were mainly communicated by publishing the changes on the websites of the national authorities. Six countries commented on the lack of efficient communication of changes in the guidelines to those responsible for implementation.

Discussion

The different approaches to risk reduction, the use of antibiotics, patient care and the implementation of control measures detected in this study may arise from uncertainties about the effectiveness of public health interventions, variations in heath care systems and differences in attitudes to risk management. Nearly all countries recommended the use of ciprofloxacin, rifampicin and ceftriaxone for chemoprophylaxis in close contacts. These are all considered effective at eradicating carriage [6], and at reducing attack rates in close contacts [3]. The recommended use of antibiotics in children and pregnant women showed more variability both in a lower age limit for children and in the type of antibiotic. This variation may reflect concerns about recommending antibiotics if not licensed for chemoprophylaxis of meningococcal disease in pregnancy or young children, as well as the availability of paediatric formulations. Further research is needed to understand the reasons for such variability.

There is uncertainty about how to define close contacts among fellow passengers on long plane, train or bus trips. How close and for how long does a fellow passenger have to be seated next to someone

Table 1

Case definition criteria for meningococcal disease. European survey on public health policies for managing cases of meningococcal disease and their contacts, 2007 (n=23)

Case definition criteria	Number of countries (% of total)
Isolation of *Neisseria meningitidis* from sterile site	22 (96%)
Isolation of meningococcal DNA from sterile site	20 (87%)
Isolation of Gram-negative diplococci from sterile site	20 (87%)
Isolation of antigen from sterile site	19 (83%)
Clinically compatible	16 (70%)
Purpura fulminans	16 (70%)
Official notification	11 (48%)
Detection of high titre in convalescent serum	6 (26%)

Table 2

Definitions of close contacts. European survey on public health policies for managing cases of meningococcal disease and their contacts, 2007 (n=23)

Criteria for close contacts	Number of countries (% of total)
People sharing the same household	23 (100%)
People with equivalent level of close contact	22 (96%)
People sharing cups or glasses	9 (39%)
Kissing on mouth	10 (43%)
Kissing on cheek	3 (13%)

Table 3

Duration and proximity criteria for administering chemoprophylaxis to fellow passengers. European survey on public health policies for managing cases of meningococcal disease and their contacts, 2007 (n=23)

Criteria for chemoprophylaxis in fellow passengers	Number of countries (% of total)
Time of travel:	
Four hours or more	2 (9%)
Seven hours or more	1 (4%)
Eight hours or more	3 (13%)
Overnight travel	1 (4%)
Not specified	16 (70%)
Proximity to case:	
Next to case	2 (9%)
Same row, row in front and back	1 (4%)
Seated "close to case"	2 (9%)
Undefined	15 (65%)

Table 4

Antibiotics recommended in chemoprophylaxis by age and in stage of pregnancy. European survey on public health policies for managing cases of meningococcal disease and their contacts, 2007 (n=23)

	Adults (18+)	Children (<18)	Pregnancy (1st trimester)	Pregnancy (2nd & 3rd trimester)
	n (%)	n (%)	n (%)	n (%)
Rifampicin	14 (61%)	16 (70%)	4 (17%)	5 (22%)
Ciprofloxacin	20 (87%)	6 (26%)	0	0
Ceftriaxone	13 (57%)	7 (30%)	12 (52%)	11 (48%)
Azithromycin	1 (4%)	3 (13%)	2 (9%)	1 (4%)

with meningococcal disease to be eligible for chemoprophylaxis? The most commonly used definition is anyone sitting in the rows in front or behind the case for a period of seven hours or longer. However, periods varied between four and 10 hours, and some countries did not consider fellow travelers for chemoprophylactic treatment at all. The United States' Centers for Disease Control and Prevention recommend prophylaxis if air-travel-associated exposure lasts more than eight hours, but there is little or no evidence to quantify the risks [7]. One Australian report describes two cases of meningococcal disease among passengers sitting several rows apart on the same plane, both with dates of onset 3-5 days after the flight [8]. Transmission on board the airplane may have occurred from an asymptomatic carrier, as no direct contact occurred between the passengers. Another area of variation was whether mouth kissing or sharing drinks justify chemoprophylaxis; the former but not the latter may be an important risk factor for transmission [9,10].

The administration of a single dose of penicillin prior to hospitalisation was recommended in one third of the countries surveyed. The literature on this topic is difficult to interpret. Some observational studies report a lower case fatality among those who received a single dose of penicillin prior to hospitalisation, while others show a higher risk of death [11]. There is likely to be confounding related to severity of illness in such observational studies as physicians will be influenced by clinical assessment in making decisions on treatment [11]. Other differences seen in the national guidelines regarded the administration of chemoprophylaxis to a patient before discharge from hospital. Most countries recommended vaccination in addition to chemoprophylaxis for contacts if illness was due to a vaccine-preventable serogroup. This policy is supported by a recent review of effectiveness (M. Hoek, article in submission).

Six countries remarked that changes in national policies were not communicated efficiently or effectively. It is possible that other countries face similar difficulties, and efforts should be made to ensure that changes in national or sub-national guidelines are communicated quickly and effectively to those responsible for case management and prevention.

The incidence of meningococcal disease in Europe has decreased over the last decade following the introduction of serogroup C conjugate vaccines. However, there are no imminent prospects for the introduction of serogroup B vaccines. The severity and rapid progression of meningococcal disease and the high risk of infection among contacts indicate a continuing need for clear public health policies. The differences between various national policies revealed in this study reflect areas of uncertainty about the effectiveness of public health interventions. The survey was based on information about national policies as reported by public health expert representatives, but several respondents also commented on varying interpretations of national guidelines at sub-national level.

At a meeting of the European Monitoring Group on Meningococci in 2007, there was strong support for an assessment of priority areas for guidance, a review of the evidence to support policy, and the development of consensus around guidance for best practice.

Acknowledgements

We would like to thank all EU-IBIS participants (http://www.euibis.org/meningo/euibis_partners_meningo.htm) and members of the European Meningococcal Disease Society (http://emgm.eu who) contributed to the discussion on the survey results:

Lucia Pastore Celentano, Reinhild Strauss, Sigrid Heuberger, Germaine Hanquet, Suzana Bukovski, Pavla Krizova, Michael Howitz, Kuulo Kutsar, Petri Ruutu, Isabelle Parent du Châtelet, Wiebke Hellenbrand, Jenny Kourea-Kremastinou, Katalin Krisztalovics, Thorolfur Gudnason, Suzanne Cotter, Marta Ciofi, Irina Lucenko, Grazina Rimseliene, Jackie Maistre Melillo, Sabine de Greeff, Øistein Løvoll, Pawel Stefanoff, Laurinda Queirós, Marina Pana, Izika Korolesa, Margareta Sláciková, Alenka Kraigher, Rosa Cano Portero, Margareta Löfdahl, Phillip Zucs and Mary Ramsay.

References

1. De Wals P, Hertoghe L, Borlee-Grimee I, De Maeyer-Cleempoel S, Reginster-Haneuse G, Dachy A, et al. Meningococcal disease in Belgium. Secondary attack rate among household, day-care nursery and pre-elementary school contacts. J Infect 1981;3(suppl 1):53-61.
2. Munford RS, Taunay Ade E, de Morais JS, Fraser DW, Feldman RA. Spread of meningococcal infection within households. Lancet. 1974;1(7869):1275-8.
3. Purcell B, Samuelsson S, Hahne S, Ehrhard I, Heuberger S, Camaroni I, et al. Effectiveness of antibiotics in preventing meningococcal disease after a case: systematic review. BMJ. 2004;328(7452):1339.
4. Begg N. Policies for public health management of meningococcal disease. J Epidemiol Community Health. 1999;53(9):516.
5. Stuart JM. Managing outbreaks, the public health response. In: Pollard AJ, Maiden MCJ, editors. Methods in molecular medicine. Meningococcal disease: methods and protocols. Totowa, NJ: Humana Press Inc; 2001. p. 257-72.
6. Fraser A, Gafter-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections. Cochrane Database Syst Rev. 2006;(4):CD004785.
7. CDC. Exposure to patients with meningococcal disease on aircrafts - United States, 1999-2001. MMWR 2001;50:485-9.
8. O'Connor BA, Chant KG, Binotto E, Maidment CA, Maywood P, McAnulty JM. Meningococcal disease - probable transmission during an international flight. Commun Dis Intell 2005:29(5):312-4.
9. Tully J, Viner RM, Coen PG, Stuart JM, Zambon M, Peckham C, et al. Risk and protective factors for meningococcal disease in adolescents: matched cohort study. BMJ. 2006;332(7539):445-50.
10. Orr HJ, Gray SJ, Macdonald M, Stuart JM. Saliva and meningococcal transmission. Emerg Infect Dis. 2003;9(10):1314-5.
11. Hahné SJ, Charlett A, Purcell B, Samuelsson S, Camaroni I, Ehrhard I, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. BMJ. 2006;332(7553):1299-303.

This article was published on 6 March 2008.

Citation style for this article: Hoek M, Hanquet G, Heuberger S, Stefanoff P, Zucs P, Ramsay M, Stuart J, on behalf of the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) . A European survey on public health policies for managing cases of meningococcal disease and their contacts. Euro Surveill. 2008;13(10):pii=8060. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8060

Analysis of the surveillance situation for viral encephalitis and meningitis in Europe

O Donoso Mantke (donosoo@rki.de)[1], A Vaheri[2], H Ambrose[3], M Koopmans[4], F de Ory[5], H Zeller[6], K Beyrer[7], A Windorfer[7], M Niedrig[1], representing the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD) Working Group for Viral CNS Diseases

1. Centre for Biological Safety (ZBS-1), Robert Koch-Institut, Berlin, Germany
2. Department of Virology, Haartman Institute, University of Helsinki, Finland
3. Centre for Infections, Health Protection Agency, London, United Kingdom
4. Laboratory for Infectious Diseases, Rijksinstituut voor Volksgezondheid en Milieu (National Institute of Public Health, RIVM), Bilthoven, the Netherlands
5. National Centre for Microbiology, Instituto de Salud Carlos III, Majadahonda, Spain
6. Unit for the biology of emerging viral infections (UBIVE), Institut Pasteur, Lyon, France
7. Governmental Institute of Public Health of Lower Saxony, Hanover, Germany

Infective processes in the brain, spinal cord and meninges are considered to be the main causes of encephalitis, myelitis and meningitis. However, most cases remain unexplained. The incidence of different viral aetiologies (zoonotic and non-zoonotic) is especially poorly estimated, due to the lack of a standard case definition and of agreed diagnostic algorithms, including harmonised diagnostic methods and sample collection. It is important to clarify the incidence of viral encephalitis/meningitis and to optimise the diagnosis of infectious neurological illness, particularly to ensure early recognition of outbreaks or emerging infections such as West Nile encephalitis. The European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD) has analysed the present surveillance situation for viral encephalitis/meningitis in Europe. Here we give an overview of the existing epidemiological sources of information in European Union (EU) Member States, mapping the laboratory capacity and identifying key requirements for a possible future surveillance study at European level. The data presented will help design a harmonised/standardised Europe-wide surveillance study investigating patients with encephalitis and/or meningitis in order to obtain more information on the role of infections in these rarely analysed syndromes, both from a clinical and an epidemiological perspective.

Introduction

Encephalitis is an irritation and inflammation of the brain parenchyma, associated with clinical evidence of brain dysfunction [1]. It often coexists with inflammation of the covering membranes of the brain and spinal cord (meningo-encephalitis). Meningeal irritation (e.g. fever, headache, general malaise, vomiting) and somnolence are signs of meningitis, while behavioural, cognitive and focal neurological symptoms and seizures are signs of the disruption of brain function. Like meningitis, encephalitis can be caused by a wide variety of infectious agents, including viruses, bacteria, fungi and parasites (Table 1). Those cases of aseptic encephalitis for which the aetiology can be determined are most often caused by viral infections: herpes simplex viruses (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), mumps virus, measles virus and enteroviruses are considered to be the major causes of viral encephalitis in immunocompetent individuals worldwide [2-5]. In addition to these common pathogens, which occur throughout Europe, arthropod-borne viruses (transmitted through insect and tick bites) can cause arboviral encephalitis with similar symptoms as herpes simplex encephalitis [6]. In Europe, the most important pathogens responsible for arboviral encephalitis are tick-borne encephalitis virus (TBEV), West Nile virus (WNV) and Sandfly fever virus (SFV) [7]. Important non-arthropod-borne viral zoonotic pathogens affecting the central nervous system (CNS) are lymphocytic choriomeningitis virus (LCMV), rabies virus and Nipah virus. In regions where they are endemic, illness due to these pathogens may be correctly diagnosed because clinicians will consider them in their differential diagnosis. However, it is more than likely that incursions of these viruses (with the probable exception of rabies virus) into new regions would not be diagnosed unless the number of cases increased to unusual levels. A fact sheet concerning epidemiological, clinical, diagnostic and treatment data for the most important viruses that may cause (meningo-) encephalitis is available at ENIVD's website, http://www.enivd.org.

Despite improvements in the diagnosis of viral encephalitis, including cerebrospinal fluid (CSF) PCR [8], the aetiology of up to 75% of encephalitis cases remained unknown in recent surveys [4]. This issue is challenging when considering early detection of new and (re-) emerging pathogens such as WNV [6,9] or potential outbreaks caused by deliberate release of pathogens [10]. An accurate diagnosis is important for surveillance activities aimed at clarifying the aetiological pattern of viral encephalitis/meningitis. However, this is impossible to achieve as long as routine investigations do not include the most common pathogens in a standardised manner. Moreover, a correct (differentiated) immediate diagnosis and the introduction of symptomatic or specific therapy may have a decisive influence on survival of patients, and may reduce the extent of brain injury.

Four studies are currently being conducted in Europe, aimed at clarifying the incidence of viral encephalitis/meningitis in humans at national level and obtaining more valid clinical and epidemiological data. Details on these studies are available from the following publications and websites:

1. A multi-centre prospective study to clarify the aetiology of encephalitis in England (2005-2008): http://www.hpa.org.uk/infections/topics_az/encephalitis/study.htm

TABLE 1

The most important infections causing central nervous system disease*

Meningitis	Encephalitis/ Meningo-encephalitis
Viral (aseptic meningitis)	**Viral**
Enteroviruses	Herpes simplex virus
Tick-borne encephalitis virus and other arboviruses†	Varicella-zoster virus
Mumps virus	Epstein-Barr virus
Herpesviruses	Mumps virus
Human immunodeficiency virus	Measles virus
Influenzaviruses	Enteroviruses
Parainfluenza virus	West Nile virus
Measles virus	Tick-borne encephalitis virus
Rotavirus	Other arboviruses†
Lymphocytic choriomeningitis virus	Human immunodeficiency virus
	Rabies virus
Bacterial (septic meningitis)	**Bacterial**
Haemophilus influenzae b	*Listeria monocytogenes*
Neisseria meningitidis	*Mycobacterium tuberculosis*
Streptococcus pneumoniae	*Mycoplasma pneumoniae*
Staphylococcus spp.	*Borrelia* spp.
Streptococcus spp.	*Rickettsia* spp.
Leptospira spp.	
Treponema pallidum	
Mycobacterium tuberculosis	
Borrelia spp.	
Fungal	**Fungal**
Cryptococcus neoformans	*Cryptococcus neoformans*
Parasitic	**Parasitic**
Acanthamoeba spp.	*Acanthamoeba* spp.
Toxoplasma gondii	*Naegleria* spp.

* adapted from: www.meduniwien.ac.at/hygiene; www.enivd.de/ENCDISEASES/fs_encdiseases.htm

† Arbovirus = arthropod-borne virus (e.g. Toscana virus)

2. The Meningitis/Encephalitis registration study in Lower Saxony, Germany (MERIN, 2003-open) and the German enterovirus surveillance study (2005-2007): http://www.nlga.niedersachsen.de
3. Epidemiological study to optimise the diagnosis and prognosis of encephalitis infections in France (2007): http://www.invs.sante.fr/surveillance/encephalites_2007/default.htm
4. A systematic laboratory-based surveillance of unexplained neurological illness to rule out flavivirus infection in The Netherlands [9].

ENIVD's current project involves a preliminary survey regarding the epidemiological situation of viral encephalitis in EU Member States. It is meant to identify the requirements for a possible future surveillance study at European level, as well as to improve the diagnostic methods and to carefully monitor the present situation especially regarding WNV, TBEV and SFV as potential emerging arboviral causes of encephalitis. The activities concerning the improvement of diagnostics and surveillance data planned by the individual ENIVD working groups for those arboviral pathogens will be presented in separate publications. In this study, the ENIVD working group for viral CNS diseases presents the results of a preliminary survey of the existing surveillance systems in Europe. A number of important issues are considered that will need to be addressed when designing a surveillance study on the aetiological pattern of viral encephalitis/meningitis at European level.

Methods

This preliminary data survey was performed from May 2006 to April 2007. PubMed (the United States' National Library of Medicine) was searched for relevant papers published between 1996 and 2006. The search terms selected were: "meningitis/encephalitis survey", "meningitis/encephalitis surveillance", "meningitis/encephalitis study", "meningitis/encephalitis epidemiology", and "meningitis/encephalitis diagnostics". Furthermore, epidemiological data were collected via internet searches or requested from national contact points by e-mail. The data were reported by national and/or regional public health authorities for infectious disease control (ministries of health, public health institutes and/or reference laboratories) or other organisations or networks (e.g. the International Scientific Working Group on Tick-borne Encephalitis) focussing on pathogens affecting the CNS. We decided to search/ask only for data from 2004 because this was the most recent year for which all datasets were completed and proofed. We focussed on "reported cases of bacterial meningitis/encephalitis", "reported cases of viral meningitis/encephalitis", and "reported cases of other or unknown aetiology".

The data were collected, analysed and verified by the national contact points in order to:

- gain an overview of the epidemiological situation in the EU Member States,
- identify existing resources that would be available in the event of a surveillance study (e.g. surveillance systems, public health institutes, clinical networks, hospitals, officially appointed laboratories, epidemiologists),
- review in particular the data on the causes of unknown aetiologies,
- and develop hypotheses on the reasons why these aetiologies are unknown.

Moreover, an expert meeting on diagnostics and surveillance of viral (meningo-) encephalitis held in Berlin in April 2006 provided information on previous, ongoing or planned national studies in six Member States that dealt with the incidence of the most relevant aetiologies of viral encephalitis/meningitis. The experiences gained from these studies are summarised here and should be taken into account in a possible future European surveillance study. This work included the selection of suitable partner institutions and clarification of whether samples would be available for further diagnostic investigation with special regard to the manner of sample collection. Furthermore, we defined the sample numbers necessary for such a study as well as established and evaluated diagnostic assays for the detection of different encephalitis-causing viral pathogens.

Results

The epidemiological situation of CNS diseases in Europe

The most recent epidemiological situation regarding CNS infections/syndromes in the 27 EU Member States (EU-27), based on disease notifications in 2004, is shown in Table 2. Bacterial causes of meningitis/encephalitis are thoroughly investigated in all Member States, at least judged by the presence of well-established surveillance infrastructures [11], and data were provided for all countries except for Belgium. In contrast, notification of viral meningitis/encephalitis cases differs between the countries because reporting policies are neither standardised nor rigorously enforced.

Although geographical differences in the occurrence of viral pathogens (either more common or endemic viruses) are likely to play a role, the variation in the incidence of viral meningitis/encephalitis across Europe that was seen in this survey is probably due to differences in the surveillance systems. One reason could be the lack of a Europe-wide standard case definition for viral CNS syndromes. Moreover, the spectrum of relevant viral pathogens reported in the surveillance systems depends on the spread of the diagnostic panels and/or notification regulations, and is therefore also very divergent.

The available diagnostic information was poor. Only few countries – namely Austria, the Czech Republic, Hungary, Poland, Slovakia, and Slovenia – could provide pathogen-specific data for more common (e.g. Herpesviruses) and endemic (e.g. TBEV) viral aetiologies. Those countries have or had a special endemic situation, and consequently a higher awareness of arboviral CNS diseases (in particular tick-transmitted ones). They may also be countries with a stronger interest to differentiate between more common and endemic aetiologies whose clinical pictures can be very similar.

Other countries only reported pathogen-specific data for major arboviral neurological diseases, like TBEV (e.g. the Baltic States, Germany and Finland) and WNV infections (e.g. Romania), without further differentiated reporting of other more common causes. Although endemic in several European countries, TBEV surveillance is not uniform nor always mandatory in Europe [12].

Only 15 (56%) of the 27 Member States provided some level of information on unexplained neurological illnesses of possible infectious aetiology. The lack of information on non-notifiable CNS syndromes in the other 12 countries indicates a data gap in surveillance. It is likely that more information is available on regional level or from surveys. This may be the case for enteroviruses, since all countries are obliged to document the absence of poliovirus circulation as part of the global eradication effort, but the data are not always publicly available. The Netherlands, for instance, has a continuous laboratory-based enterovirus surveillance that processes approximately 3,000 samples per from patients with meningitis per year. On average, 10% of those samples contain enterovirus. In addition, 400 cases are hospitalised with suspected viral meningitis in the Netherlands annually, 60 with suspected viral encephalitis, and 255 with encephalitis of unknown origin. "Suspected" means that the diagnosis derived from CSF could not be confirmed by virus detection or serology. However, the lack of data regarding the proportion of cases with other or unknown aetiology in the official notification report also makes a comparison among European countries difficult.

Existing expertise on CNS diseases in Europe

Based on literature and internet searches, we compiled a database of the specific diagnostic and/or epidemiological capacities and functions in European institutions and microbiological reference laboratories. The database has been updated regularly since the beginning of 2006, and includes 112 reference laboratories from the 27 EU Member States, covering the main bacterial and viral aetiologies of CNS infections (Table 3).

The number of staff employed in the diagnosis and control of infectious diseases who also handle pathogens that cause CNS disease ranged from five to 419 in the different Member States (including microbiologists and epidemiologists). The size of the groups can vary, depending on whether single groups/units or whole departments were described. The people working in these departments are often responsible for more than one kind of pathogen or disease. We have compiled a contact database with postal and e-mail addresses that also includes detailed information on the groups' capacities. The information can be provided on request.

The Czech Republic and Germany have the largest number of reference laboratories for pathogens causing CNS disease, followed by France and Belgium. Cyprus, Germany, Portugal and the United Kingdom have groups specialised in the diagnostics of viral CNS infections and syndromes. Of the 112 identified laboratories, 72 (64%) provide training activities for students and/or professional personnel. Seventy-eight laboratories (70%) organise and/or participate in external quality assurance (EQA) studies. However, only 31 (28%) laboratories were involved in outbreak investigations.

The most frequently reported techniques/activities with respect to the reference pathogens/diseases are antibody detection (69% of laboratories), molecular detection (of nucleic acid) (69%), typing/

Table 2

Epidemiological data: notifications of meningitis and encephalitis in Europe (EU-27) caused by bacterial and viral agents, reported in 2004*

Member State	Total population (x1000)[a]	Reported cases of bacterial meningitis/encephalitis (incidence/100,000)	Reported cases of viral meningitis/encephalitis (incidence/100,000)	Cases of other or unknown aetiology	Reference
Austria	8,171	**total: 126** mostly MNC (1.02); PNC (0.42)	**total: 59** TBE (0.66); Herpes (0.04); Measles (0.02)	20 bacterial meningitis; 14 viral meningo-encephalitis	Federal Ministry of Health, Family and Youth, BMGFJ, Austria
Belgium	10,400	not available[$]	not available[$]	not available[$]	Scientific Institute of Public Health, IPH, Belgium
Bulgaria	7,780	**total: 95** mostly MNC[b] (0.46); PNC (0.40)	**total: 699** without further information[c]	163 bacterial meningitis	National Centre of Health Informatics, NCHI, Bulgaria
Cyprus	826	**total: 5** MNC (0.61)	**total: 20** without further information[c]	9 other bacterial meningitis	Ministry of Health, Republic of Cyprus
Czech Republic	10,229	**total: 119** MNC[b] (0.96); HIB[b] (0.21)	**total: 667** TBE (4.96) ; EV (1.56)	166 other bacterial meningitis; 668 viral meningo-encephalitis	National Reference Centre for analysis of epidemiological data, NRC/SZU, Czech Republic
Denmark	5,414	**total: 266** mostly PNC (1.87); NB (1.57)	no cases reported[c]	26 bacterial meningitis	Public Health Institute, SSI, Denmark
Estonia	1,335	**total: 18** HIB (0.97); MNC (0.38)	**total:182** TBE (13.63)	18 other and unknown aetiology	Health Protection Inspectorate, Estonia
Finland	5,235	**total: 1,117** mostly STC[b] (20.48); MNC[b] (0.84)	**total: 29** TBE (0.55)	not available	National Public Health Institute, KTL, Finland
France	60,257	**total: 1,439[†]** mostly STC (1.46); MNC (0.73)	no cases reported[c]	not available	National Public Health Institute, InVS, France
Germany	82,645	**total: 531** mostly MNC (0.46); NB (0.6)[‡]	**total: 125** TBE (0.15)	not available	Robert Koch Institute, RKI, Germany
Greece	11,098	**total: 168** mostly MNC (0.80); PNC (0.64)	**total: 199** without further information[c]	376 bacterial meningitis / encephalitis; 177 other and unspecified aetiologies	Hellenic Centre for Infectious Diseases Control, KEEL, Greece
Hungary	10,124	**total: 201** mostly PNC (0.75); MNC (0.42)	**total: 122** TBE (0.75); Herpes (0.16); EV (0.15); WNV (0.03) etc.	64 infectious encephalitis; 148 meningitis	National Centre for Epidemiology, OEK, Hungary
Ireland	4,080	**total: 225** mostly MNC[b] (4.85); PNC (0.54)	**total: 28** without further information[c]	36 other bacterial meningitis	Health Protection Surveillance Centre, HPSC, Ireland
Italy	58,033	**total: 748** mostly MNC (0.59); STC (0.58)	**total: 434** without further information[c]	236 bacterial meningitis	National Public Health Institute, ISS, Italy
Latvia	2,318	**total: 25** MNC[b] (1.04); HIB[b] (0.04)	**total: 251** TBE (10.83)	not available	State Agency "Public Health Agency", SVA, Latvia
Lithuania	3,443	**total: 101** MNC[b] (2.67); HIB[b] (0.26)	**total: 425** TBE (12.34)	not available	Centre for Communicable Disease Prevention and Control, ULPKC, Lithuania
Luxembourg	459	**total: 0** no cases in 2004, in previous years *N. meningitidis*	no cases reported[c]	not available	Ministry of Health, Health Management, Luxembourg
Malta	400	**total: 15** mostly PNC (1.75); MNC (1.00)	**total: 2** without further information[c]	5 bacterial meningitis	Ministry of Health, Public Health Department, DSU, Malta
Poland	38,559	**total: 433** mostly MNC (0.31); HIB (0.19)	**total: 308[§]** TBE (0.68)	512 bacterial, 1,119 viral meningitis/encephalitis; 353 other and unspecified aetiologies	National Institute of Hygiene, PZH, Poland
Portugal	10,441	**total: 91** MNC (0.81); HIB (0.06)	no cases reported[c]	not available	National Public Health Institute, DGS, Portugal
Romania	21,790	**total: 467** MNC (1.13)	**total: 989[c]** WN meningitis (0.01)	not available	Institute of Public Health, ISPB, Romania
Slovakia	5,401	**total: 81** MNC (0.58); PNC (0.41)	**total: 207** TBE (1.29); Herpes (0.19); VZV (0.17) etc.	103 bacterial meningitis; 40 unknown viral meningitis / encephalitis	Public Health Authority of the Slovak Republic
Slovenia	1,967	**total: 29** mostly STC (0.81); MNC (0.31)	**total: 232** mostly TBE (10.37); Herpes (0.76)	25 bacterial meningitis / encephalitis; 187 unknown viral meningitis / encephalitis	Public Health Institute of the Republic Slovenia
Spain	42,646	**total: 881** MNC[b] (2.22)	no cases reported[c]	not available	National Public Health Institute Carlos III, ISCIII-CNE, Spain
Sweden	9,008	**total: 565** mostly PNC[b] (4.66); HIB[b] (0.89)	**total: 222** without further information[c]	not available	Institute for Infectious Disease Control, SMI, Sweden
The Netherlands	16,226	**total: 297** MNC[b] (1.83)	no cases reported[c]	not available	National Institute of Health and the Environment, RIVM, Netherlands
United Kingdom	59,479	**total: 916** mostly MNC (0.93); PNC (0.29)	**total: 217** without further information[c]	294 meningitis	Health Protection Agency, HPA, UK

* As reported by the national/regional public health authorities for infectious disease control (ministries of health, public health institutes, reference laboratories). When comparing the data across countries, please note that reporting criteria may vary. Incidence rates were calculated per 100,000 inhabitants.

[a] General public health statistics: http://www.who.int/about/regions/euro/en/index.html
[b] Classified as invasive bacterial disease with a broad case definition (including cases of meningitis and septicaemia).
[c] TBE is not a notifiable disease in this country.
[$] Data are not available due to incomplete surveillance network.
[†] Number of cases adjusted for the coverage of a clinical laboratory network as well as corrected for under-notification and incidences calculated per 100,000 inhabitants for meningitides with or without bacteraemia, Epibac 2004, Metropolitan, France (http://www.invs.sante.fr/surveillance/epibac/default.htm).
[‡] Incidence is based on the notification from six federal states (Berlin, Brandenburg, Mecklenburg Western Pomerania, Saxony, Saxony-Anhalt and Thuringia) with a total of 13,433,358 inhabitants.
[§] Until 2005 meningitis in the course of other infectious diseases such as mumps were not reported.

EV: Enteroviruses; HIB: *H. influenzae* type b; MNC: Meningococci; NB: Neuroborreliosis; PNC: Pneumococci; STC: *Streptococcus* spec.; TBE: Tick-borne encephalitis; VZV: Varicella-zoster virus; WN(V): West Nile (virus).

TABLE 3

List of existing resources for the surveillance of meningitis and encephalitis in Europe (EU-27) (data as reported)*

Member State	Number of ref. labs	Pathogens-	Number of staff involved	Number of labs providing training	Number of labs involved in EQA	Number of labs involved in outbreak situation
Austria	5	LB; HIB; MMR; MNC; PNC; Polio virus; TBEV; other relevant viruses	60	5	4 (1)[a]	2
Belgium	10 (2)[a]	LB; EV; HIB; Morbilliviruses; MNC; Polio virus; Rabies virus; PNC; TBEV; WNV	> 98	6 (2)[a]	6 (4)[a]	1 (2)[a]
Bulgaria	9	LB; MNC; STC; EV; MMR; Herpesviruses; other pathogens	56	3	7 (2)[a]	1
Cyprus	2[†]	EV, Herpesviruses (viral meningitis); other relevant pathogens (MNC, PNC, HIB)	> 5	1	not reported	not reported
Czech Republic	14	STC; MNC; HIB; Herpesviruses; MMR; EV; LB; Arboviruses (incl. TBEV); other relevant pathogens	172	11	12 (2)[a]	1
Denmark	2	EV; MMR; other relevant viruses; PNC; other relevant bacteria	241	2	2	1
Estonia	3 (1)[a]	MNC; HIB; LB; other bacteria; TBEV; EV; other viruses	25	not reported	2 (1)[a]	not reported
Finland	4	PNC; MNC; HIB; EV; MMR; *M.tuberculosis*; Arboviruses; other relevant pathogens	375	1	4	1
France	10	Arboviruses; LB; EV; HIB; *Listeria*; Measles virus; MNC; PNC; Rabies virus; STC	154	5	5 (5)[a]	3
Germany	11	LB; MNC; STC; MMR; EV; HIB; Herpes virus; VZV; Rabies virus; TBEV; viral CNS infections	175	7	6 (5)[a]	4
Greece	3 (1)[a]	MNC; STC; HIB; other relevant viruses	> 16	1(1)[a]	2(1)[a]	2(1)[a]
Hungary	2	MNC; EV; other relevant pathogens	49	2	2	not reported
Ireland	2 (1)[a]	MNC; HIB; other relevant viruses	> 17	1(1)[a]	1(1)[a]	1(1)[a]
Italy	2	LB; EV; HIB; MNC; STC; other relevant pathogens	419	2	1(1)[a]	1
Latvia	1	TBEV; LB; Herpes virus; CNS bacterial infections	> 35	1	1	not reported
Lithuania	1	LB; EV; TBEV; Herpes virus; Measles virus; other relevant viruses	24	not reported	1	not reported
Luxembourg	1	MNC; HIB; Measles virus; other relevant pathogens	25	1	not reported	not reported
Malta	1	PNC; HIB; MNC; other relevant pathogens	11	1	not reported	1
Poland	3	STC; Herpesviruses, EV; Arboviruses; bacterial meningitis (incl. MNC and HIB)	> 4	3	2 (1)[a]	not reported
Portugal	3	MNC; HIB; Viral CNS infections; vector-borne pathogens (i.e. *Borrelia*, WNV); other relevant pathogens	144	3	3	3
Romania	1	LB; STC; MNC; HIB; vector-borne diseases; other relevant pathogens	31	1	1	not reported
Slovakia	3	MNC; HIB; Arboviruses; other relevant pathogens	152	1	2(1)[a]	not reported
Slovenia	2 (1)[a]	MNC; HIB; Arboviruses; other relevant pathogens (incl. TBEV, STC)	> 92	1(1)[a]	1(1)[a]	not reported
Spain	6	MNC; PNC; HIB; Herpes-, Entero-, and Arboviruses; other relevant viral pathogens	18	6	6	6
Sweden	3	MNC; other relevant pathogens	404	2	3	not reported
The Netherlands	2	Bacterial meningitis; other relevant pathogens (incl. arboviruses)	> 3	1	1(1)[a]	1
United Kingdom	6 (1)[a]	LB; MNC; STC; HIB; viral CNS infections; other relevant pathogens	> 100	4	3 (3)[a]	3

* Represents laboratories officially designated as reference laboratories (Ref. labs) for the specific pathogens/diseases, or laboratories that act as national reference centres without being officially recognised as such. Even though these laboratories are considered as a resource at national/international level by their national public health authorities, the definition of "laboratory" can vary across countries as it can include groups of different size. The number of laboratories *per se* should therefore be read with caution and additional information should be sought.

[a] Not all laboratories have presented data regarding their capacities/activities. The number in brackets shows the number of laboratories without further information (partial/complete).

[†] Reference laboratory services for MNC are done by a group in another Member State.

EQA: external quality assurance; CNS: Central nervous system; EV: Enteroviruses; HIB: *H. influenzae* type b; LB: Lyme borreliosis; MMR: Measles, Mumps and Rubella; MNC: Meningococci; PNC: Pneumococci; STC: *Streptococcus* spec.; TBEV: Tick-borne encephalitis virus; VZV: Varicella-zoster virus; WNV: West Nile virus

Table 4

Overview of six different studies at national level to clarify the aetiology of viral encephalitis/meningitis

Country	Status of study	Number of cases	Pathogens	Type of samples	Applied diagnostic	Unknown aetiology	Further investigation
Finland	Recently completed† Period: 1995-1996	3,231	VZV HSV Enteroviruses Influenza A virus HHV-6 TBEV Puumala virus Inkoo ortho-bunyavirus	CSF Sera	• CSF-PCR • Intrathecal antibody screen by EIA • Systemic sero-conversion measure • Multiplex-PCR and oligionucleotide microarray (new)	30-40 %	• aetiology of aseptic meningitis in an adult population • viral aetiology of CNS infections in children • viral CNS infections in adults
United Kingdom	Ongoing Period: 2005-2008	100 / year	HSV VZV EBV Mumps virus Measles virus Enteroviruses Arboviruses	CSF Blood Throat/naso-pharyngeal swab Faeces Post-mortem tissue	• CSF-PCR • Serology • Intrathecal antibody screen • Generic amplification for unknown and unrecognised infections (e.g. SISPA)	60%	• implement a special pathogen branch
The Netherlands	Recently completed‡ Period: 1999-2003	1,276	Herpesviruses Enteroviruses Adenovirus Measles virus Mumps virus	CSF	Broad variability of lab tests	59%	• enhanced ongoing surveillance for WNV (and other arboviruses) with approx. 300 CSF samples per year
Germany	Ongoing MERIN: 2003-open National Enterovirus-Surveillance: 2005-2007	1,191 (2003-2006) 514 (April 2006)	*Borrelia* Enteroviruses HSV VZV Adenoviruses Influenza A/B virus EBV CMV Mumps virus others on special request (e.g. TBEV)	CSF Faeces Sera Throat swab	• PCR • Serology • Intrathecal antibody screen • CFT • Virus isolation/ typing	66% (MERIN)	• further promotion of the MERIN project • further romotion of the national project
France	Planned: 2006-2009 (incl. follow-up)	ca. 600 /year	HSV VZV EBV HHV-6 Enteroviruses Adenoviruses CMV Influenza A/B virus Measles/ Mumps virus Arboviruses (WNV, Toscana virus, TBEV)	CSF Blood Sera Throat swab Urine	• PCR • Serology	80 %§	• project started 2007 • promotion open
Spain	Planned: for one year	600 (adults) 400 (children)	Herpesviruses Enteroviruses Adenoviruses Measles/ Mumps virus Toscana virus WNV and other flaviviruses LCMV and rabies virus	CSF Sera	• Generic PCR • Serology • Intrathecal antibody screen	unknown rate	• project not fixed

† Ref. [5]; ‡ ISIS database, RIVM, The Netherlands; § Data from PMSI and InVS, France.

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HHV-6: Human herpes virus 6; HSV: Herpes simplex virus; LCMV: Lymphocytic choriomeningitis virus; TBEV: Tick-borne encephalitis virus; VZV: Varicella-zoster virus; WNV: West Nile virus.

CFT: Complement fixation test; CNS: Central nervous system; CSF: Cerebrospinal fluid; EIA: Enzyme immunoassay; SISPA: Sequence independent single primer amplification.

subtyping (64%), antibiotic resistance/immunity testing (55%), isolation of reference pathogens (53%), microbiological analyses (46%), antigen detection (40%), providing reference material, e.g. diagnostic reagents (23%) and electron microscopy (11%) (data not shown).

Key conditions for a future surveillance study at the European level

Based on the expert meeting in Berlin in 2006, data were obtained from previous, ongoing or planned studies in six Member States in order to clarify the incidence of the most relevant aetiologies of viral encephalitis/meningitis at national level. Table 4 shows a broad variability among these studies concerning the pathogens they focussed on, the type of samples they used, the diagnostic methods they applied and the determined or calculated rate of unknown aetiology.

The consensus was that comparative data for the incidence of most viral agents of human (meningo-) encephalitis is missing. The proportion of cases with unknown aetiology ranged from 30% to 80% in the presented studies. The reasons for unknown diagnosis could be traced to either a failure of the diagnostic tests or an inappropriate case definition, resulting in under-ascertainment of both known viruses and "new" viruses.

The following issues were considered during the expert meeting in order to design a possible future surveillance study for viral (meningo-) encephalitis at the European level:

Case definition

The diagnosis of encephalitis is often difficult to establish, since many other clinical conditions may mimic encephalitis. In addition, several arboviruses can cause a range of neurological syndromes, including meningitis or paralytic illness. Therefore, a broad case definition will be necessary in order to capture all relevant cases of acute and suspected CNS diseases (meningitis, encephalomyelitis and encephalitis) in the first stage of a study. To date, there is no standard clinical case definition that includes all relevant types of infectious CNS diseases, although this would be practical from a clinical perspective. A limited case definition (e.g. one that excludes signs of aseptic meningitis) could lead to under-ascertainment of relevant cases. A distinction between the different disease types with the final goal of identifying a specific aetiological agent could be achieved in following processes. To harmonise the clinical and diagnostic approaches in a European study, all personnel involved in case notification should be informed of such a standard case definition and should be provided with a protocol for stringent data management and diagnostic algorithms. It may become necessary to adapt specific case definitions to the situation in different countries, for example if certain pathogens are endemic in some but not other areas. Therefore, the EU case definitions currently being finalised by the European Centre for Disease Prevention and Control (ECDC) should be taken into account.

Sample collection and storage

Regarding the collection of samples, it should be considered that other types of samples besides CSF (e.g. sera, faeces, throat swabs) are also important when trying to detect a broad spectrum of relevant pathogens. Basic clinical information should always be provided with the sample material. A minimum dataset should include: age, gender, domicile of the patient, date of onset/duration of the complaints, type of complaints, travel history, vaccination history (e.g. against yellow fever, Japanese encephalitis) and context of the current epidemiological situation (e.g. outbreak, cluster).

Follow-up studies may become necessary, for example if clinical intervention measures become available in the future or new pathogens are discovered. Therefore, samples of selected cases should be shipped to a central archive, aliquoted and stored at -70°C to avoid damage of the material by frequent thawing. Sample collection along with the recommended minimum dataset will be a valuable resource for later analysis of patients' and diagnostic profiles.

Diagnostic issues

A three-step model is suggested for diagnostic procedures in order to ensure comprehensive diagnostic investigation. The first step should include the local medical investigation and usual analysis (PCR and serology) of acute cases by clinical laboratories. Clinical and epidemiological features (e.g. occupation, travel history or animal contact) should be collected at this level for differential diagnostic approaches. The second step comprises the extended analysis of suspected cases by reference laboratories for commonly recognised causes of (meningo-) encephalitis, and of less commonly recognised and travel-related causes when indicated. The third step includes the identification of specific pathogens (e.g. by new typing methods) in cases of unknown aetiology, as well as the collection of selected samples by reference laboratories and storage in a centralised archive for future use.

Standard operating procedures for testing should be shared among all participating laboratories and regularly monitored by EQA programmes to ensure diagnostic consistency. In its current project, the ENIVD has begun EQA studies for the diagnostics of TBEV and WNV [13-15], and further studies on arboviral aetiologies of CNS diseases are planned [16]. Moreover, it might be advantageous to consider the new multiplex-microarray technology presented in the Finnish study (see Table 4) [17,18] in a broad European study on viral CNS diseases. This would guarantee a unique analysis platform for all participating laboratories by including the more common pathogens of viral CNS diseases (e.g. HSV, VZV, enteroviruses) as well as relevant viral zoonotic agents (e.g. TBEV, WNV, rabies virus) according to the regional/endemic situation of the European countries or on special request.

Data management

A prerequisite for a surveillance study at European level – in which data from numerous countries are pooled – seems to be the establishment of a central hub recording and managing the entire study data (patients' clinical and epidemiological data, and CNS diagnostic data). To ensure standardised reporting, ICD-10 coding is recommended in addition to the broad case definition.

A general problem in most of the national studies presented here was the failure of clinicians to report clinical cases. The contribution of the individual clinicians regarding the provision of clinical data and material varied greatly depending on hospital and medical branch (paediatricians, for example, seemed to be more cooperative than neurologists). Efforts to reach a final aetiological diagnosis are not always considered essential, for instance when all patients diagnosed with viral encephalitis are routinely given the same antiviral therapy. The success of a study depends on the voluntary cooperation of hospitals and clinicians. One of the important issues is to motivate them, for example by offering clinicians and public health officers open access to evaluated and updated study data on the internet or free diagnostic tests.

Ethical and data protection issues

Ethical issues regarding patient data will be especially relevant in follow-up studies. These concerns might not be important during the first contact when diagnostic analysis for the aetiology of CNS disease is requested by clinicians. Nevertheless, all further analysis will require a patient agreement. It became clear during the expert meeting that this is handled quite differently in the European countries. This aspect therefore needs special attention in planning a European study and should be discussed with the different European public health authorities.

Number of samples necessary for a European study

According to the data available, the UK study recorded approximately 100 cases of viral encephalitis per year. This covers an estimated 60% of all cases of viral CNS disease in England. The experts give a ratio of 1:2:0.5 cases for encephalitis:mening itis:encephalomyelitis. The true number of all cases of viral CNS disease, based on a broad case definition as recommended above, is therefore five- to six-fold higher than the number of recorded cases. For the UK study, this was calculated to be approximately 700 cases. Based on this calculation, the expected number of viral CNS disease cases in a given country can be estimated by taking

Table 5

Estimated number of cases for a possible future study on viral central nervous system diseases in Europe*

Country	Population (x1000)[a]	Total expected number of cases per year	Number of cases per 10^5 inhabitants	Number of cases for 60 % coverage
England	50,431[†]	700	1.39	420
Austria	8,189	340[b]	4.15	200
Belgium	10,419	145	1.39	90
Bulgaria	7,726	990[b]	12.81	590
Cyprus	835	80[b]	9.58	50
Czech Republic	10,220	3,780[b]	36.97	2,270
Denmark	5,431	80	1.47	50
Estonia	1,330	250[b]	18.79	150
Finland	5,249	1,750[‡]	33.34	1,050
France	60,496	4,170[§]	6.89	2,500
Germany	82,689	1,800	2.18	1,080
Greece	11,120	275[b]	2.47	165
Hungary	10,098	370[b]	3.66	220
Ireland	4,148	100[b]	2.41	60
Italy	58,093	1,150	1.98	690
Latvia	2,307	310[b]	13.44	190
Lithuania	3,431	530[b]	15.45	320
Luxembourg	465	7	1.50	4
Malta	402	6	1.50	4
Poland	38,530	2,500[b]	6.49	1,500
Portugal	10,495	150	1.43	90
Romania	21,711	930[b]	4.28	560
Slovakia	5,401	430[b]	7.96	260
Slovenia	1,967	1,000[b]	50.84	600
Spain	43,064	850	1.98	510
Sweden	9,041	180	1.99	110
The Netherlands	16,299	1,330[$]	8.16	800
				Expected total: ~ 15.000

* Including encephalitis, meningitis, encephalomyelitis.

[a] With the exception of England, data adapted from: http://www.who.int/about/regions/euro/en/index.html (actual numbers)

[b] Estimation adapted to data from existing infectious disease reports of last years ('04, '05 and/or '06), as available

[†] Source: http://www.statistics.gov.uk/CCI/nugget.asp?ID=6 (last mid-year population estimates from UK)

[‡] Estimation based on data from Ref. [5].

[§] Estimation based on data as presented for the French study.

[$] Estimation based on data as presented for the Dutch study.

into account the respective population (with or without adaptation to existing differentiated epidemiological data) (Table 5).

The calculated numbers are only rough estimations, but can be used as a general indication of how many samples, material and work would eventually be necessary to cover approximately 60% of all cases in the respective countries. Thus, these estimates may have a limited relevance to the actual incidence of viral CNS diseases in any country.

However, the data in Table 5 show that a possible future study on viral CNS diseases at European level could be extensive regarding samples, logistics, material and costs, if all cases were analysed for all relevant aetiologies including differential diagnostics.

Discussion

The incidence of most viral agents of human (meningo-) encephalitis is not estimated well by the surveillance systems of the various European countries. This harbours the risk that potential emerging infectious diseases, such as West Nile fever, will not be recognised in time by the existing surveillance infrastructures [19]. Pooling data from several countries may help identify and monitor emerging problems more quickly. Establishing a European surveillance system for viral encephalitis/meningitis by bundling the existing resources and introducing a harmonised/standardised reporting and diagnostic system will be challenging, but is essential, and not only for future preparedness and response issues. With more specific treatments or vaccines becoming available [1,20], it will also be of interest for pharmaceutical and vaccine-producing companies and public health institutions to carefully analyse the epidemiological situation, and to adapt therapeutic interventions as well as prevention strategies accordingly. A broad standard case definition and harmonised/standardised diagnostic algorithm using a multiplex-microarray system validated for a wide range of viruses may help to discover the true incidence and aetiological pattern of viral encephalitis/meningitis within each country. This would guarantee high performance and comparability of the results consistent with EQA programmes. To improve surveillance, it is also important to quantify the extent of cases of unknown aetiology, in order to allow a comparison of the data from each country and to identify possible weaknesses in the surveillance data. Therefore, clinicians must be motivated to report all cases of viral encephalitis/meningitis and to reach a definitive aetiological diagnosis.

A future study on viral CNS diseases at European level could be extensive in work load and costs; an alternative is a survey including only a small number of countries with experts willing to cooperate and to set up such a study, in order to improve the awareness and ascertainment of viral CNS diseases. Partners interested in collaborating in a European survey network on viral CNS diseases have already been identified in 13 countries in different European regions (the Czech Republic, Poland, Russia, Slovakia, Slovenia, France, Spain, Switzerland, Denmark, Finland, Germany, the Netherlands and United Kingdom). It is advisable to use the experience and knowledge of recently completed or ongoing studies at national level (see Table 4) to allow more detailed planning of a prospective European study on viral encephalitis/meningitis.

A European study based on a close cooperation between clinicians, epidemiologists and microbiologists will provide more accurate and timely data on viral CNS diseases which are of public health interest. Such an initiative could help increase case ascertainment, reduce the rate of unknown aetiologies, develop and validate new diagnostic methods, improve recommendations and guidelines, and gain more valuable clinical and epidemiological data for research purposes.

Acknowledgements

This ENIVD study was funded by the European Commission's Directorate-General for Health and Consumer Protection (DG SANCO) under the programme AIDS and other communicable diseases grant No. 2004206. Further members of the ENIVD working group for viral CNS diseases are: Stephan Aberle, Medical University of Vienna, Austria; Raija Vainionpaa, University of Turku, Finland; Eckart Schreier, Robert Koch-Institut, Berlin, Germany; Milan Labuda, Slovak Academy of Sciences, Bratislava, Slovakia; Tatjana Avšic-Županc, Medical Faculty of Ljubljana, Slovenia; David Brown, Health Protection Agency, United Kingdom. We are indebted for further information regarding the national surveillance system to: Iva Christova, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria; Olga Kalakouta, Ministry of Health, Nicosia, Cyprus; Kuulo Kutsar, Health Protection Inspectorate, Tallinn, Estonia; Georgina Tzanakaki, National School of Public Health, Athens, Greece; Margaret A. Fitzgerald, Health Protection Surveillance Centre, Dublin, Ireland; Adriana Pistola, Cantacuzino Institute, Bucharest, Romania; Margareta Sláciková, Public Health Authority of the Slovak Republic, Bratislava, Slovak Republic; Rosa Cano, Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain; Genevieve Ducoffre, Scientific Institute of Public Health, Brussels, Belgium; and Patrick Hau, Ministère de la Santé, Luxembourg. We thank Ursula Erikli and Regina Schädler for critically reading the manuscript.

The authors wish to dedicate this work to the memory of Dr. Milan Labuda (*22.03.1945 – †31.08.2007).

References

1. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, et al. Viral encephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2005;12(5):331-43.
2. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis. 2006;43(12):1565-77.
3. Davison KL, Crowcroft NS, Ramsay ME, Brown DWG, Andrews NJ. Viral encephalitis in England 1989-1998: what did we miss? Emerg Infect Dis. 2003;9(2):234-40. Available from: http://www.cdc.gov/ncidod/eid/vol9no2/02-0218.htm
4. Glaser CA, Gilliam S, Schnurr D, Forghani B, Honarmand S, Khetsuriani N, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. Clin Infect Dis. 2003;36(6):731-42.
5. Koskiniemi M, Rantalaiho T, Piiparinen H, von Bonsdorff CH, Farkkila M, Jarvinen A, et al. Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. J Neurovirol. 2001;7(5):400-8.
6. Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. Lancet. 2002;359(9305):507-13.
7. Kallio-Kokko H, Uzcategui N, Vapalahti O, Vaheri A. Viral zoonoses in Europe. FEMS Microbiol Rev. 2005;29(5):1051-77.
8. DeBiasi RL, Tyler KL. Molecular methods for diagnosis of viral encephalitis. Clin Microbiol Rev. 2004;17(4):903-25.
9. Rockx B, van Asten L, van den Wijngaard C, Godeke GJ, Goehring L, Vennema H, et al. Syndromic surveillance in the Netherlands for the early detection of West Nile virus epidemics. Vector Borne Zoonotic Dis. 2006;6(2):161-9.
10. Bossi P, Tegnell A, Baka A, Van Loock F, Hendriks J, Werner A, et al. BICHAT guidelines for the clinical management of bioterrorism-related viral encephalitis. Euro Surveill. 2004;9(12):1-9. Available from: http://www.eurosurveillance.org/em/v09n12/0912-240.asp
11. Trotter CL, Chandra M, Cano R, Larrauri A, Ramsay ME, Brehony C, et al. A surveillance network for meningococcal disease in Europe. FEMS Microbiol Rev. 2007;31(1):27-36.
12. Günther G, Lindquist L. Surveillance of tick-borne encephalitis in Europe and case definition. Euro Surveill. 2005;10(1):2-3. Available from: http://www.eurosurveillance.org/em/v10n01/1001-221.asp
13. Niedrig M, Linke S, Zeller H, Drosten C. First international proficiency study on West Nile virus molecular detection. Clin Chem. 2006;52(10):1851-4.

14. Donoso Mantke O, Aberle SW, Avsic-Zupanc T, Labuda M, Niedrig M. Quality control assessment for the PCR diagnosis of tick-borne encephalitis virus infections. J Clin Virol. 2007;38(1):73-7.

15. Niedrig M, Avsic T, Aberle SW, Ferenczi E, Labuda M, Rozentale B, et al. Quality control assessment for the serological diagnosis of tick borne encephalitis virus infections. J Clin Virol. 2007;38(3):260-4.

16. Niedrig M, Donoso Mantke O, Schädler R. The European Network for Diagnostics of Imported Viral Diseases (ENIVD) – 12 years of strengthening the laboratory diagnostic capacity in Europe. Euro Surveill. 2007;12(4):E070419.5. Available from: http://www.eurosurveillance.org/ew/2007/070419.asp#5

17. Jääskeläinen AJ, Piiparinen H, Lappalainen M, Koskiniemi M, Vaheri A. Multiplex-PCR and oligonucleotide microarray for detection of eight different herpesviruses from clinical specimens. J Clin Virol. 2006 Oct;37(2):83-90. Epub 2006 Jul 26.

18. Jokela P, Joki-Korpela P, Maaronen M, Glumoff V, Hyypiä T. Detection of human picornaviruses by multiplex reverse transcription-PCR and liquid hybridization. J Clin Microbiol. 2005 Mar;43(3):1239-45.

19. Zeller H, Schuffenecker I. West Nile virus: an overview of its spread in Europe and the Mediterranean basin in contrast to its spread in the Americas. Eur J Clin Microbiol Infect Dis. 2004;23(3):147-56.

20. Chang GJ, Kuno G, Purdy DE, Davis BS. Recent advancement in flavivirus vaccine development. Expert Rev Vaccines. 2004;3(2):199-220.

This article was published on 17 January 2008.

Citation style for this article: Donoso Mantke O, Vaheri A, Ambrose H, Koopmans M, de Ory F, Zeller H, Beyrer K, Windorfer A, Niedrig M, representing the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD) Working Group for Viral CNS Diseases . Analysis of the surveillance situation for viral encephalitis and meningitis in Europe. Euro Surveill. 2008;13(3):pii=8017. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8017

High rates of metallo-beta-lactamase-producing *Klebsiella pneumoniae* in Greece - a review of the current evidence

A Vatopoulos (avatopou@nsph.gr)[1]
1. Department of Microbiology, National School of Public Health, Athens, Greece

For the last four years Greece has faced a large number of infections, mainly in the intensive care units (ICU), due to carbapenem-resistant, VIM-1-producing Klebsiella pneumoniae. The proportion of imipenem-resistant *K. pneumoniae* has increased from less than 1% in 2001, to 20% in isolates from hospital wards and to 50% in isolates from ICUs in 2006. Likewise, in 2002, these strains were identified in only three hospitals, whereas now they are isolated in at least 25 of the 40 hospitals participating in the Greek Surveillance System. This situation seems to be due to the spread of the blaVIM-1 cassette among the rapidly evolving multiresistant plasmids and multiresistant or even panresistant strains of mainly *K. pneumoniae* and also other *enterobacter*ial species. However, the exact biological basis of this phenomenon and the risk factors that facilitate it are not yet fully understood. Moreover, the fact that most strains display minimum inhibitory concentration (MIC) values below or near the Clinical Laboratory Standard Institute (CLSI) resistance breakpoint create diagnostic and therapeutic problems, and possibly obstruct the assessment of the real incidence of these strains.
An evidence-based consensus on the therapeutic strategy for these infections is urgently needed. The problem of VIM-producing *K. pneumoniae* was timely recognized by the Greek System for the Surveillance of Antimicrobial Resistance and various guidelines, including advice on antibiotic policy and infection control, were developed by the National Centre for Disease Control and Prevention. However, these measures have yet had a relatively small impact on the situation. The best way to handle the problem of antibiotic resistance would be the development and implementation of a national integrated strategic action plan (currently under development) affirming the political commitment of the public health administration in confronting this issue.

Introduction

Resistance to carbapenem due to the production of metallo-beta-lactamases (MBL) in Gram-negative organisms is an increasing international public health problem [1,2]. The problem of MBL-producing strains in Europe was originally confined to *Pseudomonas aeruginosa*. *P. aeruginosa* harbouring MBL of the VIM-1 type were first isolated in 1997 in Italy [3] and France [4].

In Greece the first outbreak of *P. aeruginosa* harbouring MBL occurred in a hospital in Thessaloniki in 1996, and was reported in 2000 [5]. This enzyme was soon identified as VIM-2, an enzyme similar but not identical to VIM-1 [6]. By 2001, a multicentre study revealed that VIM-2-producing *P. aeruginosa* had already been isolated in nine out of 18 hospitals examined [7].

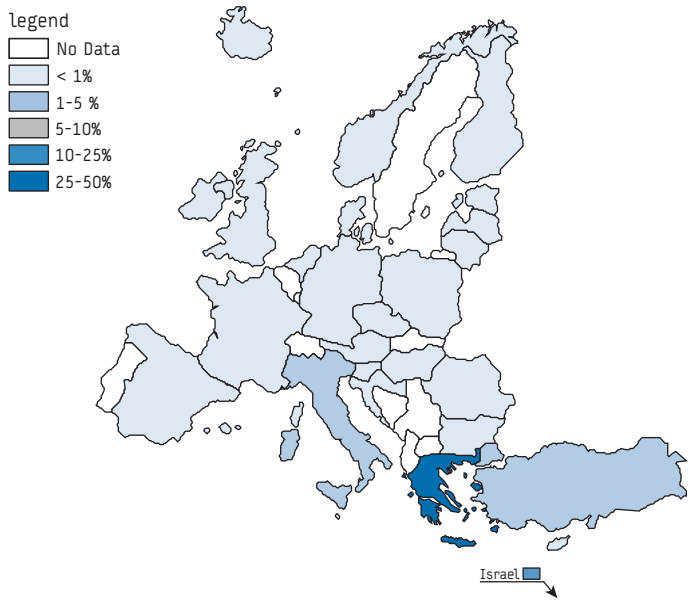
In the above context, the isolation of VIM-producing enteric bacteria (mainly *K. pneumoniae*, but also *Escherichia coli*, *Proteus mirabilis*, *Enterobacter* spp and other) in Greece since November 2001 seems to be an important new chapter in the epidemiology of this resistance mechanism.

It must be noted that sporadic isolates and small outbreaks of VIM-producing enteric bacteria have been reported in some European and Mediterranean countries [8-11], with the strains being traced back to Greece on some occasions [12]. However, Greece seems to be the only country where these clinical strains are isolated in high numbers (Figure 1). This constitutes a major public health problem for Greece and also a possible threat for the rest of Europe.

The purpose of this report is to review the current knowledge concerning the epidemiology, microbiology, molecular biology,

Figure 1

Proportion of carbapenem-resistant *Klebsiella pneumoniae* isolates in EARSS participating countries, 2006.



Data from European Antimicrobial Resistance Surveillance System (EARSS), http://www.rivm.nl/earss/database/

clinical management as well as the public health issues related to this problem.

The review is mainly based on reports published by all scientific groups working in the area of antibiotic resistance in Greece. These papers were retrieved by a systematic Medline search.

In addition, data concerning the magnitude and the development of the problem of VIM-producing enteric bacteria were derived from the Greek System for the Surveillance of Antimicrobial Resistance (GSSAR, http://www.mednet.gr/whonet) which has been in operation since 1996, and currently involves 40 hospitals around Greece. GSSAR participates in the European Antimicrobial Resistance Surveillance System (EARSS) and is in charge of the continuous analysis of the routine data generated in the hospital microbiology laboratories with the aid of the WHONET software. A brief description of the system can be found elsewhere [13].

Description of the situation

The first VIM-producing enteric bacterium in Greece was an *E. coli* isolated in November 2001, and reported early in 2003, in a hospital in Piraeus [14]. Since then VIM-producing *E. coli* have been reported sporadically [15,16], and hospital outbreaks have also occurred [17].

VIM-producing *K. pneumoniae* were first reported between September and December 2002 in the intensive care units (ICUs) of three teaching hospitals located in Athens [18]. The exact origin of the index case was not revealed.

An outbreak of MBL-producing *P. mirabilis* was described in a general hospital in Thessaloniki during the period from June 2004 to March 2005 [19], as well as in outpatients believed to have been related to a general hospital in Sheres, in Northern Greece [20].

Finally MBL production was also sporadically described in *Enterobacter cloacae* in 2003 [21], in *Enterobacter aerogenes* in 2004 [15], in *Morganella morganii* in 2005 [22] and in *Providencia stuartii* in 2007 [23].

Concerning the magnitude of the problem, the GSSAR data reveal a steep increase in the proportion of imipenem-resistant *K. pneumoniae* from less than 1% in 2001 to 20% in isolates from hospital wards and to 50% in isolates from ICUs in 2006 (Figure 2). Accordingly, these resistant strains were identified in only three hospitals in 2002, and now are isolated in at least 25 of the 40 hospitals participating in the GSSAR network (Figure 2).

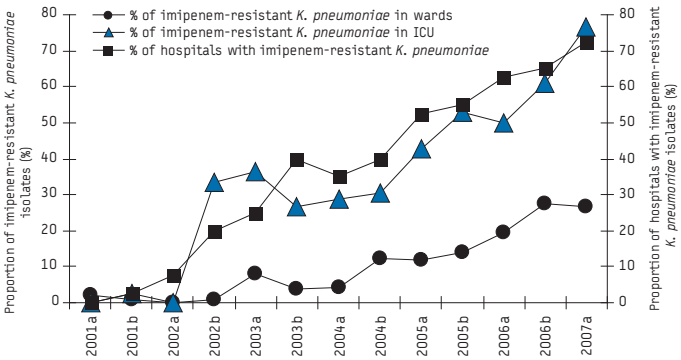
Interestingly, the proportions of imipenem-resistant enteric bacteria other than *K. pneumoniae* continue to be low (http://www.mednet.gr/whonet).

At this point it should be underlined that these data have to be interpreted with caution since resistance to carbapenem is monitored by the GSSAR network through the analysis of sensitivity data and not through the detection of the blaVIM gene (see next section).

Very little work has been done concerning the identification of risk factors for carbapenem-resistant infections. Fluoroquinolone and antipseudomonal penicillins have been proposed as independent risk factors in one matched case-control study [24].

FIGURE 2

Trends in proportion of imipenem-resistant *Klebsiella pneumoniae* isolates in hospitals in Greece, 2000-2006



Data from the Greek System for the Surveillance of Antimicrobial Resistance (http://www.mednet.gr/whonet)

Related clinical microbiology issues

Although the first VIM-producing *K. pneumoniae* and *E. coli* isolates were initially recognised by their *in vitro* resistance to carbapenem, i.e. displaying minimum inhibitory concentration (MIC) falling at the Clinical Laboratory Standard Institute (CLSI) resistant category in the *in vitro* sensitivity testing, it was soon documented that quite a few strains expressed low levels of resistance to carbapenem with MIC values at the CLSI intermediate resistance category (MIC 8 mg/L) or even at the sensitive category but with values near the breakpoint (MIC 2-4 mg/L). However, it must be emphasized that a strong inoculum effect has been reported – increasing the cell density by 102 CFU/mL raised carbapenem MICs by 2-6 doubling dilutions. This inoculum effect was more pronounced with imipenem [25].

The behaviour of these strains in the various automatic sensitivity testing systems was also studied quite early, and discrepancies were reported [26]. Moreover, due to inadequate scaling, the MBL-detecting Etest strips containing imipenem plus EDTA produced a synergy image between imipenem and EDTA, occurring as a "phantom zone", and making the interpretation of the result difficult.

On the contrary, the fact that Proteus spp, displaying intrinsically high MICs to imipenem in the wild type population (see wild-type distributions published by EUCAST at: http://www.srga.org/eucastwt/MICTAB/index.html), has resulted in many false positive reports of imipenem-resistant Proteus, mainly in laboratories that use automatic susceptibility testing methods.

All these characteristics hamper the detection of the VIM-producing strains, pose therapeutic questions and obstruct the assessment of the real incidence of these strains, due to a possible iceberg phenomenon created by the presence of the *in vitro* "sensitive" strains harbouring the blaVIM gene.

Consequently, it was soon recognised that a special phenotypic test for the detection of these strains should be adopted. The double-disk imipenem – EDTA synergy test already in use for the detection of MBL-producing *P. aeruginosa* [2,7] was suggested for

the identification of MBL production in all enteric bacteria isolates with an MIC to imipenem >=1 mg/ml [27]. However, this problem has not been studied further and official recommendations have not been issued yet.

The diversity of carbapenem resistance levels in the *K. pneumoniae* carrying blaVIM-1 gene was associated in one study [28] either with multiple copies of the gene on the plasmid backbone – a procedure generated by IS26 activity – or due to porin loss – a fact indicating that the clinical use of carbapenem and, to a lesser extent, cefepime and aztreonam, against the phenotypically susceptible isolates of this group may have possibly contributed to the selection of the high-level resistance isolates.

Related molecular epidemiology issues

Genes

The spread of MBL-producing enteric bacteria in Greece is generally found to be due to VIM-1 type genes in the form of gene cassette [14,16-19,21,22] which are genetically different to the VIM-2 type genes isolated in *P. aeruginosa* in this country [6,7].

Interestingly, the blaVIM-1 cassette (including the 81 nucleotides of the 59-base element) was found identical to that originally described in *P. aeruginosa* in Italy and other European countries [14,18,21].

A different blaVIM gene termed blaVIM-12 was isolated in one Klebsiella pneumoniae and one *E. coli* isolate. This gene could be viewed as a blaVIM-1/blaVIM-2 hybrid being identical to blaVIM-1 from the 5_ end up to nucleotide 663, and to blaVIM-2 from nucleotide 614 up to its 3_ end [29,30]. Furthermore, the 59-base element of the blaVIM-12 gene cassette (72 bp in length) was identical to the element commonly found in blaVIM-2 cassettes and differed significantly from the 59 bp of the blaVIM-1 gene cassettes [29,30].

Integrons

The VIM gene was generally found to be part of related type I integrons. The cassette region of these integrons typically contains (from 5_ to 3_) the blaVIM-1, and the aacA4, dhfrI, and aadA genes [14,18,19].

However, a type I integron carrying the blaVIM-1 gene and a 6_-N-aminoglycoside acetyltransferase (aac(6_)-Ib) gene cassette was described in an E. cloacae clinical isolate [21]. Moreover, a different integron structure suggesting a different evolution process rather than a transfer, and the spread of the mobile element among the Greek hospitals was described in a cluster of four *E. coli* isolates in Crete [17].

Similarly, a novel class 1 integron carrying a carbapenemase gene (blaVIM-1) associated with a trimethoprim (dfrA1), a streptothricin (sat1) and two aminoglycoside resistance genes (aacA7 and aadA1) was detected in a *Morganella morganii* clinical isolate [22]. Moreover, a class I integron carrying only the blaVIM-1, and the dhfrI and aadA genes was found in a plasmid isolated from three different bacterial genera [15]. Lastly, an integron solely carrying the blaVIM-1 gene was described in an *E. coli* isolate [16].

Integrons are not self-transferred elements, and are commonly associated with various transposons. An IS26 insertion into the 5_ conserved segment of an In4-type integron and an IS26-mediated recruitment of resistance genes of diverse origin have been suggested as a mechanism for the evolution of various multiresistant integrons, including those that harbour the blaVIM-1 genes [31]. However, further work on the exact mechanism of their development and dissemination is needed.

The coexistence of the blaVIM gene with various other, newer beta-lactamases, including SHV-5 [18], the IBC-1 [32], the GES7 [16] the CMY-4 [33] and the CTX-M [17] genes have also been reported.

Plasmids

The blaVIM containing integrons are mainly found to be harboured by transferable plasmids in most enteric bacteria species including *K. pneumoniae* [18], *E. coli* [14,17], *P. mirabilis* [15], *Enterobacter aerogenes* [15] and *Providencia stuartii* [23].

Interestingly, the chromosomal location of the VIM containing integrons was also documented on several occasions, including an epidemic clone of *P. mirabilis* in Thessaloniki [19], and sporadic *E. coli* [16], *Enterobacter* cloaca [21] and *Morganella morganii* [22] isolates.

The epidemiology of the blaVIM harbouring plasmids is an important prerequisite for understanding the dynamics of the growing proportion of VIM-producing strains. These plasmids were generally found to display different restriction patterns [18], although the spread of plasmids with identical patterns in isolates of the same species [17,18], or even among isolates of different species [15] has also been described. Most importantly, in at least one study, plasmids harbouring the blaVIM-1 gene were found to belong to the incompatibility group N [34], a fact consistent with the possible spread of evolving plasmids. However, these issues must be further elucidated. Plasmids of other than N incompatibility groups have also been sporadically isolated [33].

Bacterial strains

Another important condition for understanding the situation is the study of the possible clonal spread of the VIM-producing strains. Although much work needs to be done on this issue, the epidemics seem to be generally multiclonal, with clones differing between hospitals and sometimes even different clones present within a single hospital [18], with no particular clone prevailing (unpublished data from our department). A few exceptions to this rule have been reported: an outbreak in distinct regions of Greece due to a single *K. pneumoniae* clone carrying a blaVIM-1 gene [35], a small nosocomial outbreak due to a VIM-producing *E. coli* clone [17], and one caused by a VIM-producing *P. mirabilis* clone [19].

A recently published study on blood isolates from three hospitals in Athens revealed that 37.6% of all *K. pneumoniae* blood isolates were blaVIM-1-positive. 77.8% of these were taken from ICUs. PFGE identified eight clusters (A-H) with related (>80%) patterns, as well as four unique types. Microorganisms producing both VIM-1 and SHV-5 constitute the prevalent multidrug-resistant population of *K. pneumoniae* in this setting [36].

In conclusion, the large and still increasing proportion of VIM-producing *K. pneumoniae* seems to be due to the spread of the blaVIM-1 cassette among rapidly evolving multiresistant plasmids and multiresistant or even panresistant strains mainly of *K. pneumoniae* but also, of other enteric bacteria species. However,

further work is needed to elucidate the possible contribution of plasmid or bacterial clone spread.

Related clinical issues

Imipenem-resistant isolates are generally found to be multidrug-resistant, the majority displaying resistance to at least one aminoglycoside, quinolones and trimpethoprim [37, unpublished data from the GSSAR]. Interestingly, most isolates were found to be resistant to aztreonam, indicating the simultaneous presence of other extended-spectrum beta-lactamases (ESBL) as well [37].

The multidrug-resistant nature of these isolates dramatically limits the therapeutic options, leaving colistin, a toxic and difficult-to-use drug, as the only antibiotic with *in vitro* activity against VIM-producing enteric bacteria. However, VIM-producing *K. pneumoniae* displaying resistance to colistin, with an MIC up to 64 mg/L have sporadically being isolated [unpublished data from the GSSAR], and at least one outbreak has been described [38].

Taking this into account, and given the *in vitro* low levels of resistance displayed by most isolates, the question of the possible treatment of these patients with high levels of carbapenem has so far been addressed by two published reports.

The *in vivo* activity of imipenem against VIM-producing *K. pneumoniae* was assessed in a thigh infection model in neutropenic mice by Daikos et al. [39]. The authors concluded that while their results cannot provide firm conclusions regarding the treatment of infections caused by VIM-producing *K. pneumoniae* strains with MIC of imipenem in the susceptible range, they suggest that the administration of imipenem at higher doses may prove to be of some benefit.

Moreover, a retrospective analysis of 28 cases of VIM-producing *K. pneumoniae* bloodstream infections [40] revealed a striking difference in mortality between patients infected with VIM-producing *K. pneumoniae* with MIC of imipenem >4 g/mL and control group patients infected with non-VIM-producing *K. pneumoniae*. In contrast, patients infected with VIM-producing *K. pneumoniae* but with MIC of carbapenems in the susceptible range displayed no difference in mortality compared to the control group.

In addition to these studies, Galani et al. have reported both successful [15] and non-successful [21] outcomes of patients infected with low-level-resistant VIM-producing enteric bacteria and treated with imipenem.

However, all these reports must be regarded as preliminary, and well designed prospective studies are urgently needed to tackle the therapeutic issues set by VIM-producing *K. pneumoniae*, as well as the possible need to modify the clinical breakpoints to carbapenems for the blaVIM harbouring strains.

Related public health issues

It is well recognized that the main tools for confronting antibiotic resistance are antibiotic policy and infection control strategies [41].

The problem of VIM-producing *K. pneumoniae* was timely recognized by the GSSAR, and its significance adequately assessed and publicized by the Infectious Disease and Clinical Microbiology community in Greece. Moreover, the National Early Warning System for the Recognition of New and Emerging Resistance Mechanisms, which has been in operation in Greece for the last two years, was successfully used for the early tracing and reporting of VIM-producing enteric bacteria. Additionally, the National Centre for Disease Control and Prevention at the Greek Ministry of Health (KEELPNO) issued guidelines which were distributed to the hospitals as soon as a VIM-producing strain had been isolated there. These guidelines were mainly addressed to the "Infection Control Committee" of the respective hospitals and included issues on antibiotic policy and infection control.

To date, however, these measures have made a relatively small impact on the still increasing proportion of VIM-producing strains.

It is well accepted that antibiotic resistance is a difficult-to-manage public health problem, especially when it is established. This is particularly true in the case of the complex molecular epidemiology of the VIM-producing *K. pneumoniae* problem in Greece.

Furthermore, Greece is among the countries which for decades have been reporting the highest levels of resistance to most antibiotics [42,43] and therefore physicians may not always recognize the possible significance of a new mechanism of resistance.

Antibiotics are the most important risk factors in the development of resistance, and therefore an effective antibiotic policy, in addition to being an important element of good medical practice, is an important public health measure in confronting the problem of antimicrobial resistance [44,45]. Especially since Greece is among the European countries with the highest rates of antibiotic use in both hospital and community settings [46,47].

It must be emphasized, however, that for the antibiotic policy to be effective, it must be based on a good understanding of the molecular basis of the resistance mechanisms [48]. Moreover, in an area such as Greece, with high resistance rates and very few effective antibiotics left at the physician's disposal, antibiotic policy has very narrow limits. What is more, antibiotic policy must always be combined with infection control.

In addition to the above difficulties, certain characteristics of the public health system in Greece, especially the fact that public health is relatively undersized within the national health system, hinders the effort to confront antibiotic resistance. The hospital epidemiologist is not a recognized specialist in Greece and hospital epidemiology is not part of the everyday practice in Greek hospitals. Although there is expertise available in many hospitals and university laboratories, the strains isolated from cases of healthcare-associated infections are not routinely typed. Hospital outbreaks are not routinely studied and the possible role of the spread of drug-resistant clones in these outbreaks is not routinely assessed. The "Infection Control Committees" in hospitals do not have administrative authority, infection control measures are not always implemented in practice, while infectious diseases specialists, with no official training in epidemiology, are mainly focused on antibiotic policy [49,50].

In summary, a national Strategic Action Plan is a necessary public health instrument to coordinate efforts, prioritize activities, set goals and audit actions, and thus to answer all important issues related to the spread of drug-resistant enteric bacteria discussed in this paper. Such Strategic Action Plan is currently under development and hopefully will be available in the next few months. The plan will affirm the political commitment of the Greek health administration in confronting the issue of antimicrobial resistance. It will put emphasis on this public health problem and its risk factors in a way to be understood by the wider medical community, the health policymakers and the wider community. It will allocate specific tasks to the responsible bodies and coordinate and prioritize the necessary scientific research. The Action Plan will be based on the collaboration, coordination and consensus of opinions of all parties involved.

Acknowledgements

The Greek System for the Surveillance of Antimicrobial Resistance (GSSAR) is funded by the Ministry of Health and Social Solidarity of Greece (KEELPNO).

The hospitals, members of the Greek System for Surveillance of Antimicrobial Resistance are listed at: http://www.mednet.gr/whonet

References

1. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-beta-lactamases: the quiet before the storm? Clin Microbiol Rev. 2005;18:306-25.
2. Cornaglia G, Akova M, Amicosante G, Canton R, Cauda R, Docquier JD, et al. ESCMID Study Group for Antimicrobial Resistance Surveillance (ESGARS). Metallo-beta-lactamases as emerging resistance determinants in Gram-negative pathogens: open issues. Int J Antimicrob Agents. 2007;29:380-8.
3. Lauretti L, Riccio ML, Mazzariol A, Cornaglia G, Amicosante G, Fontana R, et al. Cloning and characterization of blaVIM, a new integron-borne metallo-beta-lactamase gene from a Pseudomonas aeruginosa clinical isolate. Antimicrob Agents Chemother. 1999;43:1584-90.
4. Poirel L, Naas T, Nicolas D, Collet L, Bellais S, Cavallo JD, et al. Characterization of VIM-2, a carbapenem-hydrolyzing metallo-ß-lactamase and its plasmid- and integron-borne gene from a Pseudomonas aeruginosa clinical isolate in France. Antimicrob Agents Chemother. 2000;44:891–7.
5. Tsakris A, Pournaras S, Woodford N, Palepou MF, Babini GS, Douboyas J, et al. Outbreak of infections caused by Pseudomonas aeruginosa producing VIM-1 carbapenemase in Greece. J Clin Microbiol. 2000;38:1290-2.
6. Mavroidi A, Tsakris A, Tzelepi E, Pournaras S, Loukova V, Tzouvelekis LS. Carbapenem-hydrolysing VIM-2 metallo-beta-lactamase in Pseudomonas aeruginosa from Greece. J Antimicrob Chemother. 2000;46:1041-2.
7. Giakkoupi P, Petrikkos G, Tzouvelekis LS, Tsonas S, Legakis NJ, Vatopoulos AC. WHONET Greece Study Group. Spread of integron-associated VIM-type metallo-beta-lactamase genes among imipenem-nonsusceptible Pseudomonas aeruginosa strains in Greek hospitals. J Clin Microbiol. 2003;41:822-5.
8. Luzzaro F, Docquier JD, Colinon C, Endimiani A, Lombardi G, Amicosante G, et al. Emergence in Klebsiella pneumoniae and Enterobacter cloacae clinical isolates of the VIM-4 metallo-beta-lactamase encoded by a conjugative plasmid. Antimicrob Agents Chemother. 2004;48:648–650.
9. Conceição T, Brízio A, Duarte A, Barros R. First isolation of blaVIM-2 in Klebsiella oxytoca clinical isolates from Portugal. Antimicrob Agents Chemother. 2005;49:476.
10. Tórtola MT, Lavilla S, Miró E, González JJ, Larrosa N, Sabaté M, et al. First detection of a carbapenem-hydrolyzing metalloenzyme in two Enterobacteriaceae isolates in Spain. Antimicrob Agents Chemother. 2005;49:3492–3494
11. Ktari S, Arlet G, Mnif B, Gautier V, Mahjoubi F, Ben Jmeaa M, et al. Emergence of multidrug-resistant Klebsiella pneumoniae isolates producing VIM-4 metallo-beta-lactamase, CTX-M-15 extended-spectrum beta-lactamase, and CMY-4 AmpC beta-lactamase in a Tunisian university hospital. Antimicrob Agents Chemother. 2006;50:4198-4201.
12. Kassis-Chikhani N, Decre D, Gautier V, Burghoffer B, Saliba F, Mathieu D, et al. First outbreak of multidrug-resistant Klebsiella pneumoniae carrying blaVIM-1 and blaSHV-5 in a French university hospital. J Antimicrob Chemother. 2006;57:142-5.
13. Vatopoulos AC, Kalapothaki V, Legakis NJ and the Greek Network for the Surveillance of Antimicrobial Resistance. An Electronic Network for the Surveillance of Antimicrobial Resistance in Bacterial Nosocomial Isolates in Greece. WHO Bulletin. 1999;77:595-601.
14. Miriagou V, Tzelepi E, Gianneli D, Tzouvelekis LS. Escherichia coli with a self-transferable, multiresistant plasmid coding for metallo-beta-lactamase VIM-1. Antimicrob Agents Chemother. 2003;47:395-7.
15. Galani I, Souli M, Koratzanis E, Koratzanis G, Chryssouli Z, Giamarellou H. Emerging bacterial pathogens: Escherichia coli, Enterobacter aerogenes and Proteus mirabilis clinical isolates harbouring the same transferable plasmid coding for metallo-beta-lactamase VIM-1 in Greece. J Antimicrob Chemother. 2007;59:578-9.
16. Galani I, Souli M, Koratzanis E, Chryssouli Z, Giamarellou H. Molecular characterization of an Escherichia coli clinical isolate that produces both metallo-beta-lactamase VIM-2 and extended-spectrum beta-lactamase GES-7: identification of the In8 integron carrying the blaVIM-2 gene. J Antimicrob Chemother. 2006;58:432-3.
17. Scoulica EV, Neonakis IK, Gikas AI, Tselentis YJ. Spread of bla(VIM-1)-producing E. coli in a university hospital in Greece. Genetic analysis of the integron carrying the bla(VIM-1) metallo-beta-lactamase gene. Diagn Microbiol Infect Dis. 2004;48:167-72.
18. Giakkoupi P, Xanthaki A, Kanelopoulou M, Vlahaki A, Miriagou V, Kontou S, et al. VIM-1 metallo-beta-lactamase-producing Klebsiella pneumoniae strains in Greek hospitals. J Clin Microbiol. 2003;41:3893-6.
19. Vourli S, Tsorlini H, Katsifa H, Polemis M, Tzouvelekis LS, Kontodimou A, et al. Emergence of Proteus mirabilis carrying the bla metallo-beta-lactamase gene. Clin Microbiol Infect. 2006;12:691-4.
20. Tsakris A, Ikonomidis A, Poulou A, Spanakis N, Pournaras S, Markou F. Transmission in the community of clonal Proteus mirabilis carrying VIM-1 metallo-beta-lactamase. J Antimicrob Chemother. 2007;60:136-9.
21. Galani I, Souli M, Chryssouli Z, Orlandou K, Giamarellou H. Characterization of a new integron containing bla(VIM-1) and aac(6')-IIc in an Enterobacter cloacae clinical isolate from Greece. J Antimicrob Chemother. 2005;55:634-8.
22. Takris A, Ikonomidis A, Spanakis N, Poulou A, Pournaras S. Characterization of In3Mor, a new integron carrying VIM-1 metallo-beta-lactamase and sat1 gene, from Morganella morganii. J. Antimicrob Chemother. 2007;59:739-41.
23. Miriagou V, Tzouvelekis LS, Flevari K, Tsakiri M, Douzinas EE. Providencia stuartii with VIM-1 metallo-beta-lactamase. J Antimicrob Chemother. 2007;60:183-4.
24. Falagas ME, Rafailidis PI, Kofteridis D, Virtzili S, Chelvatzoglou FC, Papaioannou V, et al. Risk factors of carbapenem-resistant Klebsiella pneumoniae infections: a matched case control study. J Antimicrob Chemother. 2007;60:1124-30.
25. Panagiotakopoulou A, Daikos GL, Miriagou V, Loli A, Tzelepi E, Tzouvelekis LS. Comparative in vitro killing of carbapenems and aztreonam against Klebsiella pneumoniae producing VIM-1 metallo-beta-lactamase. Int J Antimicrob Agents. 2007;29:360-2.
26. Giakkoupi P, Tzouvelekis LS, Daikos GL, Miriagou V, Petrikkos G, Legakis NJ, et al. Discrepancies and interpretation problems in susceptibility testing of VIM-1-producing Klebsiella pneumoniae isolates. J Clin Microbiol. 2005;43:494-6.
27. Petropoulou D, Tzanetou K, Syriopoulou VP, Daikos GL, Ganteris G, Malamou-Lada E. Evaluation of imipenem/imipenem+EDTA disk method for detection of metallo-beta-lactamase-producing Klebsiella pneumoniae isolated from blood cultures. Microb Drug Resist. 2006;12:39-43.
28. Loli A, Tzouvelekis LS, Tzelepi E, Carattoli A, Vatopoulos AC, Tassios PT, et al. Sources of diversity of carbapenem resistance levels in Klebsiella pneumoniae carrying blaVIM-1. J Antimicrob Chemother. 2006;58:669-72.
29. Pournaras S, Ikonomidis A, Tzouvelekis LS, Tokatlidou D, Spanakis N, Maniatis AN, et al. VIM-12, a novel plasmid-mediated metallo-beta-lactamase from Klebsiella pneumoniae that resembles a VIM-1/VIM-2 hybrid. Antimicrob Agents Chemother. 2005;49:5153-6.
30. Ikonomidis A, Labrou M, Afkou Z, Maniatis AN, Sofianou D, Tsakris A, et al. First occurrence of an Escherichia coli clinical isolate producing the VIM-1/VIM-2 hybrid metallo-beta-lactamase VIM-12. Antimicrob Agents Chemother. 2007;51:3038-9.
31. Miriagou V, Carattoli A, Tzelepi E, Villa L, Tzouvelekis LS. IS26-associated In4-type integrons forming multiresistance loci in enterobacterial plasmids. Antimicrob Agents Chemother. 2005;49:3541-3.
32. Galani I, Souli M, Chryssouli Z, Katsala D, Giamarellou H. First identification of an Escherichia coli clinical isolate producing both metallo-beta-lactamase VIM-2 and extended-spectrum beta-lactamase IBC-1. Clin Microbiol Infect. 2004 Aug; 10(8):757-60.
33. Colinon C, Miriagou V, Carattoli A, Luzzaro F, Rossolini GM. Characterization of the IncA/C plasmid pCC416 encoding VIM-4 and CMY-4 beta-lactamases. J Antimicrob Chemother. 2007;60:258-62.

34. Carattoli A, Miriagou V, Bertini A, Loli A, Colinon C, Villa L, et al. Replicon typing of plasmids encoding resistance to newer beta-lactams. Emerg Infect Dis. 2006;12:1145-8.

35. Ikonomidis A, Tokatlidou D, Kristo I, Sofianou D, Tsakris A, Mantzana P, et al. Outbreaks in distinct regions due to a single Klebsiella pneumoniae clone carrying a bla VIM-1 metallo-beta-lactamase gene. J Clin Microbiol. 2005;43:5344-7.

36. Psichogiou M, Tassios PT, Avlamis A, Stefanou I, Kosmidis C, Platsouka E, et al. Ongoing epidemic of blaVIM-1-positive Klebsiella pneumoniae in Athens, Greece: a prospective survey. J Antimicrob Chemother. 2008;61:59-63.

37. Miriagou V, Tzelepi E, Daikos GL, Tassios PT, Tzouvelekis LS. Panresistance in VIM-1-producing Klebsiella pneumoniae. J Antimicrob Chemother. 2005;55:810-1.

38. Antoniadou A, Kontopidou F, Poulakou G, Koratzanis E, Galani I, Papadomichelakis E, et al. Colistin-resistant isolates of Klebsiella pneumoniae emerging in intensive care unit patients: first report of a multiclonal cluster. J Antimicrob Chemother. 2007;59:786-90.

39. Daikos GL, Panagiotakopoulou A, Tzelepi E, Loli A, Tzouvelekis LS, Miriagou V. Activity of imipenem against VIM-1 metallo-beta-lactamase-producing Klebsiella pneumoniae in the murine thigh infection model. Clin Microbiol Infect. 2007;13:202-5.

40. Daikos GL, Karabinis A, Paramythiotou E, Syriopoulou VP, Kosmidis C, Avlami A, et al.VIM-1-producing Klebsiella pneumoniae bloodstream infections: analysis of 28 cases. Int J Antimicrob Agents. 2007;29:471-3.

41. Shlaes DM, Gerding DN, John JF Jr, Craig WA, Bornstein DL, Duncan RA, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis. 1997;25:584-99.

42. The Greek Society for Microbiology: Antibiotic Resistance among gram negative bacilli in 19 Greek Hospitals. J Hosp Infect. 1989;14:177-181.

43. Legakis NJ, Tzouvelekis LS, Tsakris A, Legakis JN, Vatopoulos AC. On the incidence of antibiotic resistance among aerobic Gram-negative rods isolated in Greek hospitals. J. Hosp. Infect. 1993 ;24:233-237.

44. Keuleyan E, Gould M. Key issues in developing antibiotic policies: from an institutional level to Europe-wide. European Study Group on Antibiotic Policy (ESGAP), Subgroup III. Clin Microbiol Infect. 2001;7; Suppl 6:16-21.

45. Lipsitch M, Samore M. Antimicrobial use and antimicrobial resistance: a population perspective. Emerg Infect Dis. 2002;8:347-354.

46. Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H. European Surveillance of Antibiotic Consumption (ESAC) Project Group. Hospital consumption of antibiotics in 15 European countries: results of the ESAC Retrospective Data Collection (1997-2002). J Antimicrob Chemother. 2006;58:159-67.

47. Ferech M, Coenen S, Malhotra-Kumar S, Dvorakova K, Hendrickx E, Suetens C, et al. ESAC Project Group. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. J Antimicrob Chemother. 2006;58:401-7.

48. Rahal JJ, Urban C, Segal-Maurer S. Nosocomial antibiotic resistance in multiple Gram-negative species: experience at one hospital with squeezing the resistance balloon at multiple sites. Clin Infect Dis. 2002;34:499–503.

49. Petrikkos G, Markogiannakis A, Papapareskevas J, Daikos GL, Stefanakos G, Zissis NP, et al. Differences in the changes in resistance patterns to third- and fourth-generation cephalosporins and piperacillin/tazobactam among Klebsiella pneumoniae and Escherichia coli clinical isolates following a restriction policy in a Greek tertiary care hospital. Int J Antimicrob Agents. 2007;29:34-8.

50. Ntagiopoulos PG, Paramythiotou E, Antoniadou A, Giamarellou H, Karabinis A. Impact of an antibiotic restriction policy on the antibiotic resistance patterns of Gram-negative microorganisms in an Intensive Care Unit in Greece. Int J Antimicrob Agents. 2007;30:360-5.

This article was published on 24 January 2008.

Citation style for this article: Vatopoulos A. High rates of metallo-beta-lactamase-producing Klebsiella pneumoniae in Greece - a review of the current evidence. Euro Surveill. 2008;13(4):pii=8023. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8023

The role of public health officers in preparedness planning and management of health crises

R Strauss (reinhild.strauss@bmgfj.gv.at)[1], R Muchl[1], M Kunze[2], H Hrabcik[1]
1. Bundesministerium für Gesundheit, Familie und Jugend (Federal Ministry for Health, Family and Youth), Vienna, Austria
2. Medizinische Universität Wien, Zentrum für Public Health (Medical University Vienna, Centre for Public Health), Vienna, Austria

The contribution of public health officers is of crucial importance in both the preparedness planning process and the response to health threats since the implementation of public health measures lies within the competence of the public health system. Thus, public health officers on regional and district level have to be involved in every stage of the planning process for crisis management. Federal structures of health systems as equivalent to the political structure of a country pose specific challenges for both the planning process and the response itself. The most important instrument for the evaluation of crisis plans, including the assessment of the public health officers' preparedness, is the performance of exercises. The success of a simulation exercise depends mainly on careful planning process, clear evaluation criteria and a work plan, that allows for necessary improvements of crisis plans of all involved organisations. Simulation exercises are an integrated element of preparedness activities on all administrative levels of the public health system. Depending on the nature of the exercise public health officers on regional and district level are involved as planners or as players.

Crisis management planning

Specific experiences of Austria

Austria has a federal political and administrative structure comprising nine federal states ("Länder") which represent the regional level. Regarding health issues, the Ministry of Health (Bundesministerium für Gesundheit, Familie und Jugend, henceforth MoH) is responsible on the national level whereas the regional health boards hold responsibilities on the level of federal states. The autonomy of the federal states is guaranteed in the Austrian constitution. Generally, crisis management is not centralised but lies within the domain of the federal states, however, there is a political mechanism called "mittelbare Bundesverwaltung" (indirect federal administration), which allocates responsibility in certain health-related areas, including infectious disease control, to the national level [1]. This political mechanism is of relevance in crisis preparedness planning since the relevant authorities at the national level can ask the respective federal states to prepare for health threats in an adequate manner. Usually, preparedness planning concerning infectious diseases is done in a coordinated way by the regional and national public health bodies. One example is the common purchase of stocks of necessary medicines and medicinal products for crisis situations.

To overcome any potentially conflicting crisis management concepts on national and regional levels, the MoH usually implements the following planning process:

- on the national level, strategic framework crisis plans following international standards for different scenarios (e.g. smallpox, anthrax, influenza pandemic) are developed [2-7];
- all heads of the regional health boards and the medical universities are invited to actively participate in the writing and evaluation of crisis plans;
- the final strategic framework plans are then made available to the regional health boards to provide basis for the development of regional operative plans;
- the strategic plans are regularly updated by the MoH and sent for evaluation to the regional health boards and the scientific community.

This procedure of crisis management planning in the field of public health has proved to be very successful. To date, specific plans for smallpox, anthrax and influenza pandemic have been developed [8-10]. The major advantage of this planning strategy is that the regional public health boards that are responsible for the implementation of the crisis management plans are involved in the discussion of the proposed measures at the earliest stage of their planning.

Simulation exercises

General principles

The most important instrument used in the evaluation of crisis management plans is the performance of simulation exercises. To ensure that the exercise is successful, it needs to be carefully planned:

- Firstly, the aim and the type of exercise have to be determined. Different types of exercises are available and the choice should be done according to the aims: tabletop exercises are useful for testing procedures whereas command post exercises are optimal for testing communication. Drills and internal exercises are the most appropriate methods for testing operations.
- Secondly, the scenario has to be realistic and relevant for all the players but also rich enough to push the system tested to the limits. Clear objectives have to be defined and the timeframe has to be sufficient to allow for constructive response. It needs to be decided whether to use real time or compressed time: compressed-time scenarios allow for exercises that cover weeks or months whereas real-time scenarios are better to test operational issues.
- Thirdly, clear evaluation criteria have to be set up. Ideally, the evaluation process is supported by (external) observers. After the exercise, a specific working program has to be developed, including a road map allocating tasks to working groups. The

results of the working groups have to be incorporated into the crisis management plans and follow-up exercises should be performed in order to evaluate the improvements. However, exercises must be spaced out appropriately and contain only a few repetition elements, otherwise the compliance of players might decrease with negative consequences affecting the quality of the performance. In fact, scenarios should be planned with a long term vision to ensure the best output. At the beginning, an internal exercise to test internal procedures and operations should be done. Then partners and stakeholders should be involved in a table top exercise to test the external procedures. Once these procedures are optimised, a command post exercise to test the communication between the parties involved should be performed.

Simulation exercises have to be performed on national, regional and district level. Depending on which administrative level the exercise is performed at, the role of the public health officers is different: in a national exercise the public health officers of the regional and district levels act as players, in a regional exercise which is planned by the public health officers working in the regional health board the district public health officers act as players, and, finally, in a district level exercise the district public health officer are the planners while the players are located in the different health care facilities.

International exercises NEW WATCHMAN and COMMON GROUND

In 2005, the European Commission initiated two international simulation exercises - the smallpox exercise NEW WATCHMAN in October and the influenza pandemic exercise COMMON GROUND in November [11,12].

Nearly all EU Member States as well as Switzerland, Iceland and Norway, the European Commission, the European Agency for the Evaluation of Medicinal Products (EMEA), the European Centre for Disease Prevention and Control (ECDC), the European Vaccine Manufacturers (EVM), several pharmaceutical companies and the World Health Organization (WHO) participated in these exercises. The UK Health Protection Agency (HPA) acted as exercise control and was supported by a Canadian consultant company which had a long lasting experience in doing this kind of exercises especially in the military field.

The main aims of the exercises were to evaluate:

- the communication between and within the relevant authorities in the EU Member States and at the EU level;
- the interoperability of the national plans;
- the division of tasks and responsibilities between the international organisations (EC, WHO, ECDC). The exercises were run as a command control exercise: each participating organisation had to name the controllers and players. The controllers' function was to monitor the flow of the exercise on site. Therefore these persons were involved in the preparation of the exercise at the EU level. In case of unforeseen difficulties it was the task of the controllers to step in and to bring the exercise back on track. The players had to react to the given events and solve the problems as quickly and effectively as possible.

Even though in these communication exercises no active role was foreseen for public health officers, the regional health boards were able to follow the exercises, because the controllers in the MoH forwarded them all the information. This was done in preparation of a national influenza pandemic exercise. Furthermore, several topics that needed further discussion on the national level were identified.

National influenza pandemic exercise VAN SWIETEN

VAN SWIETEN was the first Austrian national exercise to evaluate the crisis management of a national emergency due to an infectious disease [13,14]. In general, the EU exercise COMMON GROUND was used as a model in designing the scenario, aims and objectives of the national exercise, and it was further developed by taking into consideration the results of the evaluation of COMMON GROUND. The aim of the exercise was to evaluate the communication and the cooperation between the national and the regional level institutions during a pandemic situation. In contrast to the EU exercises, it was a staff exercise with controllers only being present at the national level. All public health officers at the regional level were actively involved while the involvement of the district level personnel was voluntary.

The main objectives of the exercise were to evaluate:

- the communication between the MoH and the nine regional health boards as well as the other involved ministries;
- the general preparedness plan for an influenza pandemic in Austria;
- the interoperability of the regional plans.

The most important elements of the exercise were therefore:

- surveillance during a pandemic;
- preventive and control measures such as the use of antiviral drugs and the pandemic vaccine;
- logistic issues;
- cross-border issues, such as "health shopping" and travel restrictions.

The scenario of this two-day-long exercise was divided into three blocks and covered in real time several months (November 2006 to April 2007). Each block was played in compressed time. In block 1 (morning of exercise day 1, representing 23 November, 2006), players had to react according to pandemic phase 5 to a situation in which clusters of human infections with a new influenza virus subtype appeared in South-East Asia. In block 2 (afternoon of exercise day 1, representing the period between 24 November and 20 December, 2006), players had to manage pandemic phase 6 with no availability of pandemic vaccine. In block 3 (exercise day 2, representing the period between 21 December, 2006 and 12 April, 2007) the logistics for the use of the pandemic vaccine during the second pandemic wave (phase 6) had to be handled.

VAN SWIETEN was evaluated by the same methods as used in the evaluation of COMMON GROUND [12]. The evaluation process revealed the need for intensive work in several areas:

- continuous interministerial cooperation concerning the issue of border control and/or closure of borders, closure of airports and "health shopping";
- specific plans for business continuity;
- planning presumptions (definition of triggers for certain measures such as closing schools or release of neuraminidase prophylaxis for frontline personnel).

However, one of the most important conclusions of the evaluation process was the need for strengthening the public health sector. A well functioning public health system is the backbone of successful crisis management in the field of infectious diseases and thus

needs to be supported concerning human and financial resources. Furthermore, public health officers need to have a continuous access to training on high level. Therefore in 2006, the Austrian MoH started a special initiative to send key personnel of the regional health boards to international training seminars and workshops [15]. In this way, a group of well trained public health experts will be established who can function as multipliers on regional level by training the local staff. Additionally, the MoH organises crisis management training seminars on national level.

Conclusion

Public health officers on all administrative levels play a crucial role in crisis planning and in the management of crisis situations. Thus the public health sector has to be involved in every crisis management planning process in order to implement all operative issues right from the start. The roles and competencies of the different administrative levels have to be clearly defined in practical terms and the functionality of the standardised operational procedures has to be tested repeatedly in exercises.

Public health officers have different roles in preparedness planning and crisis management depending on the administrative level they are working at: while a public health officer at the district level is mainly involved in operational issues, a public health officer at the regional level is responsible for coordinative and strategic measures within the federal state. Thus their involvement has to be implemented accordingly: operational training such as delivery of neuraminidase inhibitors or vaccine is addressed at the district level while strategic training such as planning hospital care throughout the federal state is addressed at the regional level.

Exercises are the most important tool to evaluate crisis plans and thus the level of preparedness among public health officers. In order to design scenarios that are as realistic as possible, public health officers on all administrative levels have to be involved already in the exercise preparation. By this it is guaranteed that all relevant issues are included in order to improve the performance in case of a real crisis.

References

1. Weber K. Die mittelbare Bundesverwaltung. Schriftenreihe des Instituts für Föderalismusforschung Band 41. Wien: Braumüller; 1987.
2. WHO. WHO Global Preparedness Plan 2005. Available from: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5/en/index.html
3. Department of Health, UK. Guidelines for smallpox response and management in the post-eradication era (smallpox plan). Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4070830
4. Henning KJ, Brennan PJ, Hoegg C, O'Rourke E, Dyer BD, Grace TL. Health system preparedness for bioterrorism: bringing the tabletop to the hospital. Infect Control Hosp Epidemiol. 2004;25(2):146-55.
5. Barbera J, Macintyre A, Gostin L, Inglesby T, O'Toole T, De Atley C, et al. Large-scale quarantine following terrorism in the United States: scientific examination, logistic and legal limits, and possible consequences. JAMA. 2001;286(21):2711-7.
6. CDC. Bioterrorism Preparedness and anthrax. Available from: http://www.epi.state.nc.us/epi/anthrax.html
7. Tomaso H, Al Dahouk S, Fock RRE, Treu TM, Schlögel R, Strauss R, et al. Management in der Behandlung von Patienten nach Einsatz biologischer Agenzien. Notfall & Rettungsmedizin. 2003;6:603-14
8. Strauss R. Influenza Pandemieplan – Strategie für Österreich. Available from: http://www.bmgfj.gv.at/cms/site/attachments/3/6/8/CH0019/CMS1126084167391/pp_inetversion12_06.pdf
9. Reisp E. Krisenplan Aviäre Influenza und Newcastle Disease. Available from: http://www.bmgfj.gv.at/cms/site/attachments/3/6/8/CH0019/CMS1126084167391/kp_ai_ncd.pdf
10. Strauss R. Der österreichische Pockenplan. Available from: http://www.arztenews.at
11. European Commission. NEW WATCHMAN – Final exercise report. Available from: http://ec.europa.eu/health/ph_threats/com/watchman.pdf
12. European Commission. COMMON GROUND – Final exercise report. Available from: http://ec.europa.eu/health/ph_threats/com/common.pdf
13. Strauss R, Muchl R, Kunze M, Hrabcik H. Simulationsübungen – ein integraler Bestandteil umfassender Pandemieplanung. Available from: http://www.verwaltung.steiermark.at/cms/dokumente/10039771_21212/dc944064/Jahresbericht2006Endversion.pdf
14. Strauss R, Muchl R, Hain C, Kunze M, Hrabcik H. VAN SWIETEN – Erste österreichweite Pandemieübung. Mitt Sanit Verwalt. 2007;108(7):2-3.
15. Strauss R, Karnthaler U, Gössler R, Morawetz R, Van Loock F, Baka A, et al. ETHREAT – European Training for Health Professionals on Rapid Response to Health Threats. Mitt Sanit Verwalt. 2007;108(7):3-5.

This article was published on 13 March 2008.

Citation style for this article: Strauss R, Muchl R, Kunze M, Hrabcik H. The role of public health officers in preparedness planning and management of health crises. Euro Surveill. 2008;13(11):pii=8071. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8071

Strengthening Europe's epidemic intelligence capacity: the first collaboration between a European Union Member State and the European Centre for Disease Prevention and Control

D Coulombier[1], M Ciotti[1], G Freitas[2], A Frota[2], C Varela[1], P Vasconcelos (Paula.Vasconcelos@ecdc.europa.eu)[1], T Fernandes[2]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden
2. Directorate-General of Health, Ministry of Health, Lisbon, Portugal

The European Centre for Disease Prevention and Control (ECDC) has a mandate to identify, assess and communicate current and emerging threats to human health from communicable diseases in the European Union (EU) [1]. The identification of threats is undertaken through the use of 'epidemic intelligence', the systematic collection and collation of information from a variety of sources, usually in real-time, which is then verified and analysed and, if necessary, activates response.

The implementation of the new International Health Regulations (IHR) in June 2007 has led to a need for more sensitive and specific public health event detection tools. Upon request, the ECDC can support EU Member States to assess and strengthen their threat detection and response capacity. Following the establishment of its Emergency Operations Centre (EOC) in May 2007, the ECDC developed a plan, defining epidemic intelligence activities in times of "peace" and times of crisis, and the necessary resources (human and material) to deal with both. The epidemic intelligence team, working full-time in the EOC, uses a set of advanced information technology tools to detect potential threats, paying special attention to events threatening more than one EU Member State. The team's activities are divided into four main components:

- The maintenance of a database (the Threat Tracking Tool) to store, process and report potential health threats for Europe;
- The holding of a daily morning briefing, where all threats are discussed, and the ECDC's actions decided based on the team's risk assessment;
- A 24-hour on-duty system to ensure continuous epidemic intelligence operations;
- The production and distribution of reports on a daily and weekly basis.

The ECDC's long-term strategy includes supporting EU Member States in developing and/or strengthening epidemic intelligence activities and related facilities [2]. In line with this strategy, an expert from Portugal's Directorate-General of Health spent one week in July 2007 working in the ECDC's epidemic intelligence team. The agenda was organised in order to facilitate the integration and familiarisation of the expert in the Centre's daily and weekly epidemic intelligence activities and to acquire a broader perspective of public health signals, alerts and threats that, recognised at Member State level, may correspond to a threat to other Member States. The expert joined the ECDC's epidemic intelligence team in screening and filtering news sources; followed messages from the Early Warning and Response System and other alert mechanisms; took part in the daily briefings; inputted the information into the database and circulated the resulting reports; tested the ECDC's teleconference and videoconference systems with Portugal; and took part in videoconferences with both Portugal and the European Commission.

All involved recognised that the integration of expertise from Member States in the ECDC's epidemic intelligence work contributes to a better understanding of the main needs and priorities regarding personnel, facilities, tools, equipments and products at Member State level. For Portugal, the main priorities were to identify areas of work needing greater organisation and coordination; to increase the collaboration between departments and units performing indicator-based and event-based surveillance at national, regional and local levels, and potentially at European and international level; and to facilitate communication between the risk assessment and the risk management levels.

The experience helped ECDC identify a model to support Member States with epidemic intelligence activities, and acted as the first operational step toward promoting networking in this field, and a better understanding of procedures, equipment and tools among Member States.

Based on the needs and priorities identified, the specific learning objectives, targets, and methods for a training-of-trainers epidemic intelligence workshop to take place in Portugal in the spring of 2008 were defined. This will be supervised by experts from the ECDC.

The findings and lessons learned from this initiative were shared with all EU Member States during the 3rd ECDC Consultation on Epidemic Intelligence in Europe, which took place in Stockholm on 5-6 December 2007. Several delegates expressed their interest in the initiative, and it was suggested that representatives from Member States could be placed at the ECDC for a period to participate in the Centre's daily activities and that Member States could also join in the Centre's daily epidemic intelligence briefings via teleconference.

References

1. Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control. Available from: http://www.ecdc.europa.eu/About_us/Key_Documents/ecdc_regulations.pdf
2. Paquet C, Coulombier D, Kaiser R, Ciotti M. Epidemic intelligence: a new framework for strengthening disease surveillance in Europe. Euro Surveill 2006;11(12):212-4. Available from: http://www.eurosurveillance.org/em/v11n12/1112-223.asp

This article was published on 7 February 2008.

Citation style for this article: Coulombier D, Ciotti M, Freitas G, Frota A, Varela C, Vasconcelos P, Fernandes T. Strengthening Europe's epidemic intelligence capacity: the first collaboration between a European Union Member State and the European Centre for Disease Prevention and Control. Euro Surveill. 2008;13(6):pii=8034. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8034

Mumps outbreak ongoing since October 2007 in the Republic of Moldova

H Bernard (bernardh@rki.de)[1,2], N G Schwarz[3,4], A Melnic[5], V Bucov[5], N Caterinciuc[5], R G Pebody[6,4], M Mulders[7], C Aidyralieva[7], S Hahné[7,8]

1. Robert Koch Institut (RKI), Berlin, delegated to Bavarian Health and Food Safety Authority (LGL), Oberschleissheim, Germany
2. Postgraduate Training for Applied Epidemiology (PAE, German Field Epidemiology Training Program, FETP), Germany
3. Institut de Veille Sanitaire (French National Institute of Health, InVS), Paris, France
4. European Training Programme for Intervention Epidemiology (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
5. National Scientific and Practical Centre of Preventive Medicine (NSPCPM), Chisinau, Republic of Moldova
6. Health Protection Agency (HPA), London, United Kingdom
7. World Health Organization (WHO) Regional Office for Europe, Copenhagen, Denmark
8. Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment, RIVM), Bilthoven, The Netherlands

The Republic of Moldova is experiencing a nationwide mumps outbreak, with a total of 19,550 notified cases as of 23 March 2008.

The outbreak started in October 2007, with 105 cases notified in that month compared to an average number of 24 cases per month notified between January and September 2007. Between 1 October and 31 December 2007, 1,524 cases were notified.

In the Republic of Moldova, mumps monovalent vaccination was introduced in 1983 as a single-dose schedule targeting children aged 15-18 months-old. Since 2002, a second dose has been administered to six- to seven-year-olds (birth cohorts from 1995 onwards), using a combined vaccine for measles, mumps, and rubella (MMR). Reported mumps vaccination coverage has been high since its introduction, except for a period in the early 1990s when a vaccine shortage occurred due to political changes. Successful catch-up campaigns subsequently improved vaccination coverage in those birth cohorts affected by the vaccine shortage. According to routine national surveillance data, coverage with one dose of mumps vaccine is ≥94% in individuals born in 1989-1993. Coverage with two doses is ≥96% in individuals born in 1995-2000. Coverage in the 1994 birth cohort is 99% and 21% with one and two doses, respectively. The most recent large mumps outbreak in the Republic of Moldova occurred in 1996-1998, with 28,845 cases reported, predominantly from birth cohorts 1983-1990 (60%).

In February 2008, the country's Ministry of Health invited an international outbreak investigation team coordinated by the World Health Organization Regional Office for Europe, to identify the extent of the mumps outbreak and assess cases and their possible risk factors for acquiring mumps, and to provide recommendations for the current outbreak.

The following is a preliminary description of the extent and characteristics of the outbreak until 2 March.

Methods

In the Republic of Moldova, mumps cases are notified by family doctors, hospitals and health centres to 44 Regional Centres for Preventive Medicine (RCPMs), with date of onset, initial diagnosis, hospitalisation, and vaccination history where available. The RCPMs aggregate and transmit the data to the National Scientific and Practical Centre for Preventive Medicine (NSPCPM) on a monthly and annual basis. In addition to the routine communicable diseases reporting, a weekly transmission of mumps data to the NSPCPM was introduced on 17 December 2007 to monitor the outbreak. These reports are based on the emergency notifications of suspected cases and contain information on age, vaccination status, hospitalisation, and number of cases in educational institutions. Here we describe the cases reported weekly between 17 December 2007 and 2 March 2008 (n=13,853).

Mumps is notified when suspected on clinical grounds by a physician. For a minority of cases (n=388, 3%), laboratory testing was carried out. Mumps IgM antibody testing in patients' sera (n=367) was performed at the NSPCPM using a mumps IgM ELISA kit (Novalisa, Novatec Immundiagnostica GmbH, Germany). Polymerase chain reaction (PCR) of clinical specimens (n=21) including throat swabs, oral fluid, and urine, was performed at the National Institute for Public Health and the Environment (RIVM) in the Netherlands, and at the Health Protection Agency (HPA), Centre for Infections, in the United Kingdom (UK).

Outbreak description

Between 1 October 2007 and 2 March 2008, a total of 14,729 mumps cases were notified in the Republic of Moldova. Case notifications increased rapidly in the weeks following the holidays around New Year's Day. The outbreak is ongoing at the time of writing this report, with a peak of 2,096 cases in week 9 of 2008 (Figure 1). The monthly incidence increased from below one case per 100,000 population in the months preceding the outbreak to 25 cases per 100,000 in December 2007 and over 170 cases per 100,000 in February 2008.

Case description

The majority of cases (n=11,128; 80%) were 15 to 24 years old (birth cohorts 1983-1992), and 60% (n=8,298) were male (Figure 2). By the end of February, all regions of the Republic of Moldova were affected by the outbreak.

Vaccination data were available for 67% (9,223 of 13,853 cases) and 96% of them had been vaccinated. Of these, 96% had received one dose of mumps vaccine and 4% had received two doses.

In total, 5,649 cases (41%) were hospitalised for epidemiological (isolation) and clinical indications, and where care was not available (e.g. students living in dormitories). Information about complications was not available at the national level. No deaths have been reported.

Of 367 serum samples taken from clinical cases (one to 28 days after onset of parotid swelling), 234 (64%) were positive for anti-mumps IgM at the NSPCPM. 313 of the 367 sera were collected eight to 28 days after disease onset, 68% of which were positive. The highest proportion of positive results was found in the sera collected between 11 and 20 days after disease onset (72%). Of 21 case sera tested with PCR at RIVM (three cases) and HPA (18 cases), 20 were positive for mumps virus. The identified genotype G5 has recently been found in several other countries including Croatia, Denmark, Germany, the UK, Canada, and the United States (US) (personal communication with Dr K. Brown/Dr L. Jin, HPA).

Public health measures

For this outbreak, the NSPCPM recommended hospitalisation for epidemiologic indications of those cases for whom isolation was not guaranteed at home, particularly for cases living in dormitories and boarding schools. Recommended isolation was 10 days from onset of parotid swelling.

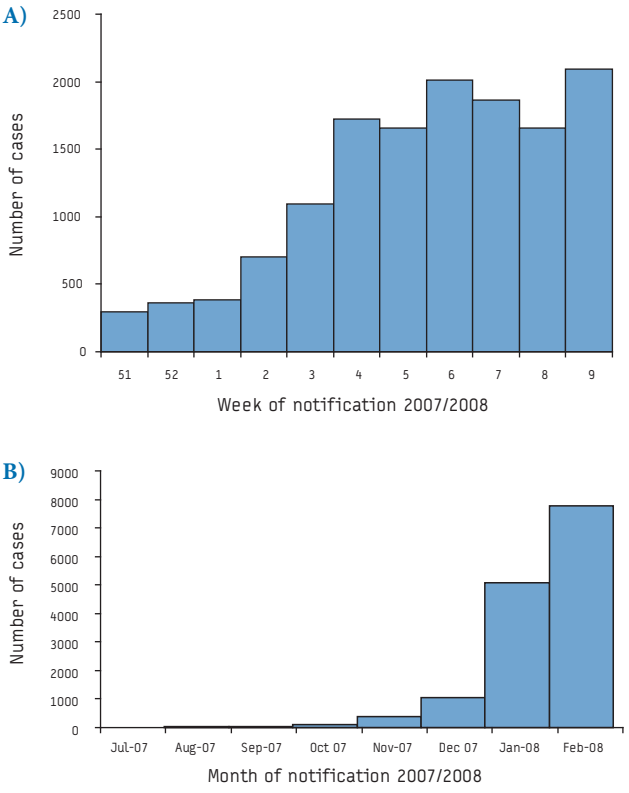
In January 2008, the Ministry of Health and the NSPCPM initiated the procurement of 600,000 doses of MMR vaccine for a Supplemental Immunisation Activity (SIA). As of 6 March 2008, a total of 42,500 doses had arrived in the Republic of Moldova and were distributed to health facilities. The SIA began in week 9 of 2008 targeting individuals in all settings born between 1989 and 1994 (including pupils, students and postgraduate students in all educational institutions; teaching staff born between 1984 and 1988; army, police, and border troops). Information on the total number of MMR vaccine doses administered to date during the SIA is not available.

Discussion

The Republic of Moldova is facing a large ongoing mumps outbreak in teenagers and young adults, the majority of whom have previously been vaccinated with one dose of monovalent mumps vaccine. Mumps outbreaks comparable to this one with respect to size and affected age group have occurred recently in several countries, including the UK, the US, and Canada. In the outbreak in the UK [1,2,3], 79% of cases in 2004 occurred in individuals born between 1980-1989. Almost two thirds of the cases were unvaccinated, however, 30% had received a single dose of MMR. In the outbreaks in the US and Canada [4], 49% of the cases had been vaccinated twice. Mumps vaccine failure has often been attributed to primary vaccine failure, i.e. an insufficient immune response after vaccination [5]. More recent studies have suggested that secondary vaccine failure, i.e. decreasing antibody titres over

Figure 1

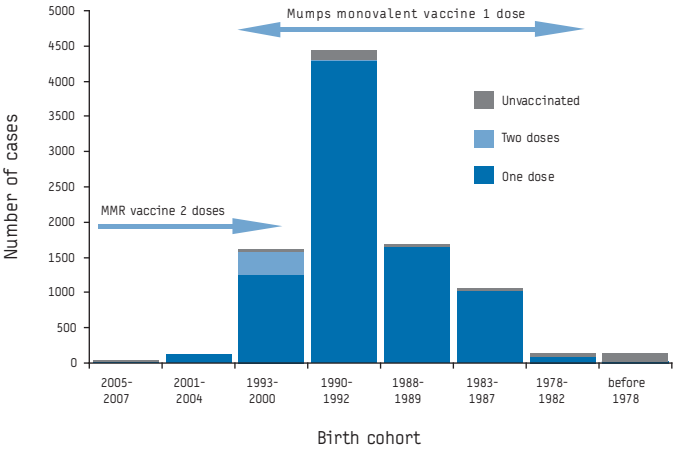
Mumps cases
A) by week (17 December 2007 to 2 March 2008, n=13,853) and B) by month (July 2007 to February 2008, n=14,438) of notification, Republic of Moldova*



* Data source: NSPCPM, Republic of Moldova

Figure 2

Mumps cases with known vaccination status by aggregated birth cohorts, vaccination status, and vaccination schedules corresponding to birth cohorts*, Republic of Moldova, 17 December 2007 to 2 March 2008 (n=9,223)**



* Subdivided data on vaccination schedule for cases in birth cohorts 1993–2000 and 1978–1982 not available at the national level
** Data source: NSPCPM, Republic of Moldova

time (waning immunity), contributes to the recurrence of mumps outbreaks [6,7]. In the current outbreak, the high reported vaccine coverage with a single dose of mumps vaccine among the cases suggests that "failure to vaccinate" did not play a major role as the cause of the outbreak. Primary and secondary vaccine failure [5,8] for one dose of mumps vaccine are currently being investigated in a further epidemiological study.

A high proportion of cases in this outbreak were hospitalised, mainly to ensure isolation but also for clinical and social indications. However, as mumps is most infectious from two days before to four days after onset of illness, and inapparent infections can be communicable, hospital admission is not expected to prevent the majority of transmission in the population [9].

Outbreak control is ongoing with vaccination of high risk groups with MMR vaccine, consistent with a recent WHO position paper on mumps [10]. To address potential concerns of adverse events following immunisation (AEFI), AEFI surveillance including laboratory investigation of suspected meningitis cases and training of primary health care staff and epidemiologists will accompany this immunisation campaign.

Acknowledgements

The authors would like to thank the staff of the RCPMs for providing the data, Dr R van Binnendijk (RIVM), Dr K Brown (HPA) and Dr L Jin for providing laboratory data, Dr V Bremer (ECDC/EPIET) for helpful comments on the manuscript, T Gavrilenco for translating, the Ministry of Health of the Republic of Moldova, Dr I Bahnarel (NSPCPM), and Dr P Ursu (WHO Country Office, Republic of Moldova) for their support during the mission.

Note: H Bernard and NG Schwarz contributed equally to this article.

References

1. Cohen C, White JM, Savage EJ, Glynn JR, Choi Y, Andrews N, et al. Vaccine effectiveness estimates, 2004-2005 mumps outbreak, England. Emerg Infect Dis. 2007;13(1):12-7.
2. Savage E, Ramsay M, White J, Beard S, Lawson H, Hunjan R, et al. Mumps outbreaks across England and Wales in 2004: observational study. BMJ. 2005;330(7500):1119-20.
3. Peltola H, Kulkarni PS, Kapre SV, Paunio M, Jadhav SS, Dhere RM. Mumps outbreaks in Canada and the United States: time for new thinking on mumps vaccines. Clin Infect Dis. 2007;45(4):459-66.
4. Centers for Disease Control and Prevention. Mumps epidemic - United Kingdom, 2004–2005. MMWR Morb Mortal Wkly Rep. 2006; 55(7):173-5. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5507a1.htm
5. Briss PA, Fehrs LJ, Parker RA, Wright PF, Sannella EC, Hutcheson RH, et al. Sustained transmission of mumps in a highly vaccinated population: assessment of primary vaccine failure and waning vaccine-induced immunity. J Infect Dis. 1994;169(1):77-82.
6. Park DW, Nam MH, Kim JY, Kim HJ, Sohn JW, Cho Y, et al. Mumps outbreak in a highly vaccinated school population: assessment of secondary vaccine failure using IgG avidity measurements. Vaccine. 2007;25(24):4665-70.
7. Vandermeulen C, Roelants M, Vermoere M, Roseeuw K, Goubau P, Hoppenbrouwers K. Outbreak of mumps in a vaccinated child population: a question of vaccine failure? Vaccine 2004;22(21-22):2713-6.
8. Hersh BS, Fine PE, Kent WK, Cochi SL, Kahn LH, Zell ER, et al. Mumps outbreak in a highly vaccinated population. J Pediatr. 1991;119(2):187-93.
9. Robertson S. Mumps. In: Heymann DL, editor. Control of Communicable Diseases Manual. 18th ed. The American Public Health Association; 2004. p. 409-13.
10. WHO. Mumps virus and vaccines. Weekly epidemiological record 2007;82(7):51-60. Available from: http://www.who.int/entity/wer/2007/wer8207.pdf

This article was published on 27 March 2008.

Citation style for this article: Bernard H, Schwarz NG, Melnic A, Bucov V, Caterinciuc N, Pebody RG, Mulders M, Aidyralieva C, Hahné S. Mumps outbreak ongoing since October 2007 in the Republic of Moldova. Euro Surveill. 2008;13(13):pii=8079. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8079

Isolation of a *Vibrio parahaemolyticus* pandemic strain from a marine water sample obtained in the northern Adriatic

G Caburlotto[1], V Ghidini[1], M Gennari[1], M C Tafi[1], M M Lleo (maria.lleo@univr.it)[1]
1. Department of Pathology, Section of Microbiology, University of Verona, Verona, Italy

Vibrio parahaemolyticus is a halophilic bacterium capable of causing food- and waterborne gastroenteritis, wound infections, and septicaemia in humans. The wide distribution of *V. parahaemolyticus* in the marine and estuarine environments is known to depend on the water temperature: it has been suggested that the bacterium might survive in sediments during the winter and be released into the water column in late spring or early summer when the temperature rises to 15°C or higher [1].

The microorganism is frequently isolated from a variety of raw seafood and shellfish. Consumption of raw or undercooked seafood contaminated with *V. parahaemolyticus* may lead to the development of acute gastroenteritis characterized by diarrhoea, headache, vomiting, nausea, and abdominal cramps. This bacterial species is a common cause of foodborne illnesses in many Asian countries, including China (31.1% of foodborne outbreaks reported between 1991 and 2001), Japan (reported to account for 20–30% of foodborne infection cases from 1981 to 1993) and Taiwan (1,495 cases reported between 1981 and 2003, representing 69% of all bacterial foodborne outbreaks in this period) [2,3,4]. Moreover, it is recognized as the leading cause of human gastroenteritis associated with seafood consumption in the United States [5]. In Europe, the risk of *V. parahaemolyticus* infections is considered to be very low [6,7] and for this reason the monitoring of this microorganism has been excluded from the most important European infectious disease surveillance networks. However, sporadic outbreaks have been reported in countries such as Spain (important outbreaks reported in 1989, 1999 and 2004) [8] and France (a serious outbreak reported in 1997) [9].

Less commonly, this bacterial species can cause infections in the skin when an open wound is exposed to warm seawater (>15°C). Severe wound infections and septicaemia have also been reported mainly in immunosuppressed, children and aged people. Recently seven cases of skin infections caused by *V. parahaemolyticus* species have been described in Denmark linked to bathing in the Baltic Sea [10].

V. parahaemolyticus infection has traditionally been associated with two virulence factors – thermostable direct haemolysin (TDH) and TDH-related haemolysin (TRH) [6]. While more than 90% of the clinical isolates present the *tdh* gene, to date pathogenic strains containing *tdh* and/or *trh* genes have been detected with low frequency (usually 0.3 to 3%) in the total *V. parahaemolyticus* environmental population [11].

During a hospital-based survey in Calcutta, India, a sudden increase in the proportion of infections associated with *V. parahaemolyticus* serotype O3:K6 was detected [2]. This highly virulent strain accounted for 63% of all *V. parahaemolyticus* strains isolated from patients in Calcutta between September 1996 and April 1997 and was subsequently obtained in high rates from patients in other southeast Asian countries and from travellers arriving in Japan from this region [12,13]. Increased incidences of gastroenteritis caused by this serovar have been reported in many countries since 1996 [12,13,14]. Therefore, as a result of its rise in incidence with identical phenotypic and genotypic features, this emerging *V. parahaemolyticus* strain has been termed a 'pandemic strain'. Currently the so-called 'pandemic group' [15] includes the 'pandemic' O3:K6 strain and the newly emerged O4:K68, O1:K25, O1:K26, and O1:K untypeable strains.

While all the strains of *V. parahaemolyticus* are identified by the species-specific genetic markers *tlh* and *toxR* genes, 'pandemic' *V. parahaemolyticus* strains can be identified by group-specific GS-PCR based on the sequence variation in the *toxRS* gene [15]. A strain possessing both *tdh* and *toxRS/new* can be considered a 'pandemic strain'. In addition, most of the 'pandemic strains' have a novel open reading frame *orf8*, which corresponds to a filamentous phage f237 [16].

During a series of sampling campaigns organized within the framework of the international VibrioSea project* and conducted in the north of the Adriatic Sea in the area of the Venetian lagoon from June 2006 to November 2007, a collection of environmental *V. parahaemolyticus* strains was obtained. They were isolated mainly during the warm season (from May to October) and have been found in water, plankton and sediment samples.

After the biochemical identification, using the Biomérieux API ID system, all the strains were confirmed as *V. parahaemolyticus* by PCR detection of the species-specific markers, genes *tlh* and *toxR* [17]. Screening conducted on the whole collection revealed, in one of the analyzed strains (strain VPeVE*pan*), the presence of the virulence gene *tdh* and the 'pandemic'-specific marker, gene *orf8*. The presence of each one of these genes was confirmed by

PCR with a second pair of primers selected in a different area of the same nucleotide sequence. The strain also tested positive to a group-specific PCR (GS-PCR) conducted with a pair of primers selected in the *toxRS* gene. The strain was isolated in May 2007 in a marine water sample taken from the coastal site in the locality Caleri, close to the estuary of the Adige and Brenta rivers, 500 m from the coastline). Serological characterization and molecular typing is ongoing and the genes are currently being sequenced in order to compare this strain with other 'pandemic strains' of environmental and clinical origin, isolated in Europe and Asia.

On the basis of these findings and the data from the literature, this strain should be considered to have the potential to cause human illness because it carries the three 'pandemic' genetic markers. To the best of our knowledge, this is the first strain of *V. parahaemolyticus* isolated in the Italian coastal environment and the first isolated directly from an environmental water sample in Europe containing the genetic markers characterizing 'pandemic strains' (*tdh*, *orf8*, *toxRS/new*). Previously, 'pandemic strains' similar to the ones isolated in Asia, had been detected in the Galicia region of Spain [14] and in France [18], yet these strains were in all cases clinical isolates or strains isolated from seafood and not from the environment itself.

The results reported here indicate that the environmental strains belonging to human pathogenic *Vibrio* species isolated in Europe should be considered as potential carriers of virulence genes including those encountered in 'pandemic strains'. Because of their pathogenic potential their presence should be placed under surveillance as they could represent a risk for human health.

*The VibrioSea project is an ongoing international research project funded by Centre National d'Etudes Spatiales (CNES) and Institut Pasteur, France.

Acknowledgements

The authors would like to thank Giorgio Socal, Franco Bianchi, Fabrizio Bernardi and Mauro Bastianini from Istituto di Scienze Marine – Consiglio Nazionale delle Ricerche (ISMAR-CNR), Venice, Italy, for their help and collaboration in the sampling campaigns during which the described *V. parahaemolyticus* strain has been isolated.

References

1. Kaneko T, Colwell RR. Ecology of Vibrio parahaemolyticus in Chesapeake Bay. J Bacteriol. 1973;113(1):24-32
2. Nair GB, Ramamurthy T, Bhattacharya SK, Dutta B, Takeda Y, Sack DA. Global dissemination of Vibrio parahaemolyticus serotype O3:K6 and its serovariants. Clin Microbiol Rev. 2007;20:39-48.
3. Liu X, Chen Y, Wang X, Ji R. Foodborne disease outbreaks in China from 1992 to 2001 national foodborne disease surveillance system. Wei Sheng Yan Jiu. 2004;33:725-727.
4. Muramatsu K. Comparison of epidemiological markers for Vibrio parahaemolyticus isolated from food poisoning. Kansenshogaku Zasshi. 1999;73:179-186.
5. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, Griffin PM, Tauxe RV. Food-related illness and death in the United States. Emerg Infect Dis. 1999;5:607-625.
6. Yi-Cheng Su and Chengchu Liu. Vibrio parahaemolyticus: A concern of seafood safety. Food Microbiology 2007;24:549-558.
7. Opinion of the Scientific Committee on Veterinary measures relating to public health on Vibrio vulnificus and Vibrio parahaemolyticus. European Commission, 2001.
8. Lozano-León A, Torres J, Osorio CR, Martínez-Urtaza J. Identification of tdh-positive Vibrio parahaemolyticus from an outbreak associated with raw oyster consumption in Spain. FEMS Microbiol Lett. 2003,226:281-284.
9. Robert-Pillot A, Guénolé A, Lesne J, Delesmont R, Fournier JM, Quilici ML. Occurrence of the tdh and trh genes in Vibrio parahaemolyticus isolates from waters and raw shellfish collected in two French coastal areas and from seafood imported into France. Int J Food Microbiol. 2004;91:319-325.
10. Andersen PH. Infections with seawater bacteria. EPI-NEWS 2006;(26-32):1. Available from: http://www.ssi.dk/graphics/en/news/epinews/2006/PDF/2006-26_32-final-www_2.pdf
11. Nordstrom JL, Vickery MC, Blackstone GM, Murray SL, DePaola A. Development of a multiplex real-time PCR assay with an internal amplification control for the detection of total and pathogenic Vibrio parahaemolyticus bacteria in oysters. Appl. Environ. Microbiol. 2007;73:5840-5847.
12. Chiou CS, Hsu SY, Chiu SI, Wang TK, Chao CS. Vibrio parahaemolyticus serovar O3:K6 as cause of unusually high incidence of food-borne disease outbreaks in Taiwan from 1996 to 1999. J Clin Microbiol. 2000;38:4621-4625.
13. Vuddhakul V, Chowdhury A, Laohaprertthisan V, Pungrasamee P, Patararungrong N, Thianmontri P, Ishibashi M, Matsumoto C, Nishibuchi M. Isolation of a pandemic O3:K6 clone of a Vibrio parahaemolyticus strain from environmental and clinical sources in Thailand. Appl Environ Microbiol. 2000;66:2685-2689.
14. Martinez-Urtaza J, Simental L, Velasco D, DePaola A, Ishibashi M, Nakaguchi Y, Nishibuchi M, Carrera-Flores D, Rey-Alvarez C, Pousa A. Pandemic Vibrio parahaemolyticus O3:K6, Europe. Emerg Infect Dis. 2005;11:1319-1320.
15. Okura M, Osawa R, Iguchi A, Arakawa E, Terajima J, Watanabe H. Genotypic analyses of Vibrio parahaemolyticus and development of a pandemic group-specific multiplex PCR assay. J Clin Microbiol. 2003;41:4676-4682.
16. Myers ML, Panicker G, Bej AK. PCR detection of a newly emerged pandemic Vibrio parahaemolyticus O3:K6 pathogen in pure cultures and seeded waters from the Gulf of Mexico. Appl. Environ. Microbiol. 2003;69:2194-2200.
17. Kim YB, Okuda J, Matsumoto C, Takahashi N, Hashimoto S, Nishibuchi M. Identification of Vibrio parahaemolyticus strains at the species level by PCR targeted to the toxR gene. J. Clin. Microbiol. 1999;37:1173-1177.
18. Quilici ML, Robert-Pillot A, Picart J, Fournier JM. Pandemic Vibrio parahaemolyticus O3:K6 spread, France. Emerg Infect Dis. 2005;11:1148-1149.

This article was published on 13 March 2008.

Citation style for this article: Caburlotto G, Ghidini V, Gennari M, Tafi MC, Lleo MM. Isolation of a Vibrio parahaemolyticus pandemic strain from a marine water sample obtained in the northern Adriatic. Euro Surveill. 2008;13(11):pii=8068. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8068

Identification of a rabid dog in France illegally introduced from Morocco

French multidisciplinary investigation team

Introduction

On 26 February 2008, the National Reference Centre for Rabies at the Institut Pasteur in Paris, France, confirmed the diagnosis of rabies in a domestic dog living in Grandpuits, Seine-et-Marne district, a suburb of Paris. The dog was a nine-month-old mixed-breed female, named Cracotte (pictures available at http://www.invs.sante.fr/display/?doc=surveillance/rage/actu.htm). It developed its first symptoms on 15 February, had bitten its owner and one neighbour and had been euthanized on 19 February. The viral strain was identified by the National Reference Centre for Rabies as a strain belonging to Lyssavirus genotype 1, Africa 1 lineage, originating from Morocco. According to its owner, Cracotte had never been outside France. France has been declared officially rabies-free since 2001. An investigation was undertaken to identify the source of infection and modes of transmission for Cracotte in order to identify potentially exposed individuals and animals and to carry out an assessment of the risk of rabies virus transmission in France.

Investigation

Origin of infection and chain of transmission

The owners of Cracotte had a second dog, a female black mixed-breed Labrador named Youpee. Youpee was euthanized on 5 January after an illness of short duration. Retrospectively, its symptoms were compatible with rabies. Youpee had been in contact with a dog named Gamin during a stay in the Gers district of southern France in November 2007. Gamin was euthanized on 12 November 2007 because of an illness that, retrospectively, would be compatible with rabies. Both Youpee and Gamin had been incinerated and had not been tested for rabies. Gamin had been illegally introduced into France from Morocco, and is the likely index dog that infected Youpee, that subsequently infected Cracotte.

Areas and periods at risk

The probable index case Gamin and its two owners left Morocco by ferry on 20 October 2007 and reached France by car via Portugal and Spain. The owners reported having spent three days in Portugal on a beach (precise location unknown), then drove through Spain without stopping. They arrived in the Hautes-Pyrénées district on 28 October 2007 and stayed there with a friend in an industrial area that had no other inhabitants until 1 November 2007. According to the owners and their host, Gamin was kept inside the car and had no contact with persons except for their host, and no contact with other animals, during these three days. The owners then drove to the Gers district, where they stayed and where Gamin was euthanatized the 12 November 2007. Gamin and Youpee stayed together in the Gers district, where Youpee was probably contaminated by Gamin. Youpee and its owner left the Gers district for Seine-et-Marne by train on 29 November 2007. It stayed in Seine et Marne until it was euthanized on 5 January 2008. Youpee and its owner traveled by train outside the district for three days (15-17 December) to Lisieux (Calvados district, Normandy).

The at-risk period for transmission of rabies to humans or animals is considered to begin from the first day of estimated viral excretion of the dogs and to be ongoing (due to possible secondary animal cases). We assumed that viral excretion started 15 days before the onset of symptoms of illness. As of 13 March 2008, the geographical areas and periods at risk are as follows:

- Montestruc-sur-Gers (Gers district) and surroundings, from 1 November 2007;
- Grandpuits (Seine-et-Marne district) and surroundings, from 15 December 2007;
- Lisieux (Calvados district) and surroundings, from 15 December 2007.

Control measures

An active tracing of people and animals in contact with the three dogs has been carried out by health and veterinary authorities in the three districts. To date, 177 people with close contacts with one of the three dogs have been identified and referred to the rabies vaccination centres; 152 of them have been vaccinated and several also received immunoglobulins. A national rabies hotline has been implemented for the public at the Ministry of Health (00.33/800.13.00.00). Local and national press releases have been issued to relay the message that any individual who could have had a potentially contaminating contact with one of the three dogs or with any other dog in the at-risk area during the at-risk period should contact the hotline. Pictures of the dog have been shown on television, in newspapers and on the internet. Owners of dogs that might have been exposed to the infected dogs have been advised to contact their district veterinary services. As of 10 March, no additional exposed individuals have been identified among the 1,071 people who have called the hotline. No human nor animal contact with the rabid dog Youpee has yet been identified among the passengers during the trip by train of its owner (between Paris and Lisieux cities on 15 and 17 December).

Dogs and cats having been in contact with one of the three dogs have been euthanized or placed under observation. To date, seven dogs and a cat were euthanized and all tested negative for rabies. Owners of dogs and cats in the three districts have been recommended to keep their cats indoors, put their dogs on leashes and have their pets legally identified. The veterinary services are maintaining a high level of vigilance.

The French hospital emergency medical services and general practitioners were informed, via email, of the event and of the need for anti-rabies prophylaxis for patients with any potentially contaminating contact with one of the three dogs or any other unknown dog or cat, especially in the three districts involved. All rabies clinics were informed by the National Reference Centre for Rabies. Moreover, pediatricians, intensive care physicians, neurologists and infectious disease experts have all been informed by email in order to strengthen awareness and increase the likelihood of early diagnosis in the event of a human case. To date, no suspect human cases have been reported.

The last case of indigenous human rabies transmitted by a carnivore in France occurred in 1924. Human cases of imported rabies are rare, with only 20 cases identified in France between 1970 and 2008 (90% of them from Africa). Since 2000, nine imported cases have been reported in Western Europe [1]. Two of them contracted their infection in Morocco [2,3]. In France, rabies was endemic in foxes, especially along the German border in eastern France, until the 1990s [4]. In 2001, after 30 years of extensive control measures, including oral vaccination of foxes, and in the absence of cases of rabies identified in terrestrial carnivores since 1998, the World Organisation for Animal Health declared France free of rabies in terrestrial animals. Surveillance of rabies in carnivores has been maintained in order to detect any re-introduction of the virus.

This event is not the first illegal introduction of a carnivore from a rabies-endemic country into France [5,6]. In 2004, three cases of canine rabies were diagnosed. All three dogs were illegally imported from Morocco and reached France after having been transported through Spain by car. No secondary transmission to humans or carnivores occurred during those events. The sanitary regulations regarding rabies vaccination status of all carnivores entering the European Union are essential for rabies control, and must be strictly applied in European areas that have been declared rabies-free. This applies to France in particular, as the illegal pet importation route from Morocco through Spain to France has previously been reported.

For further information, please contact Alexandra Mailles at the Institut de Veille Sanitaire (a.mailles@invs.sante.fr) or the National Reference Centre for rabies at the Institut Pasteur (cnrrage@pasteur.fr).

*The French investigation team: Gérard Allibert, Direction départementale des services vétérinaires (DDSV) de Seine-et-Marne; Philippe Barret, DDSV Hautes-Pyrénées; Martine Bernardi, DDSV du Calvados; Pascal Birba, DDSV Hautes-Pyrénées; Laurine Bouteiller, Direction générale de l'alimentation (DGAl); Hervé Bourhy, Centre nationale de référence (CNR) de la rage; Pascal Capdepon, Direction département des affaires sanitaires et sociales (DDASS) des Hautes-Pyrénées; Jacques Chemardin, Direction générale de la santé (DGS); Laurent Dacheux, CNR de la rage; Olivier Debaere, DGAl; Catherine Delattre, DDASS du Calvados; Henriette De Valk, Institut de veille sanitaire (InVS); Véronique Dubois, DDSV Hautes-Pyrénées; Raphael Fayaz, DDSV du Calvados; Catherine Famose, DDSV du Gers; Maryvonne Goudal, CNR de la rage et centre anti-rabique (CAR) de Paris; Madeleine Lesage, DGS; Colette Luent, DDSV Hautes-Pyrénées; Norbert Lucas, DDSV du Calvados; Alexandra Mailles, InVS; Elodie Marti, DDSV du Gers; Marie-Claire Paty, DGS; Gilles Portejoie, DDSV de Seine-et-Marne; Sylvain Posière, DDSV Seine-et-Marne; Christine Saura, InVS; Laurent Stein, DDASS du Gers; Véronique Vaillant, InVS; Renaud Verdon, CAR du centre hospitalier universitaire de Caen (Calvados); Marie-Claude Zaslavsky, DDASS de Seine-et-Marne; Pascaline Zeller, DDSV Hautes-Pyrénées.

References

1. Bourhy H, Dacheux L, Strady C, Mailles A. Rabies in Europe in 2005. Euro Surveill 2005;10(11):213-6. Available from: http://www.eurosurveillance.org/em/v10n11/1011-222.asp
2. Krause R, Bago Z, Revilla-Fernandez S, Loitsch A, Allerberger F, Kaufmann P, Smolle KH, Brunner G, Krejs GJ. (2005) Travel-associated rabies in Austrian man. Emerging Infectious Diseases 11: 719-721.
3. Rabies – Germany (Hamburg) ex Morocco, Promed. Available from: http://www.promedmail.org/pls/otn/f?p=2400:1202:9783610374088857::NO::F2400_P1202_CHECK_DISPLAY,F2400_P1202_PUB_MAIL_ID:X,37114
4. Toma B. Fox rabies in France. Euro Surveill 2005;10(11):220-2. Available from: http://www.eurosurveillance.org/em/v10n11/1011-224.asp
5. World Health Organization Communicable Disease Surveillance & Response. Rabies in France. Disease Outbreak News. 1 September 2004. Available from: http://www.who.int/csr/don/2004_09_01a/en
6. Servas V, Mailles A, Neau D, Castor C, Manetti A, Fouquet E et al. An imported case of canine rabies in Aquitaine: Investigation and management of the contacts at risk, August 2004-March 2005. Euro Surveill 2005;10(11):222-5. Available from: http://www.eurosurveillance.org/em/v10n11/1011-225.asp

This article was published on 13 March 2008.

Citation style for this article: French multidisciplinary investigation team. Identification of a rabid dog in France illegally introduced from Morocco. Euro Surveill. 2008;13(11):pii=8066. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8066

Identification of a rabid dog in France illegally introduced from Morocco: comment

Lara Payne (lara.payne@ecdc.europa.eu)1, on behalf of the Preparedness and Response Unit threat event team*[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

As highlighted in the above article by a multidisciplinary investigation team from France, there have been previous reports of dogs being illegally introduced to France and subsequently identified with rabies infection. No human cases related to these events have been identified to date. Although exposure to rabies from animals in the European Union (EU) remains a rare event, in the absence of post-exposure prophylaxis before symptoms rabies is invariably a deadly infection in humans. The French authorities have implemented extensive measures, including the tracing of humans and animals possibly in contact with the suspected rabid dogs, and awareness of the event has been relayed to the general public through the media in order to assist in identifying other possible human or animal contacts.

The index dog was reported to have been in Portugal for a few days while travelling to France. Thus, information to the public has also been published by the Portuguese health authorities on the website of the Ministry of Health (http://www.dgs.pt). It cannot be excluded that other EU citizens who have visited those particular geographical areas in France or Portugal during these periods may have been bitten or scratched by the index dog. The European Centre for Disease Prevention and Control (ECDC) thus published a threat assessment of this event on its website (http://www.ecdc.europa.eu/pdf/threat%20assessment%20080311_.pdf) to raise awareness among clinicians for returning travellers from the at-risk areas during the at-risk periods who may have been in contact with these dogs.

This event in animals also emphasises the importance of good communication between animal and human health authorities, in each country and at the EU level, in identifying and responding to any subsequent threat to human health from animal health events.

* The Preparedness and Response Unit threat event team included: D Coulombier, L Payne, C Varela, M Ciotti, H Needham, B Ciancio

This article was published on 13 March 2008.

Citation style for this article: Payne L, on behalf of the Preparedness and Response Unit threat event team*. Identification of a rabid dog in France illegally introduced from Morocco: comment. Euro Surveill. 2008;13(11):pii=8067. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8067

Asian tiger mosquito (*Aedes albopictus*) - a threat for Switzerland?

M N Wymann (monica.wymann@bag.admin.ch)[1], E Flacio[2], S Radczuweit[2], N Patocchi[3], P Lüthy[4]
1. Swiss Federal Office of Public Health, Berne, Switzerland
2. Mosquito Working Group, Dipartimento della sanità e socialità, Bellinzona, Switzerland
3. Foundation Bolle di Magadino, Magadino, Switzerland
4. Institute of Microbiology, Swiss Federal Institute of Technology, Zurich, Switzerland

The Asian tiger mosquito, Aedes albopictus (Stegomya albopicta) originating from south-east Asia, has spread primarily by the trade of used tyres to the United States, Europe, Latin America and Africa [1]. In Italy, the mosquito species was first detected in Genoa in 1990 and has since spread to several parts of the country, including border areas with Switzerland [2]. In 2000, an active monitoring system was established in southern Switzerland. The first tiger mosquito was detected in the canton of Ticino in 2003 [3]. Monitoring was gradually intensified due to growing mosquito densities in northern Italy. As the long-distance migration of Ae. albopictus depends on passive transport, the monitoring system consisted of strategically positioned oviposition traps along main traffic axes, including parking lots within industrial complexes, border crossings and shopping centres. In 2007, this monitoring system consisted of over 70 checkpoints with a total of 300 traps. Bi-weekly control visits to all traps were conducted between April and November 2007. As soon as eggs were detected, the surrounding vegetation within a perimeter of about 100 metres was sprayed with permethrin against adult mosquitoes. Stagnant water was treated with Bacillus thuringiensis and in some cases with diflubenzuron to control the larval stages.

Between 2003 and 2006, the tiger mosquito density (1.4-3.3% positive traps) detected by the monitoring system was low enough to support the hypothesis that individual adults had been introduced sporadically from Italy but had not been able to establish locally. However, the situation changed significantly in 2007. Within the border city of Chiasso, a dramatic increase of positive traps and a higher number of eggs were both observed, indicating that a local mosquito population had established (Figure 1 and 2). At the same time, based on information offered by a member of the public, the first tiger mosquito was confirmed in Switzerland north of the Alps, in the canton of Aargau.

Ae. albopictus has a high vector competence for chikungunya and dengue viruses [4]. The establishment of this mosquito species therefore represents a potential threat for the autochthonous transmission of viral infections. An autochthonous transmission of chikungunya by Ae. albopictus occurred in Italy in 2007, with over 200 confirmed cases [5].

In response to the establishment of the vector species, and in line with the recommendations of the European Centre for Disease Prevention and Control (ECDC) following the outbreak in Italy [5], chikungunya was made a notifiable disease in Switzerland in January 2008. In addition, the monitoring strategy of Ae. albopictus will be adapted to the new situation by intensifying the surveillance in Chiasso and its neighbouring communities. Based on the experience

Figure 1

Proportion of positive ovitraps checked during the monitoring program on *Ae. albopictus* in Ticino, Switzerland, 2007 (without Chiasso)

(Positive traps resulted in immediate insecticidal and larvicidal treatments of the surrounding)

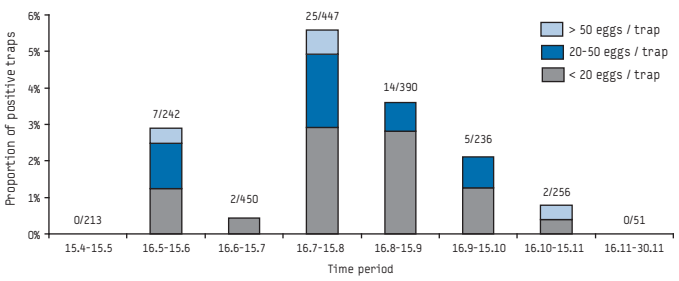
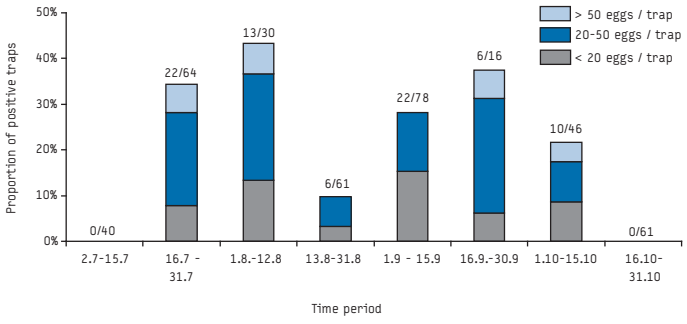


Figure 2

Proportion of positive ovitraps checked in Chiasso during the monitoring program on *Ae. albopictus* in Ticino, Switzerland, 2007

(Positive traps resulted in immediate insecticidal and larvicidal treatments of the surrounding)



gained in southern Switzerland, a national monitoring and control strategy will be developed in 2008/09, covering environmental and public health aspects, thereby elaborating an implementation plan on the national, regional and local levels.

References

1. Reiter P, Sprenger D. The used tire trade: a mechanism for the worldwide dispersal of container breeding mosquitoes. J Am Mosq Control Assoc 1987;3:494-501.
2. Knudsen AB, Romi R, Majori G. Occurrence and spread in Italy of Aedes albopictus, with implications for its introduction into other parts of Europe. J Am Mosq Control Assoc1996;12:177-83.
3. Flacio E, Lüthy P, Patocchi N, Guidotti F, Tonolla M, Peduzzi R. Primo ritrovamento di Aedes albopictus in Svizzera. Bollettino della Società ticinese di Scienze Naturali 2004;92:141-142.
4. Gratz NG. Critical review of the vector status of Aedes albopictus. Med Vet Entomol 2004;18:215-27.
5. ECDC. Mission report on Chikungunya in Italy, 17-21.09.2007. Joint ECDC/WHO visit for European risk assessment. Available from: http://www.afpmb.org/bulletin/vol27/071020_CHK_report.pdf

This article was published on 6 March 2008.

Citation style for this article: Wymann MN, Flacio E, Radczuweit S, Patocchi N, Lüthy P. Asian tiger mosquito (Aedes albopictus) - a threat for Switzerland?. Euro Surveill. 2008;13(10):pii=8058. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8058

Oseltamivir resistance in human seasonal influenza viruses (A/H1N1) in EU and EFTA countries: an update

Influenza Project Team (influenza@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

Following the publications in Eurosurveillance on 31 January [1,2], the European Centre for Disease Prevention and Control (ECDC), the European Influenza Surveillance Scheme (EISS), the World Health Organization (WHO) and their partners have agreed to update the data on the occurrence of resistance of influenza A/H1N1 viruses to oseltamivir appearing on the ECDC and EISS websites on a weekly basis (every Thursday afternoon). Data on the ECDC website are for European Union (EU) and European Free Trade Association (EFTA) countries. The WHO has also published a global table, which it will also refresh weekly. All these data are available through an HTML page on the ECDC web-site [3]. The European data made available through EISS and the EU DG Research-funded European Surveillance Network for Vigilance Against Viral Resistance (VIRGIL) are based on the data that have been uploaded to the EISS antiviral resistance data-base by a fixed time on a Wednesday for publication on a Thursday.

Comparing this week's data with last week's, there are some obvious changes. As more samples have been tested in France the proportion of H1N1 samples with resistant strains doubled (17% to 39%), while in Norway it slightly decreased from over 70% to 64%, although Norway still has the highest proportion of resistant H1N1 strains in the EU/EFTA. However, these changes probably mostly reflect vigorous testing undertaken both by national influenza centres and the VIRGIL laboratories in the United Kingdom's Health Protection Agency with the WHO Collaborating Centre in London. Hence, week on week changes need to be interpreted cautiously, as they are more a reflection of having more testing than any changes in the under-lying epidemiology. For example, virologists in France and Germany have worked especially hard in the last week to test many more specimens. As a result, there are quite substantial changes in the overall prevalence of the resistant viruses in European countries. However, since data are available for many countries and the observed prevalence ranges from zero to over 60%, a 'European average' should probably not be considered a useful statistic.

At present, specimens are being gathered opportunistically and are relatively unselected (they can come from both sentinel groups and hospital patients). Clinicians looking at these data and considering whether patients presenting with presumed influenza have a resistant virus need to bear these facts in mind. They should also appreciate that the stated proportion of resistant isolates applies only to A/H1N1 viruses. These are the predominant strain this winter, as observed in the EISS collaborators' laboratories. However, while the A/H3 strains are few this season, around one third of specimens tested are influenza B viruses. As noted in the ECDC's interim risk assessment [4], the appearance of resistant viruses does not seem to be related to the use of oseltamivir in any simple way. It should also be emphasised that the current seasonal influenza vaccine is expected to be as effective against these new resistant viruses as they are against sensitive A/H1N1 viruses, since the match between the circulating viruses and the vaccine selection is good this year.

The EISS antiviral database has been modified to capture more information that will allow the partners engaged in this work to undertake descriptive analyses, notably on time trends. This emphasises the importance of the work of laboratories and by those who contribute clinical and epidemiological data in both gathering and forwarding those data, even retrospectively. At the same time, the partners are designing more focused studies, which will answer questions requiring comparisons of features in persons with the resistant viruses and those infected with sensitive viruses.

The WHO data (outside of Europe) are interesting, but still very preliminary. Resistant viruses have been detected in North America, China (Hong Kong) and Australia, although not yet in Japan, which is thought to have higher levels of use of oseltamivir than any other country.

* The Influenza Project Team: B Ciancio, K Fernandez de la Hoz, P Kreidl, H Needham, A Nicoll, F Plata, C Varela, A Würz, C Yilmaz

References

1. Nicoll A, Ciancio B, Kramarz P. Observed oseltamivir resistance in seasonal influenza viruses in Europe interpretation and potential implications. Euro Surveill 2008;13(5). Available from: http://www.eurosurveillance.org/edition/v13n05/080131_1.asp
2. Lackenby A, Hungnes O, Dudman SG, Meijer A, Paget WJ, Hay AJ, Zambon MC. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Euro Surveill 2008;13(5). Available from: http://www.eurosurveillance.org/edition/v13n05/080131_2.asp
3. Oseltamivir resistance in human seasonal influenza type A/H1N1 isolates in Europe (EU, EEA, EFTA countries). Table. Available from: http://ecdc.europa.eu/Health_topics/influenza/antivirals.html
4. Interim ECDC Risk Assessment. Emergence of seasonal influenza viruses type A/H1N1 with oseltamivir resistance in some European countries at the start of the 2007-8 influenza season. 27 January 2008. Available from: http://www.ecdc.europa.eu/pdf/080127_os.pdf

This article was published on 7 February 2008.

Citation style for this article: Influenza Project Team . Oseltamivir resistance in human seasonal influenza viruses (A/H1N1) in EU and EFTA countries: an update. Euro Surveill. 2008;13(6):pii=8032. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8032

Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe

A Lackenby[1], O Hungnes[2], S G Dudman[2], A Meijer[3,4], W J Paget[3], A J Hay[5], M C Zambon (maria.zambon@hpa.org.uk)[1]
1. Health Protection Agency, Centre for Infection, London, United Kingdom
2. Norwegian Institute of Public Health, Oslo, Norway
3. EISS Coordination Centre, Nivel Institute, Utrecht, the Netherlands
4. National Centre for Public Health and the Environment, Bilthoven, the Netherlands
5. WHO Collaborating Centre, MRC National Institute of Medical Research, London, United Kingdom

Surveillance of the antiviral susceptibility of influenza viruses circulating in Europe has been established since 2004 through the European Union-funded European Surveillance Network for Vigilance against Viral Resistance (VIRGIL), in collaboration with the European Influenza Surveillance Scheme (EISS), the World Health Organization (WHO) and national influenza centres. Results from analysis of early winter (November 2007 – January 2008) A(H1N1) virus isolates has revealed that a significant proportion, approximately 14% of these European strains (see Table), are resistant to oseltamivir (Tamiflu), the most widely used anti-influenza drug, but retain sensitivity to zanamivir (Relenza) and amantadine/rimantadine.

As of week 03/2008, 16 European countries have reported significant influenza activity (Austria, Belgium, Bulgaria, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Northern Ireland, Poland, Portugal, Romania, Slovenia, Spain and Switzerland). Of the total virus detections since week 40/2007 (N=3447), 81% have been influenza A and 19% influenza B, and the predominant viruses circulating in most countries have been A(H1N1) similar to the A/Solomon Islands/3/2007 vaccine strain [1]. The presence of oseltamivir-resistant viruses circulating in the community in several European countries (Denmark, Finland, France, Germany, Netherlands, Norway, Portugal, Sweden and United Kingdom) is in marked contrast to the previous winter seasons of 2004/2005, 2005/2006, and 2006/2007, when oseltamivir resistance was detected in <1% of circulating strains from 24 countries.

A total of 437 influenza A(H1N1) viruses, isolated between November 2007 and January 2008, were tested using measurement of neuraminidase (NA) enzyme activity in the presence of oseltamivir to determine the drug-sensitivity (IC50) of the viral enzyme (2) in conjunction with sequence analysis of the viral neuraminidase gene. To date, oseltamivir-resistant viruses have been detected in nine countries (Table 1); in particular, 26 of 37 (70%) in Norway, 15 of 87(17%) in France, 3 of 43 (7.0%) in Germany and 8 of 162(5%) in the United Kingdom carry the same mutation, causing the substitution of histidine by tyrosine at residue 274 (H274Y) of the neuraminidase, which is known to confer a high level resistance to oseltamivir. Viruses bearing this mutation, when tested in enzyme assays, showed a reduction of approximately 400 fold in susceptibility to oseltamivir (IC50 values increased from approximately 1nM to more than 400nM). All these viruses remain sensitive to the other anti-neuraminidase drug zanamivir and to the anti-M2 drugs amantadine and rimantadine.

The resistant (H274Y) viruses have been isolated from both adults and children, ranging from 1 month to 61 years in age, with the majority of viruses being isolated from adults. So far, there is no information that any of these viruses, in any country, has been obtained from a person who has either been treated or been in close contact with another individual who has been treated with oseltamivir. We therefore conclude that the identification of these oseltamivir-resistant viruses as a substantial proportion of circulating viruses, particularly in Norway, is the first clear evidence that influenza A(H1N1) virus with the H274Y mutation can readily transmit between individuals.

Table 1

A(H1N1) viruses resistant to Oseltamivir in Europe, winter season 07/08 (Nov 2007-Jan 2008)

Country	Total tested	Oseltamivir resistant by IC50(nM) or by 274Y	Percentage resistance with 95% confidence intervals
Austria	5	0	0% (0-43 %)
Denmark	10	1	10% (2-40%)
Finland	7	2	29% (8-64%)
France	87	15	17% (11-27%)
Germany	43	3	7% (2-19%)
Greece	5	0	0% (0-43%)
Hungary	5	0	0% (0-43%)
Italy	13	0	0% (0-23%)
Latvia	4	0	0% (0-49%)
Netherlands	16	1	6% (1-28%)
Norway	37	26	70% (54-83%)
Portugal	6	2	33% (10-70%)
Slovakia	5	0	0% (0-43%)
Slovenia	1	0	0% (0-79%)
Spain	11	0	0% (0-26%)
Sweden	13	1	8% (1-33%)
Switzerland	7	0	0% (0-35%)
United Kingdom	162	8	6% (3-9%)
Total	**437**	**59**	**14% (11-17%)**

More extensive surveillance within Europe and in other parts of the world is required to establish the relative prevalence and geographical distribution of these resistant viruses, and to evaluate their potential impact on the effectiveness of drug use. The spectrum of clinical illness associated with infection by oseltamivir-resistant viruses remains to be fully determined, although limited information from initial clinical cases does not suggest unusual disease syndromes. Although the resistant viruses have been isolated from November through January, the ability of these viruses to persist throughout the influenza season, and from one season to the next, will require continuous world-wide surveillance by the WHO Global Influenza Surveillance Network. Determining the origins and genesis of these drug-resistant strains, which appear to have emerged in regions of the world where there is little drug pressure, will be important in understanding the emergence and persistence of oseltamivir resistance in relation to the evolution of influenza viruses and drug use.

Acknowledgements

We would like thank all members of EISS laboratories for contributing viruses and data, particularly VIRGIL colleagues Dr Bruno Lina (Lyon) and Dr Sylvie van der Werf (Paris). Funding support from EU FP6 Programme for VIRGIL Contract No 503359.

References

1. European Influenza Surveillance Scheme. Increased influenza activity in Europe. EISS Weekly Electronic Bulletin 2008; 25 January 2008: 250. Available from: http://www.eiss.org
2. Methodology used for testing in vitro susceptibility of influenza viruses to oseltamivir and zanamivir was described by the Neuraminidase Inhibitor Susceptibility Network (NISN) in Wetherall et al, J Clin Microl. 2003;41;742-50. Surveillance of the antiviral susceptibility of influenza viruses circulating in Europe is supported by the EU-funded VIRGIL programme (Contract No 503359), in collaboration with EISS and the WHO.

This article was published on 31 January 2008.

Citation style for this article: Lackenby A, Hungnes O, Dudman SG, Meijer A, Paget WJ, Hay AJ, Zambon MC. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Euro Surveill. 2008;13(5):pii=8026. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8026

A secondary case of meningococcal disease in an ambulance worker, Berkshire, November 2007

A Petsas[1], A Sharma[1], O Aghadiuno[1], M Abid (muhammad.abid@hpa.org.uk)[1], K Paranthaman[1]
1. Thames Valley Health Protection Unit, Oxford, United Kingdom

Secondary cases of meningococcal disease among healthcare workers are rare and avoidable. In this report, we describe a secondary infection in a healthcare worker who did not have significant contact with respiratory secretions of the index case.

Case report

In mid-November 2007, a paramedic crew attended a house call to a drowsy and agitated patient suspected to have meningococcal meningitis. One of the two ambulance crew members, a technician in her thirties, managed the head end of the patient, assisted in transferring her to a chair and down the stairs into the ambulance.

Whilst in the ambulance, the technician remained at the patient's head end placing an oxygen face mask which the patient repeatedly attempted to remove during the journey. The ambulance technician was not wearing a mask at the time. The patient did not cough or splutter and suction was not used. The patient did not require intubation or any airway adjuncts during transfer to the local hospital. On arrival to the hospital, the ambulance technician assisted in transferring the patient to the emergency department. The total contact time between the patient and the ambulance technician was approximately 40 minutes. There was no history suggestive of direct exposure of the ambulance technician to large particle droplets/secretions from the patient.

On notification of suspected meningococcal disease to the Thames Valley Health Protection Unit, close contacts of the index case were identified and chemoprophylaxis was given based on national guidance [1]. The ambulance staff involved did not fulfil the criteria for close contacts and therefore were not offered chemoprophylaxis. PCR of cerebrospinal fluid in the index case subsequently confirmed *Neisseria meningitidis*.

Four days after the event, the ambulance technician developed symptoms of malaise, cough, sore throat and fever. Symptoms of headache and neck stiffness ensued a day later leading to admission to hospital the following day. She had no history of immunosuppression. As meningococcal infection was suspected, empirical treatment was started with antibiotics. Blood cultures grew *N. meningitidis* after two days of incubation. PCR of the cultured organism identified meningococcus serogroup B with the DNA sequence VR1(17); VR2(23); VR3(37), identical to the sequence seen in the PCR from cerebrospinal fluid of the index case. The history of exposure, time correlation to development of symptoms and DNA sequencing results strongly suggest that the ambulance worker contracted the infection from the index case. Both cases made an uneventful recovery. The other ambulance crew member who attended the original call have remained asymptomatic and well.

Discussion

To the best of our knowledge, this is the first reported secondary case of meningococcal disease in a healthcare worker, who did not have significant contact with respiratory secretions of the index case. A retrospective study of the risk in healthcare workers in England and Wales identified three probable cases of secondary meningococcal infections in healthcare workers over a fifteen year period [2]. Previous reports describe significant contact with respiratory secretions such as mouth to mouth resuscitation, intubation or patient coughing/spluttering during airway management. Despite the twenty-five-fold increased relative risk of infection in healthcare workers compared to general population, the absolute risk remains extremely low (0.8/105). It is estimated that 144,000 healthcare worker contacts would need to receive chemoprophylaxis in order to prevent one case [2,3].

Current guidelines in the United Kingdom on chemoprophylaxis for healthcare workers state that it is recommended only for those not wearing masks or other mechanical protection, whose mouth or nose is directly exposed to infectious respiratory droplets/secretions within a distance of three feet (90 cm) from a probable or confirmed case of meningococcal disease [3]. This degree of exposure is unlikely to occur unless using suction, inserting an airway adjunct, intubation, or if the patient coughs during airway management. For prevention of secondary disease in healthcare workers, the use of surgical masks is encouraged to reduce the risk of exposure. Similarly, in the USA, healthcare workers are recommended to wear surgical masks when working within three feet (90 cm) of patients known, or suspected to be infected with micro-organisms transmitted by large-particle droplets (>5 micrometres diameter) [4]. This recommendation is based on laboratory evidence that surgical masks can protect the wearer against droplet transmission [5,6].

Indiscriminate use of chemoprophylaxis can lead to potentially serious complications such as antibiotic related adverse reactions, development of resistance and elimination of non-pathogenic Neisseria species leading to reduced immunity against pathogenic species and therefore higher likelihood of invasive disease [7,8].

Conclusion

The transmission of meningococcal meningitis in the manner described in this case is extremely rare; therefore extending chemoprophylaxis to all healthcare workers involved in the initial management is not justifiable. In light of this case report, we believe it is prudent to recommend the use of surgical masks by healthcare workers, especially paramedics, during the management of patients with suspected meningococcal infection.

Acknowledgements

We are grateful to Dr James Stuart for his assistance in this investigation.

References

1. Heath Protection Agency Meningococcus Forum. Guidance for public health management of meningococcal disease in the UK. London: HPA, 2006. Available from: http://www.hpa.org.uk/infections/topics_az/meningo/guidelines.htm
2. Gilmore J, Stuart N. Andrews. Risk of secondary meningococcal disease in health-care workers. Lancet. 2000;366(9242):1654-5.
3. Stuart JM, Gilmore AB, Ross A, Patterson W, Kroll JS, Kaczmarski EB, et al; PHLS Communicable Disease Surveillance Center. Preventing secondary meningococcal disease in health care workers: recommendations of a working group of the PHLS meningococcus forum. Commun Dis Public Health. 2001;4(2):102-5. Available from: http://www.hpa.org.uk/cdph/issues/CDPHVol4/no2/secondary%20meningococcal.pdf
4. Garner JS. Guideline for isolation precautions in hospital. The Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol. 1996;17(1):53-80.
5. Chen CC, Willeke K. Aerosol penetration through surgical masks. Am J Infect Control. 1992 Aug;20(4):177-84.
6. Weber A, Willeke K, Marchioni R, Myojo T, McKay R, Donnelly J, Liebhaber F . Aerosol penetration and leakage characteristics of masks used in the health care industry. Am J Infect Control 1993;21:167-73.
7. Kristiansen BE, Knapskog AB. Secondary prevention of meningococcal disease. BMJ. 1996;312(7031):591-2. 8. Yagupsky P, Ashkenazi S, Block C. Rifampicin-resistant meningococci causing invasive disease and failure of chemoprophylaxis. Lancet. 1993;341(8853):1152-3.

This article was published on 24 January 2008.

Citation style for this article: Petsas A, Sharma A, Aghadiuno O, Abid M, Paranthaman K. A secondary case of meningococcal disease in an ambulance worker, Berkshire, November 2007. Euro Surveill. 2008;13(4):pii=8020. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8020

Autochthonous chikungunya virus transmission may have occurred in Bologna, Italy, during the summer 2007 outbreak

T Seyler (thomas.seyler@iss.it)[1,2], C Rizzo[1], A C Finarelli[3], C Po[3], P Alessio[4], V Sambri[5], M L Ciofi Degli Atti[1], S Salmaso[6]

1. Communicable Disease Epidemiology Unit, National Centre of Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità (National Public Health Institute, ISS), Rome, Italy
2. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
3. Public Health Service, Emilia-Romagna Region, Bologna, Italy
4. Azienda Unità Sanitaria Locale (Local Health Unit, AUSL) of Bologna, Department of Public Health, Bologna, Italy
5. University of Bologna, Azienda Ospedaliera Universitaria di Bologna, Microbiologia, Bologna, Italy
6. National Centre of Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità (National Public Health Institute, ISS), Rome, Italy

In Italy, a national surveillance system for chikungunya fever coordinated by the National Public Health Institute has been in place since August 2006. In summer 2007, an outbreak of chikungunya fever affected the Italian provinces of Ravenna, Cesena-Forli and Rimini [1-3]. As of 16 December 2007, health authorities identified 214 laboratory-confirmed cases with date of onset from 15 July to 28 September 2007. Most cases (161) occurred in the two neighbouring villages of Castiglione di Cervia and Castiglione di Ravenna, but limited local transmission also took place in the cities of Ravenna, Cesena, Cervia, and Rimini. In September 2007, two confirmed cases (two women aged 68 and 70) were reported among residents of the city of Bologna (373,026 inhabitants). Both had a history of travel in the affected areas (municipality of Cervia). No unusual increase in the density of *Aedes albopictus* mosquitoes in the Bologna area was noted at that time (September).

On 17 December 2007, the Regional Health Authority of Emilia-Romagna reported that three further residents of Bologna had tested positive for IgG and IgM antibodies against chikungunya virus by using a commercially available immunofluorescence test performed in Bologna on 14 December on blood samples taken on 5 December. Confirmation from the national laboratory at the National Public Health Institute is pending. The three patients (two women aged 78 and 79, and a boy aged 14) had developed fever, arthralgia and rash on 7, 18 and 23 September respectively, but had not been identified as suspected cases of chikungunya fever at that time. Blood samples were taken as one patient complained of persisting joint pain and the other two had had similar symptoms.

All three patients lived on the first floor of the same building, with a garden. The building is 2.5 km from the closest previously identified cases with a travel history to Cervia, reported in September. According to direct interviews, these three patients did not visit or stay in the area of the two imported cases, and vice versa. In addition, none of these last three cases reported having been abroad or having visited the affected areas at the time of the outbreak.

As these cases remained undetected at an early stage, no specific vector control measures were implemented in their premises. However, monthly routine preventive measures in Bologna from April to October included the use of larvicide in public areas. The apartment block was was not considered a “public area” for larvicide treatment.

This finding suggests that transmission may have occurred 75 km away from the initial cluster. This could be explained by the importation of the virus in the area where the three cases live through an undetected (asymptomatic) viraemic patient. Another possible explanation is passive vector mobility (e.g. infected mosquitoes transported by car from the initial cluster), since the flight range (active mobility) is usually considered to be less than 1 km, The sensitivity of the surveillance system relies on the continued dissemination of information to physicians regarding the clinical symptoms (i.e. fever and severe arthralgia) that should prompt laboratory investigation for chikungunya virus infection. The present report highlights the need for reinforcing information and surveillance.

References

1. Angelini R, Finarelli A, Angelini P, Po C, Petropulacos K, Macini P, et al. An outbreak of chikungunya fever in the province of Ravenna, Italy. Euro Surveill. 2007;12(9):E070906.1. Available from: http://www.eurosurveillance.org/ew/2007/070906.asp#1
2. Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Silvi G, et al. Chikungunya in north-eastern Italy: a summing up of the outbreak. Euro Surveill. 2007;12:E071122.2. Available from: http://www.eurosurveillance.org/ew/2007/071122.asp#2
3. Rezza G, Nicoletti L,Angelini R, Romi R. Finarelli AC, Panning M, et al. Infection with Chikungunya virus in Italy: an outbreak in a temperate region. Lancet. 2007;370(9602):1840-6.

This article was published on 17 January 2008.

Citation style for this article: Seyler T, Rizzo C, Finarelli AC, Po C, Alessio P, Sambri V, Ciofi Degli Atti ML, Salmaso S. Autochthonous chikungunya virus transmission may have occurred in Bologna, Italy, during the summer 2007 outbreak. Euro Surveill. 2008;13(3):pii=8015. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8015

Fatal case of human rabies (Duvenhage virus) from a bat in Kenya: the Netherlands, December 2007

PPAM van Thiel (p.p.vanthiel@amc.uva.nl)[1], JAR van den Hoek[1,2], F Eftimov[3], R Tepaske[4], H J Zaaijer[5], L Spanjaard[6], HEL de Boer[7], GJJ van Doornum[8], M Schutten[8], ADME Osterhaus[8], PA Kager[1]

1. Division of Infectious Diseases, Tropical Medicine and Aids, Academic Medical Center, University of Amsterdam, the Netherlands
2. Cluster of Infectious Diseases, Public Health Service, Amsterdam, the Netherlands
3. Department of Neurology, Academic Medical Center, University of Amsterdam, the Netherlands
4. Intensive Care Unit, Academic Medical Center, University of Amsterdam, the Netherlands
5. Department of Medical Microbiology, Unit Clinical Virology, Academic Medical Center, University of Amsterdam, the Netherlands
6. Department of Medical Microbiology, Unit Hospital Epidemiology, Academic Medical Center, University of Amsterdam, the Netherlands
7. Occupational Health Services, Academic Medical Center, University of Amsterdam, the Netherlands
8. Department of Virology, Erasmus Medical Center, Rotterdam, the Netherlands

On 19 November 2007, a 34-year-old woman was admitted to the Academic Medical Center of the University of Amsterdam in the Netherlands with dysarthria, hypesthesia of both cheeks and unsteady gait, all of which started the day before. She had also experienced dizziness, nausea and general malaise since 16 November.

On 24 October, at the start of a two-week holiday trip through Kenya, a small bat had flown against her face. While she was hitting away the animal, it made two bleeding scratches on the right side of her nose. The incident took place in a camping site between Nairobi and Mombasa, at dusk, while she was brushing her teeth. The wound was washed with soap and cleaned with an alcohol solution. The warden of the campsite and medical personnel of the neighbouring health centre were not aware of the existence of rabies in bats in the area and no further action was recommended. The woman and her husband then continued the holiday trip.

Treatment

On admission, passive and active post-exposure prophylaxis (PEP) for rabies was initiated. The patient's neurological clinical picture deteriorated quickly. As rabies was very likely, on day seven of admission, the "Wisconsin rabies treatment protocol" was initiated, an experimental treatment protocol that has resulted in the survival of the only patient who recovered from rabies infection without prior vaccination [1]. As this treatment is experimental, clinical evidence is still lacking, and patients subsequently treated in a similar or modified way in Thailand [2], United States [3], and Germany [4] did not survive. The treatment was only started after consultation of the family and with their agreement. The diagnosis of infection with lyssavirus, genotype 4 - Duvenhage virus (DUVV) was confirmed in a nuchal biopsy taken on the second day of admission. This confirmation by cloning and sequencing of the PCR products was obtained three days after the treatment had begun, when the patient was still alive. Despite all efforts, the patient died on 8 December, 23 days after the onset of illness.

Preventive measures for contacts

There are no laboratory-confirmed cases documenting the transmission of rabies from rabies-infected patients to healthcare providers or household contacts, either by direct contact or by fomites or environmental surfaces, possibly due to extensive prophylactic treatment of these contacts [5,6,7]. In the case described here, the patient had been in close contact with several family members during the first days of illness. On admission, protective measures were taken but it was regarded as prudent to advise all close family contacts (n = 11) and attending hospital employees (n = 30) to receive passive and active post-exposure prophylaxis (PEP). Five days before the onset of illness, the patient had spent a weekend with friends, with possible exposure to saliva. Chances of infection at that stage were practically nil, but for various reasons it was decided to offer this group of six people the vaccine series of five injections without HRIG (human anti-rabies immunoglobulin). Literature shows that approximately 50 contacts per case required PEP, and in one case the number exceeded 200 [8].

Conclusion

Rabies is a fatal zoonotic disease in humans, preventable if adequate measures are applied shortly after a suspected infection. The main reservoir of rabies (lyssavirus, genotype 1) are dogs and other animals belonging to the *Canidae* family, but all mammalian animals in endemic areas are capable of contracting and transmitting the disease [9].

The Duvenhage virus is associated with insectivorous bats and has so far been isolated from two human cases bitten by bats in South Africa (in 1970 and 2006), and two insectivorous bats in South Africa (1981) and Zimbabwe (1986) [10]. To date, no cases of rabies infection from a bat have been described in Kenya.

This fatal incident shows that in a rabies endemic area PEP has to be applied in case of every, however minor, bite or scratch exposure to a mammalian animal, including bats [10].

A clinical case report and a report on the virological, immunological and histopathological results will be presented as soon as ongoing investigations are finished.

References

1. Willoughby RE Jr, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ, et al. Survival after treatment of rabies with induction of coma. N Engl J Med 2005 Jun 16;352(24):2508-14.
2. Hemachudha T, Sunsaneewitayakul B, Desudchit T, Suankratay C, Sittipunt C, Wacharapluesadee S, et al. Failure of therapeutic coma and ketamine for therapy of human rabies. J. Neurovirol 2006 Oct;12(5):407-9.
3. Centers for Disease Control and Prevention. Human rabies- Indiana and California, 2006. MMWR. April 20, 2007 / 56(15);361-365. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5615a1.htm; and JAMA 2007;297:2340-3. Available from: http://jama.ama-assn.org/cgi/content/full/297/21/2340
4. Schmiedel S, Panning M, Lohse A, Kreymann KG, Gerloff C, Burchard G, Drosten C. Case report on fatal human rabies infection in Hamburg, Germany, March 2007. Euro Surveill 2007;12(5):E070531,5. Available from: http://www.eurosurveillance.org/ew/2007/070531.asp#5
5. World Health Organization. WHO expert consultation on rabies. WHO Tech Rep Ser 2005; Abstract 931, pg. 88.
6. Human rabies prevention -- United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1999;48:1. Available from: http://www.cdc.gov/MMWR/preview/mmwrhtml/00056176.htm
7. Helmick CG, Tauxe RV, Vernon AA. Is there a risk to contacts of patients with rabies? Rev Infect Dis 1987; 9:511.
8. M. Stantic-Pavlinic. Rabies treatment of healthcare staff. Swiss Med Weekly, 2002. Available from: www.smw.ch
9. Rupprecht CE, Hanlon CA, Hemachuda T. Rabies re-examined. Lancet Infect Dis 2002 ;2 :327-43.
10. Paweska JT, Blumberg LH, Liebenberg C, Hewlett RH, Grobbelaar AA, Leman PA, et al. Fatal Human Infection with Rabies-related Duvenhage Virus, South Africa. Emerg Inf Dis 2006 Dec;12(12):1965-7. Available from: http://www.cdc.gov/ncidod/eid/vol12no12/06-0764.htm

This article was published on 10 January 2008.

Citation style for this article: van Thiel PP, van den Hoek JA, Eftimov F, Tepaske R, Zaaijer HJ, Spanjaard L, de Boer HE, van Doornum GJ, Schutten M, Osterhaus A, Kager PA. Fatal case of human rabies (Duvenhage virus) from a bat in Kenya: the Netherlands, December 2007. Euro Surveill. 2008;13(2):pii=8007. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8007

Letters

Meningococcal disease in an ambulance worker

Francesco Maria Fusco (fusco@inmi.it)[1], Vincenzo Puro[1]
1. National Institute for Infectious Diseases "Lazzaro Spallanzani", Rome, Italy

To the Editor: We read the interesting communication by Petsas et al. about a secondary case of meningococcal disease in an ambulance worker that was recently published in your journal [1]. In the described case, the worker was not considered as a close contact, and chemoprophylaxis was not offered.

In our opinion, this was wrong for at least two reasons. First of all, the ambulance worker did not use droplet precautions, i.e. he did not wear a surgical mask although this is recommended. Indeed, it is very unlikely that the distance between his face and the patient's head was never less than 90 cm, given that he gave support in moving the patient from a chair, down the stairs and up to the ambulance, always standing at the patient's head holding an oxygen face mask in place.

Moreover, an additional factor that could have increased the risk of transmission was the use of the oxygen face mask during the transport. Experimental studies suggest that oxygen face masks produce turbulent fluxes of aerosols, which could contain potentially infectious droplets [2,3]. In one experiment, a subject inhaled saline mist and exhaled through three different models of oxygen masks, in order to illustrate the pattern of dispersal of pulmonary gas. In two commonly used masks, exhaled gas formed a plume emanating from the side vents. In a second study, a human lung model (respiration rate, 12 breaths/min) was designed to test the potential for a simple oxygen mask in a common setting (4 litres/min) to disperse potentially infectious exhaled air into the surrounding area. A laser sheet was used to illuminate the exhaled air from the mask, which contained fine tracer smoke particles. These experimental observations evaluated the distance reached by aerosols produced by a patient correctly wearing an oxygen face mask, and showed that the exhaled air at the peak of the simulated exhalation reached a distance of approximately 40 centimetres.

A potential role of oxygen face masks in the transmission of droplet-transmitted diseases (in particular of SARS and other respiratory diseases prone to cause epidemics) is also considered in some guidelines, in which the use of standard low flow oxygen (oxygen flow rates of under 6 litres/minute) [4], or the addition of an expiratory port with a bacterial/viral filter are recommended [5].

In the described case, the patient was drowsy and agitated, and he repeatedly attempted to remove the oxygen face mask during the journey, probably causing repeated and unpredictable clouds of aerosol containing infectious droplets.

We strongly agree with the authors' conclusion that the correct application of droplet precautions, including the use of surgical masks, should always be observed when caring for a suspected case of meningitis. When oxygen supplementation is needed, further precaution measures, such as the use of standard low flow oxygen or placement of bacterial/viral filters should be considered.

References

1. Petsas A, Sharma A, Aghadiuno O, Abid M, Paranthaman K. A secondary case of meningococcal disease in an ambulance worker, Berkshire, November 2007. Euro Surveill. 2008;13(4). Available from: http://www.eurosurveillance.org/edition/v13n04/080124_1.asp
2. Hui DS, Ip M, Tang JW, Wong AL, Chan MT, Hall SD, et al. Airflows around oxygen masks: A potential source of infection? Chest. 2006;130(3):822-6.
3. Somogyi R, Vesely AE, Azami T, Preiss D, Fisher J, Correia J, et al. Dispersal of respiratory droplets with open vs closed oxygen delivery masks: implications for the transmission of severe acute respiratory syndrome. Chest. 2004;125(3):1155-7.
4. Lim WS, Anderson SR, Read RC; SARS Guidelines Committee of the British Thoracic Society; British Infection Society; Health Protection Agency. Hospital management of adults with severe acute respiratory syndrome (SARS) if SARS re-emerges--updated 10 February 2004. J Infect. 2004;49(1):1-7.
5. World Health Organization. Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care. WHO interim guidelines. June 2007. Available from: http://www.who.int/csr/resources/publications/WHO_CDS_EPR_2007_6c.pdf

This article was published on 6 March 2008.

Citation style for this article: Meningococcal disease in an ambulance worker. Euro Surveill. 2008;13(10):pii=8061. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8061

Authors' reply: Meningococcal disease in an ambulance worker

Anna Petsas[1], Muhammad Abid (muhammad.abid@hpa.org.uk)[1]
1. Thames Valley Health Protection Unit, Oxford, United Kingdom

To the Editor: Fusco *et al.* raise some very interesting points regarding the spread of respiratory secretions in the form of aerosols caused by oxygen therapy [1]. We believe this does indeed warrant further investigation, and a review of the guidelines regarding the chemoprophylaxis of staff involved in airway management. However, the current guidelines only recommend chemoprophylaxis in instances where facial contact with droplets or secretions is clearly noted. They further suggest that this is unlikely to occur unless using suction during airway management, inserting an airway, intubating, or the patient coughing in one's face.

The question remains as to whether all staff involved in handling the airway in patients with suspected meningococcal disease should wear face masks. This includes ambulance staff, emergency staff and anaesthetists who are commonly involved in intubating such patients. These high risk groups are currently not actively advised to wear face masks.

This case has certainly raised awareness of this issue. Further discussion and research around this topic is necessary.

References

1. FM Fusco, V Puro. Meningococcal disease in an ambulance worker. Euro Surveill. 2008;13(10). Available from: http://www.eurosurveillance.org/edition/v13n09/080306_5.asp

This article was published on 6 March 2008.

Citation style for this article: Authors' reply: Meningococcal disease in an ambulance worker. Euro Surveill. 2008;13(10):pii=8062. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8062

Looking for tips to find icebergs - surveillance of haemolytic uraemic syndrome to detect outbreaks of Shiga toxin-producing *E. coli* infection

Dirk Werber (werberd@rki.de)[1], Christina Frank[1], Maria Wadl[1,2], Helge Karch[3], Angelika Fruth[4], Klaus Stark[1]
1. Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
2. Postgraduate Training for Applied Epidemiology („PAE", German Field Epidemiology Training Programme)
3. Institute of Hygiene, National Consulting Laboratory on Haemolytic Uraemic Syndrome, University of Münster, Germany
4. National Reference Centre for Salmonella and other Bacterial Enteric Pathogens, Robert Koch Institute, Wernigerode, Germany

To the Editor: In a recent article, De Schrijver et al. described an outbreak of Verocytotoxin-producing *Escherichia coli*, syn. Shiga toxin-producing *E. coli* (STEC), linked to the consumption of ice cream produced at a farm in the province of Antwerp, Belgium [1]. Interestingly, the outbreak was identified through the time-clustering of patients who had developed haemolytic uraemic syndrome (HUS) and from whom STEC O145 was isolated. HUS – a triad of acute renal injury, micro-angiopathic haemolytic anaemia and thrombocytopenia – predominantly affects children. A subset of STEC-infected patients (circa 5-15% in patients infected with serotype O157:H7) develop HUS, and more than 80% of childhood HUS is attributable to STEC infection [2].

E. coli O157:H7 dominates STEC disease statistics in many countries. Routine detection of this serotype in stool, by use of sorbitol-MacConkey (SMAC) agar, is well-established, timely and inexpensive. Other ("non-O157:H7") STEC serotypes cannot be identified on SMAC agar because these strains ferment sorbitol. Their diagnosis is more complex and requires a sequential approach that entails screening for Shiga toxin or Shiga toxin genes, followed by isolation and serotyping of STEC. However, many laboratories do not screen stool for Shiga toxin or Shiga toxin genes; in some countries, non-O157:H7 STEC are not routinely sought at all. This results in a substantial under-ascertainment of non-O157:H7 STEC. Compared to most other bacterial pathogens, even the prominent STEC O157:H7 infections are less likely to be diagnosed, for at least two reasons: firstly, the culturing of stool on SMAC agar is underused (e.g. diagnosis is often sought only in patients with bloody diarrhoea) or not routinely performed at all (e.g. in Belgium [1]). Secondly, in countries where STEC identification is based solely on screening for Shiga toxin or Shiga toxin genes, under-diagnosis of O157:H7 infections is likely if laboratories are paid a fixed fee, which does not cover the cost of subsequent strain isolation and serotyping (e.g. in Germany).

Identifying STEC outbreaks through a cluster of HUS patients has been a characteristic of other non-O157:H7 STEC outbreaks, e.g. a large STEC O111 outbreak in Australia [3] and a recent STEC O103 outbreak in Norway [4]. Both were food-borne, and the food vehicle was identified, potentially allowing food safety to improve. Notably, even within the O157 serogroup, several outbreaks caused by the emerging sorbitol-fermenting (SF) strain of STEC O157:H- in Germany were only detected by an increase in the number of paediatric HUS patients. Likewise, an investigation of an outbreak of SF STEC O157:H- infection in the United Kingdom was triggered by epidemiologic investigations of paediatric HUS patients [5].

We believe that a timely, preferably active, surveillance of HUS patients could improve the detection of outbreaks caused by virulent STEC strains. Focussing on paediatric HUS patients is likely to suffice since most cases are children. In the past, HUS surveillance studies were time-limited and focussed primarily on clinical and microbiological characteristics of the infection. In contrast, the aspect of identifying STEC outbreaks through HUS surveillance has received only little attention. In fact, it may seem counterintuitive to use a post-infectious syndrome as an outbreak indicator because signal detection is clearly delayed (HUS commences about a week after onset of diarrhoea and the time elapsed between exposure and development of HUS is about two weeks). But, as outlined, outbreaks of non-O157:H7 and probably even O157 infections are easily missed in current STEC surveillance. Additional systematic and prompt data collection of HUS patients in a surveillance framework may partially compensate for difficulties in current STEC surveillance schemes. This would also make the most of the extensive microbiological and epidemiological investigation that is often routinely conducted in individual HUS patients.

References

1. De Schrijver K, Buvens G, Possse B, Van den Branden D, Oosterlynck C, De Zutter L, et al. Outbreak of verocytotoxin-producing E.coli O145 and O26 infections associated with the consumption of ice cream produced at a farm, Belgium, 2007. Euro Surveill. 2008;13(7). Available from: http://www.eurosurveillance.org/edition/v13n07/080214_5.asp
2. Gerber A, Karch H, Allerberger F, Verweyen HM, Zimmerhackl LB. Clinical course and the role of shiga toxin-producing Escherichia coli infection in the hemolytic-uremic syndrome in pediatric patients, 1997-2000, in Germany and Austria: a prospective study. J Infect Dis. 2002;186(4):493-500.
3. Community outbreak of hemolytic uremic syndrome attributable to Escherichia coli O111:NM--South Australia 1995. MMWR Morb Mortal Wkly Rep. 1995; 44(29):550-1,557-8. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/00038232.htm
4. Schimmer B, Eriksen HM, Nygård K, Grahek-Ogden D, Madssen T, Hajdu A, et al. An outbreak of haemolytic uraemic syndrome associated with minced beef, Norway, January-February 2006: preliminary report. Euro Surveill. 2006;11(3):E060302.1. Available from: http://www.eurosurveillance.org/ew/2006/060302.asp
5. Eurosurveillance Editorial team. E. coli O157 infections in the UK. Euro Surveill. 2006;11(6):E060601.2. Available from: http://www.eurosurveillance.org/ew/2006/060601.asp#2

This article was published on 28 February 2008.

Citation style for this article: Looking for tips to find icebergs - surveillance of haemolytic uraemic syndrome to detect outbreaks of Shiga toxin-producing E. coli infection. Euro Surveill. 2008;13(9):pii=8053. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8053

Author's reply: Looking for tips to find icebergs - surveillance of haemolytic uraemic syndrome to detect outbreaks of Shiga toxin-producing *E. coli* infection

Koen De Schrijver (koen.deschrijver@ua.ac.be)[1]
1. Department of Epidemiolgy, University of Antwerp Belgium

To the Editor: We appreciate the comments by Dr Werber et al. [1] regarding our article on an outbreak of Shiga toxin-producing *Escherichia coli* (STEC) O145 in Belgium. We agree with the authors that active surveillance of haemolytic uraemic syndrome (HUS) patients allows the detection of outbreaks of virulent STEC strains and that under–ascertainement of verocytotoxin-producing *E. coli* (VTEC) is explained by the non-routine practice of culturing stools, by the under-use of sorbitol-MacConkey (SMAC) agar, and by the fact that most clinical laboratories do not test for these micro-organisms in routine gastroenteritis samples. In Belgium, well equipped clinical laboratories are systematically looking for enteropathogens such as VTEC in bloody stools or when HUS is suspected. In this outbreak, the clustering of HUS cases was an additional argument for further laboratory analysis. Moreover, we hope that we have shown that the prompt and systematic data collection of HUS patients can offer some added value in VTEC surveillance and help to identify the source of VTEC infections.

References

1. Werber D, Frank D, Wadl M, Karch H, Fruth A, Stark K. Looking for tips to find icebergs - surveillance of haemolytic uraemic syndrome to detect outbreaks of Shiga toxin-producing E. coli infection. Euro Surveill. 2008;13(9). Available from: http://www.eurosurveillance.org/edition/v13n09/080228_4.asp

This article was published on 28 February 2008.

Citation style for this article: Author's reply: Looking for tips to find icebergs - surveillance of haemolytic uraemic syndrome to detect outbreaks of Shiga toxin-producing E. coli infection. Euro Surveill. 2008;13(9):pii=8054. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8054

Letters

Chikungunya virus in north-eastern Italy: a consequence of seasonal synchronicity

Rémi N. Charrel (remi.charrel@medecine.univ-mrs.fr)[1], Xavier de Lamballerie[1]
1. Department of emerging viruses UMR190, Aix Marseille University - Institute for Research and Development, Marseille, France

To the Editor: In their recent article on the outbreak of chikungunya virus infection in North-eastern Italy, Angelini *et al.* [1] raised an important question: Why did no other outbreaks of chikungunya fever occur earlier in other regions of Italy or more widely in Europe? Why did they not occur already in 2005-2006, after the epidemic in La Reunion and other Indian Ocean islands - Comoros, Mayotte, the Seychelles, Mauritius and Madagascar, as a consequence of viraemic travellers carrying chikungunya virus when returning from the epidemic areas? Among the possible explanations, the authors listed (a) the fact that only few regions (including the affected areas) have a high concentration of competent vectors, and (b) social and behavioural factors of the returning travellers.

We would suggest to consider seasonal synchronicity as a third factor that has obviously played a decisive role in the outbreak in July to September in the surroundings of Ravenna (Emilia Romagna), Italy.

The outbreak in the Indian Ocean islands has raged for a six-month period, from January to June 2006, and had an estimated number of cases approaching one million. The epidemic in the islands then subsided rapidly due to decreased mosquito activity in the dry season in southern hemisphere. In 2007, chikungunya virus did not re-emerge in the Indian Ocean area as feared. Consequently, viraemic travellers from Europe must have been returning to their home countries at a time when the mosquitoes that serve as vectors for chikungunya virus were either not circulating or still scarce in Europe.

In contrast, first cases of chikungunya fever in India were reported in February 2006. Ultimately, this epidemic spread to many districts in India and many cases occurred in the course of the year 2006. The activity of *Aedes aegypti* and *Ae. albopictus* in India is constant throughout the year; cases have been reported continuously up to December 2007. As a consequence, travellers could have become infected with chikungunya virus in India, and returned during the viraemic period to European regions at a time when competent vectors were active there (summer). Due to the overlapping mosquito season in India and Europe, travellers returning from India can thus fuel an epidemic by infecting native mosquito populations in Europe.

Seasonal synchronicity, and related temporal overlapping of arthropod activity, is a critical factor that needs to be considered in the prediction or modelling of the emergence potential of vector-borne diseases.

Previous experience with West Nile virus in the United States suggests that a newly introduced vector-borne virus can establish itself and re-emerge after overwintering through trans-ovarial transmission [2-4]. We believe that the 2007 situation in Emilia Romagna should stimulate large scale studies aimed at the surveillance of chikungunya virus infected *Ae. albopictus* that could hatch from the infected eggs laid by females at the end of their active period. Although three studies suggested that chikungunya virus was not transmitted trans-ovarially [5-7], there is a need to confirm these data through additional studies. Whether chikungunya virus-infected eggs have the potential to initiate a new epidemic in summer 2008 is unknown, but must be taken into account as a serious issue for Italy and other European countries.

References

1. Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Silvi G, et al. Chikungunya in north-eastern Italy: a summing up of the outbreak. Euro Surveill 2007;12:E071122.2. Available from: http://www.eurosurveillance.org/ew/2007/071122.asp#2.
2. Baqar S, Hayes CG, Murphy JR, Watts DM. Vertical transmission of West Nile virus by Culex and Aedes species mosquitoes. Am J Trop Med Hyg. 1993;48:757-62.
3. Dohm DJ, Sardelis MR, Turell MJ. Experimental vertical transmission of West Nile virus by Culex pipiens (Diptera: Culicidae). J Med Entomol. 2002;39:640-4.
4. Goddard LB, Roth AE, Reisen WK, Scott TW. Vertical transmission of West Nile Virus by three California Culex (Diptera: Culicidae) species. J Med Entomol. 2003;40:743-6.
5. Hundekar SL, Thakare JP, Gokhale MD, Barde PV, Argade SV, Mourya DT. Development of monoclonal antibody based antigen capture ELISA to detect chikungunya virus antigen in mosquitoes. Indian J Med Res. 2002;115:144-8.
6. Mourya DT. Absence of transovarial transmission of Chikungunya virus in Aedes aegypti and Ae. albopictus mosquitoes. Indian J Med Res. 1987;85:593-5.
7. Jupp PG, McIntosh BM, Dos Santos I, DeMoor P. Laboratory vector studies on six mosquito and one tick species with chikungunya virus. Trans R Soc Trop Med Hyg. 1981;75:15-9.

This article was published on 3 January 2008.

Citation style for this article: Chikungunya virus in north-eastern Italy: a consequence of seasonal synchronicity. Euro Surveill. 2008;13(1):pii=8003. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8003

Author's reply - Chikungunya virus in north-eastern Italy: a consequence of seasonal synchronicity

Giovanni Rezza[1], Loredana Nicoletti[1], Giancarlo Majori[1] and Antonio Cassone[1] (cassone@iss.it)
1. Department of Infectious, Parasitic and Immunomediated Diseases, Istituto Superiore di Sanità, Rome, Italy

To the Editor: We agree with RN Charrel [1] in that seasonal synchronicity (i.e. presence of active Aedes spp. mosquitoes), among others, is an important factor that may increase the risk of an outbreak of chikungunya fever in a country with temperate climate. This theory assumes that viraemic travellers return to their home during the season of vector's activity (i.e. the hot season in Europe), while at the same time, the virus is still circulating in the affected tropical country.

According to Charell, lack of synchronicity explains why southern France was not affected by local outbreaks during the outbreak in La Reunion. He further points out that the seasonal synchronicity with the epidemic in India was an important determinant of the Italian outbreak. As an obvious corollary, seasonal synchronicity needs to be considered in the prediction or modelling of the emergence potential of vector-borne diseases.

However, the other factors we listed in our report, as well as in the full research article we published in the Lancet [2,3], i.e. the high concentration of competent vectors, and social and behavioural factors with regard to the returning travellers, may still make the difference. For instance, seasonal synchronicity alone does not explain why local outbreaks occurred in a narrow area of north-east Italy, but not in other Italian and European areas with a sustained presence of Aedes albopictus. Beyond the factors mentioned above (i.e. vector concentration and behavioural factors), there are surely other factors that may increase the chance of local outbreaks, such as the number of people returning from areas affected by concomitant epidemics, which are ill defined and need to be investigated.

Charell points out the possibility of overwintering of Ae. albopictus through trans-ovarial infection. There are no consistent reports on the occurrence and rate of this phenomenon but the Italian outbreak may clearly offer a unique opportunity to assess through surveillance activities and experimental investigation the potential for trans-ovarial infection of chikungunya virus. Since we cannot completely exclude that chikungunya fever outbreaks will recur during the next hot season, all the efforts should be addressed to strengthen vector and human surveillance. We plan to investigate this and other aspects of the triad relationship virus-mosquito-humans in our institute. As suggested elsewhere [4,5], international collaboration in this critical public health field is very much welcomed.

References

1. RN Charrel, X de Lamballerie. Letter to the Editor – Chikungunya in north-eastern Italy: a consequence of seasonal synchronicity. Euro Surveill. 2008;13(1). Available from: http://www.eurosurveillance.org/edition/v13n01/080103_03.asp
2. Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Silvi G, et al. Chikungunya in north-eastern Italy: a summing up of the outbreak. Euro Surveill. 2007;12:E071122.2. Available from: http://www.eurosurveillance.org/ew/2007/071122.asp#2.
3. Rezza G, Nicoletti L,Angelini R, Romi R. Finarelli AC, Panning M, et al. Infection with Chicungunya virus in italy: an outbreak in a temperate region. Lancet. 2007;370(9602):1840-6.
4. Chretien JP, Linthicum KJ. Chicungunya in Europe: what's next? Lancet. 2007;370(9602):1805-6.
5. Horwood J. Infectious disease surveillance update. Lancet Infect Dis. 2007;7(12):707.

This article was published on 3 January 2008.

Citation style for this article: Author's reply - Chikungunya virus in north-eastern Italy: a consequence of seasonal synchronicity. Euro Surveill. 2008;13(1):pii=8004. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8004

National Bulletins

AUSTRIA

Mitteilungen der Sanitätsverwaltung
Bundesministerium für Gesundheit Familie und Jugend, Vienna.
Monthly, print only. In German.
http://www.bmgfj.gv.at/cms/site/inhalte.htm?thema=CHO024

BELGIUM

Vlaams Infectieziektebulletin
Ministerie van Welzijn, Volksgezondheid en Gezin
Quarterly, print and online. In Dutch.
http://www.vlaanderen.be/epibul

Bulletin d'information de la section d'Epidémiologie
Institut Scientifique de la Santé Publique, Brussels
Monthly, online. In French.
http://www.iph.fgov.be/epidemio/epifr/episcoop/episcoop.htm

BULGARIA

Bulletin of the National Centre of Infectious and Parasitic Diseases, Sofia.
Print version. In Bulgarian.
http://www.ncipd.org/

CYPRUS

Newsletter of the Network for Surveillance and Control of Communicable Diseases in Cyprus
Medical and Public Health Services, Ministry of Health, Nicosia
Biannual, print and online. In Greek.
http://www.moh.gov.cy

CZECH REPUBLIC

Zpravy CEM (Bulletin of the Centre of Epidemiology and Microbiology)
Centrum Epidemiologie a Mikrobiologie Státního Zdravotního Ústavu, Prague.
Monthly, print and online. In Czech, titles in English.
http://www.szu.cz/cema/adefaultt.htm

EPIDAT (Notifications of infectious diseases in the Czech Republic)
http://www.szu.cz/cema/epidat/epidat.htm

DENMARK

EPI-NEWS
Department of Epidemiology, Statens Serum Institut, Copenhagen.
Weekly, print and online. In Danish and English.
http://www.ssi.dk

ENGLAND AND WALES

Health Protection Report
Health Protection Agency, London.
Weekly, online only. In English.
http://www.hpa.org.uk/hpr

FINLAND

Kansanterveys
Department of Infectious Disease Epidemiology, National Public Health Institute, Helsinki.
Monthly, print and online. In Finnish.
http://www.ktl.fi/portal/suomi/julkaisut/kansanterveyslehti

FRANCE

Bulletin épidémiologique hebdomadaire
Institut de veille sanitaire, Saint-Maurice Cedex.
Weekly, print and online. In French.
http://www.invs.sante.fr/beh/default.htm

GERMANY

Epidemiologisches Bulletin
Robert Koch-Institut, Berlin
Weekly, print and online. In German.
http://www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html

HUNGARY

Epinfo (az Országos Epidemiológiai Központ epidemiológiai információs hetilapja)
National Center For Epidemiology, Budapest.
Weekly, online. In Hungarian.
http://www.oek.hu/oek.web?to=839&nid=41&pid=7&lang=hun

ICELAND

EPI-ICE
Landlæknisembættið
Directorate Of Health, Seltjarnarnes
Monthly, online. In Icelandic and English.
http://www.landlaeknir.is/pages/272

IRELAND

EPI-INSIGHT
Health Protection Surveillance Centre, Dublin.
Monthly, print and online. In English.
http://www.ndsc.ie/hpsc/EPI-Insight

ITALY

Notiziario dell'Istituto Superiore di Sanità
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome.
Monthly, online. In Italian.
http://www.iss.it/publ/noti/index.php?lang=1&tipo=4

Bolletino Epidemiologico Nazionale (BEN)
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome.
Monthly, online. In Italian.
http://www.epicentro.iss.it/ben

LATVIA

Epidemiologijas Biletens
Sabiedribas veselibas agentura
Public Health Agency, Riga.
Online. In Latvian.
http://www.sva.lv/epidemiologija/biletens

LITHUANIA

Epidemiologijos žinios
Užkreciamuju ligu profilaktikos ir kontroles centras
Center for Communicable Disease Prevention and Control, Vilnius.
Online. In Lithuanian.
http://www.ulpkc.lt/ulpkc.laikrastis.php

NETHERLANDS

Infectieziekten Bulletin
Rijksinstituut voor Volksgezondheid en Milieu
National Institute of Public Health and the Environment, Bilthoven
Monthly, print and online. In Dutch.
http://www.rivm.nl/infectieziektenbulletin

NORTHERN IRELAND

Communicable Diseases Monthly Report
Communicable Disease Surveillance Centre, Northern Ireland, Belfast.
Monthly, print and online. In English.
http://www.cdscni.org.uk/publications

NORWAY

MSIS-rapport
Folkehelseinstituttet, Oslo.
Weekly, print and online. In Norwegian.
http://www.folkehelsa.no/nyhetsbrev/msis

A selection of report titles from the national epidemiological bulletins in the European Union and Norway are translated and published online each month in the Eurosurveillance Monthly release section of our website, http://www.eurosurveillance.org

POLAND

Meldunki o zachorowaniach na choroby zakazne i zatruciach w Polsce
Panstwowy Zaklad Higieny,
National Institute of Hygiene, Warsaw.
Fortnightly, online. In Polish and English.
http://www.pzh.gov.pl/epimeld/index_p.html#01

PORTUGAL

Saúde em Números
Ministério da Saúde,
Direcção-Geral da Saúde, Lisbon.
Sporadic, print only. In Portuguese.
http://www.dgsaude.pt

ROMANIA

Info Epidemiologia
Centrul pentru Prevenirea si Controlul Bolilor Transmisibile,
National Centre of Communicable Diseases Prevention and Control, Institute of Public Health, Bucharest.
Sporadic, print only. In Romanian.
http://www.cpcbt.ispb.ro

SCOTLAND

Health Protection Scotland Weekly Report
Health Protection Scotland, Glasgow.
Weekly, print and online. In English.
http://www.hps.scot.nhs.uk/ewr/index.aspx

SLOVENIA

CNB Novice
Inštitut za varovanje zdravja, Center za nalezljive bolezni, Institute of Public Health, Center for Infectious Diseases, Ljubljana.
Monthly, online. In Slovene.
http://www.ivz.si

SPAIN

Boletín Epidemiológico Semanal
Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid.
Fortnightly, print and online. In Spanish.
http://www.isciii.es/jsps/centros/epidemiologia/boletinesSemanal.jsp

SWEDEN

EPI-aktuellt
Smittskyddsinstitutet, Stockholm.
Weekly, online. In Swedish.
htpp://www.smittskyddsinstitutet.se/publikationer/smis-nyhetsbrev/epi-aktuellt

TQ-AD-07-001-EN-C

Eurosurveillance

In our next issue:

- Special focus on hepatitis B and C
- Several reports on measles situation in Europe
- A review article on the epidemiology of tick-borne encephalitis in 2007 and a survey of cases in Europe
- A perspective paper on the need for a family-centred approach to hygiene promotion
- Presentation of networks/projects dedicated to the molecular typing of bacteria

And many more interesting articles

Contributions to Eurosurveillance are welcomed. Full instructions to authors are available at our website, http://www.eurosurveillance.org

Publications Office
Publications.europa.eu

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Visit our website at
www.eurosurveillance.org

The **Eurosurveillance** print edition is a compilation of short and long articles that have previously been published on our website.

All the articles in this issue are available online: you can print each page separately or download the whole quarterly in pdf format.

The website archives all articles since 1995, and offers a search facility.

To receive Eurosurveillance's free **electronic releases** and e-alerts by e-mail, please subscribe on our website.

Papers published in the monthly release are indexed for MedLine since January 2001, and papers published in the weekly release from January 2005 (with the exception of short, non-scientific notices) are also indexed for MedLine.

The Index Medicus abbreviation for Eurosurveillance is Euro Surveill.

ISSN 1025 496X
6,000 copies