VOL.9 Issue 2 / 2004

Eurosurveillance

EUROPEAN COMMUNICABLE DISEASE QUARTERLY

FUNDED BY DG HEALTH AND CONSUMER PROTECTION
OF THE COMMISSION OF THE EUROPEAN COMMUNITIES

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Eurosurveillance VOL.9 Issue 2 / 2004

Peer-reviewed European information on communicable disease surveillance and control

Articles published in Eurosurveillance are indexed by Medline/Index Medicus

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PREVENTION OF CONGENITAL RUBELLA INFECTION: A CHALLENGE FOR EVERY COUNTRY IN EUROPE

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The current issue of Eurosurveillance provides the common theme of the epidemiology and control of congenital rubella infection (CRI) across Europe. It provides a stark reminder that despite the availability of a safe and effective vaccine for many years, CRI - the consequence of rubella infection during pregnancy, remains an important public health problem both in the European Union and the wider WHO European Region. The following articles outline the various operational challenges facing national immunisation programmes in Europe. They vividly illustrate large differences in disease burden and inequalities in access to preventive health services both between and within countries. Four groups of countries can be distinguished.

CRI prevention is an issue about which no country can afford to be complacent

• The reports from Finland [1] and Denmark [2] describe the impact of longstanding, strong two-dose childhood measles-mumps-rubella (MMR) immunisation programmes that have successfully interrupted domestic rubella transmission. However, the importance of maintaining high coverage with MMR, ensuring travellers to high incidence countries are protected and strengthening surveillance are stressed.

• The articles from the UK [3] and France [4] describe the apparent interruption of transmission of rubella, but highlight recent declines in routine vaccine coverage together with the presence of older susceptible age groups and the need to take action to prevent the re-emergence of CRI.

• Reports from Italy [5] and Greece [6] describe the consequences of infant MMR vaccination programmes implemented at low coverage with a consequent shift in the age of infection to older age groups. This perverse programmatic effect has been partially mitigated in Italy through the on-going adolescent girl selective programme, but has had a disastrous public health impact in Greece, where no such adolescent or adult selective programme is in place. The need for significant strengthening of the CRI control and surveillance programmes is stressed.

• In the report from Romania [7], which apart from vaccinating a limited number of older women presently has no CRI prevention programme, describes a huge rubella outbreak, with many cases occurring in pregnant women. The impact in terms of CRS cases and abortions will unfold over the coming months and years.

Many articles highlight national inequalities: both regional as in Italy [5] or for minority groups [8,3] such as migrant populations in Spain and UK, born in countries that lacked rubella vaccination programmes. The outbreak described in Spain demonstrates the vulnerability of such groups, and how they can be neglected even within sophisticated health services.

These inequalities both between and within countries combined with constant movement of people across Europe mean that rubella in one country can easily affect another and demonstrates the importance of achieving CRI control throughout the Region. The WHO European region has established a target for CRI prevention (<1 case of CRS per 100 000 live births by 2010) [9]. The key control strategies needed to achieve this are well established - provision of direct protection to females and in those countries with a strong immunisation programme, universal vaccination in early childhood. High quality surveillance data for rubella and CRS together with serological monitoring of high-risk groups and the general population have been critical components in guiding the implementation and on-going evaluation of national immunisation programmes [9,10]. CRI prevention is an issue about which no country, regardless of the current strength of their control programme, can afford to be complacent.

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THE NEED TO HARMONISE MANAGEMENT OF HIV EXPOSURE IN EUROPE

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Harmonised European recommendations for the management of HIV exposure have been needed for some time. Important and impressive work has been achieved by two groups of experts from a total of 14 countries, and their conclusions and recommendations are reported in the two papers from Jesús Almeda *et al* and Vincenzo Puro *et al* [1,2].

Two characteristic settings are specified, although the difference between each is debatable if the issue is to avoid or prevent an established infection after exposure to HIV (or, indeed, HCV or HBV). As the authors point out, post-exposure prophylaxis (PEP) is the standard of care for healthcare workers (HCW) in almost all countries including the United States, but not for the management of sexual, injecting drug use or other non-occupational exposures to HIV.

In the case of HCW occupational exposure, the authors' task was to standardise several national recommendations and strategies. For non-occupational exposure, the aim was to establish European guidelines, as very few national recommendations exist.

As these articles show, the rationale, background, management, and choice of treatment for PEP are very similar in both situations.

It is very important for healthcare workers to know that their institution has guidelines to protect them from occupational risks. In such situations, the source patient is usually accessible for rapid testing, which helps with risk evaluation and the therapeutic decision. Healthcare workers can also seek information and care on site immediately following exposure, which is very important for the outcome of the post-exposure care.

The time elapsed between exposure and initiation of treatment is of major importance

In cases of sexual exposure, access to the physician, and the physician's decision are more difficult and will take longer, since the source patient is often unknown or unavailable for testing. Moreover, the outcome (HIV status at 6 months) is frequently not properly assessed because patients are lost to follow up.

Despite these major differences, both type of exposure deserve the same multidisciplinary and comprehensive network of specialists for post-exposure care. Because the efficacy of PEP is linked to the delay of therapy initiation, it is important for medical teams and institutions to consider risk assessment as an emergency and to provide a ready accessibility to evaluation and PEP 24 hours a day. In our experience, sexually exposed patients frequently seek advice or care at night or at weekends, which are not the best times for a full assessment of the situation; in these cases we recommend starting PEP as soon as possible after counselling, with reassessment of the patient by a specialist the following morning so that the PEP indication can be reconsidered. It is preferable to stop antiretroviral treatment after one or two days than to realise that it is too late to start it if indicated.

Informing healthcare workers and the general public about the limitations of PEP: four weeks of therapy with potential side effects and toxicity, and a follow up with medical visits and blood test. PEP cannot be used as a 'morning after pill', as is sometimes requested by patients after risky sexual behaviour. On the other hand, it is important to know that PEP can be recommended for rape victims and should be available in these situations. For medical teams or physicians, these recommendations will help in giving adequate counselling and care or in referring the person to a specialist unit after a first evaluation. However, post-exposure care is time consuming for the specialist team, as it is not only the initial assessment and prescription that will contribute to the success of the PEP. Monitoring adherence to therapy, clinical tolerance and toxicity, psychological impact, and organising scheduled visits and testing are all mandatory for the success of the care. Recommendations on the choice of drugs will have to be updated regularly, as knowledge is moving quickly in the field of antiretroviral therapy. The most important point is that PEP is not indicated for an infected or sick person and that the risk-benefit ratio is therefore of major importance. In our institution we consider the assessment and the decision whether of not to treat to be the most important part of post-exposure care. The drugs have to reach the HIV target cells for replication before effective integration of the HIV genome, which is why the time elapsed between exposure and initiation of treatment is so important.

As the authors mention, a triple combination with two nucleoside analogues and a protease inhibitor are a good choice in terms of efficacy. We would also take the number of pills and the number of doses per day into consideration, as compliance is essential. In terms of risk and tolerance, we would not recommend nevirapine or abacavir (as recommended here) because of early toxicities such as hypersensitivity or hepatitis, but we do not use efavirenz either because of the dizziness and sleeping problems that may occur during the first days of therapy, and which would compromise the therapy in these anxious patients.

Finally, we will all benefit from these European recommendations which are both well documented and very informative. Little is known about the impact of NONOPEP on behaviour, or its efficacy, and so I would strongly support the idea, mentioned in the conclusion, of the need for a prospective evaluation of its use in the European countries.

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PREVENTING CONGENITAL RUBELLA INFECTION IN THE EUROPEAN REGION OF WHO: 2010 TARGET

JS Spika, FX Hanon, S Wassilak, R Pebody, N Emiroglu*

The World Health Organization (WHO) Regional Office for Europe has recently published a strategic plan and surveillance guidelines for measles and congenital rubella infection. The strategy prioritises measles control activities but encourages the introduction of rubella vaccine when measles vaccine coverage has reached >90 %; although, many western European countries with suboptimal measles vaccine coverage are already using the combined measles, mumps and rubella (MMR) vaccine. Women in these countries may have an especially high risk of having an infant with congenital rubella syndrome. WHO is seeking to improve the surveillance for rubella and congenital rubella syndrome as a means to obtain better information on the burden of these diseases and engage policy decision makers in the need to support the WHO European Region's strategies for rubella.

Euro Surveill 2004;9:4-5
Key words : Rubella, Europe, WHO, congenital rubella syndrome, vaccine

Introduction

HEALTH21 [1], the health policy framework prepared by the WHO Regional Office for Europe and endorsed by the WHO Regional Committee for Europe in 1998, identified a number of targets for communicable disease control, including the target of less than one case of congenital rubella syndrome per 100 000 live births by 2010. Until September 2003 when the 44th Directing Council of the Pan American Health Organization endorsed a rubella elimination goal, the WHO European Region was the only WHO region to have a target for rubella infection. The Regional Office has recently published a strategic plan for measles and congenital rubella infection [2] and companion surveillance guidelines [3].

The current approach taken by the WHO Regional Office for Europe to meet the rubella target, closely links prevention of congenital rubella infection with the interruption of indigenous measles transmission. Priority is given to achieving very high coverage (>95%) with two doses of a measles containing vaccine through strengthening routine immunisation programmes. Countries with measles vaccine coverage of < 90% and who are not already using rubella vaccine in their childhood immunisation programmes are encouraged to first strengthen their routine programmes and increase coverage with measles vaccine before introducing a rubella vaccination programme.

One of the six key strategies in the strategic plan [2] is to use the opportunity provided by supplementary immunisation activities (SIA) for measles to target populations susceptible to rubella. During the past three years, Albania [4], Kyrgyz Republic [5] and Moldova have undertaken national SIA for measles using measles-rubella (MR) vaccine, linking them to rubella vaccination campaignstargeting women of childbearing age. In October 2003, Kosovo authorities conducted an SIA using MR vaccine and are planning a rubella vaccine SIA campaign for women.

In 2003, 42 (82%) of 51 member states included rubella vaccine with the first dose of measles vaccine; 40 countries used measles-mumps-rubella vaccine (MMR). Two additional countries (4%) had rubella vaccine programmes only for adolescent girls, and two others are planning to introduce childhood MMR vaccination in 2004. With the expansion of the WHO European Region to include Cyprus, which currently uses MMR, over 90% of member states will have childhood immunisation programmes for rubella.

Ensuring indirect protection of women of childbearing age by achieving high routine infant coverage with rubella-containing vaccine is another key strategy identified in the strategic plan. As already documented as occurring in Greece [6], women may be at especially high risk of having an infant with congenital syndrome in some western European countries where MMR has been used in childhood programmes with insufficient coverage, which is reflected by their recent outbreaks of measles [7].

Rubella surveillance issues in the WHO European Region

The WHO Regional Office for Europe has collected annual reported rubella incidence although, some member states have not reported incidence as there is no national surveillance for rubella.. From 2004, all member states are strongly encouraged to report rubella cases to the Regional Office on a monthly basis, using the online data entry tool developed for reporting of measles and rubella, although other methods of data transfer using the forms identified in the surveillance guidelines [3] are supported. Persons responsible for measles and rubella surveillance can set up an account on the server at measles@euro.who.int.

Recommendations for reporting of aggregate or case-based data for rubella depend on the current level of measles and rubella control [3]. Countries with measles under some or limited control are

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asked to report aggregate rubella cases by vaccine status and age group. Countries with a comprehensive rubella vaccination programme and countries approaching measles elimination should report case-based data.

The number of congenital rubella syndrome (CRS) cases reported from countries in the WHO European Region is very low and most likely due to weak surveillance programmes for this condition. The number of CRS cases reported over the last three years were: 2000, 53 cases; 2001, 19 cases; and 2002, 8 cases; 38% of these cases were reported from Romania. Effective surveillance for CRS requires inclusion of, and participation by paediatricians, obstetricians, cardiologists and ophthalmologists.

The WHO Regional Office for Europe held a technical consultation on measles and rubella surveillance issues in March 2003. Participants identified the following needs for applied research with regard to surveillance for CRS:

1. Frequency, aetiology and sensitivity of methods for detection of rash fever in pregnancy need to be assessed over time in areas with moderate to high rubella control

2. Optimal methods (sensitivity and cost) need to be defined for identification of cases of CRS

3. Optimal definitions to identify circulation of rubella virus in the community are needed, i.e. what is the size of a cluster that would suggest a rubella outbreak in a community, supporting further public health interventions

4. Ethical and legal implications of serologic testing for susceptibility to rubella in antenatal care and after diagnosis of rash-fever need to be assessed regarding possible errors of a misclassification and their potential impact on the integration of surveillance activities into routine antenatal services.

Reporting of outbreaks of both measles and rubella is being introduced within the WHO European Region. An outbreak reporting form has been developed [3]. Member states are strongly encouraged to use the online entry tool developed for this purpose and available at the Regional Office website http://www.euro.who.int/vaccine.

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ORIGINAL ARTICLES

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SEROLOGICAL SURVEILLANCE OF RUBELLA IN EUROPE: EUROPEAN SERO-EPIDEMIOLOGY NETWORK (ESEN2)

A Nardone and E Miller*

Serological surveillance is an important resource to evaluate vaccine programmes, especially for diseases such as rubella, where a suboptimal programme can lead to an increase in morbidity. A coordinated vaccine policy in Europe is needed and the aim of the European Sero-Epidemiology Network (ESEN2) is to standardise serological surveillance in 22 countries for eight diseases, including rubella.

Euro Surveill 2004;9:5-7
Key words : Rubella, Europe, surveillance, European network

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Rubella vaccines were first licensed in the late 1960s [1], since when immunisation programmes have been implemented in many European countries. The chief strategies for rubella immunisation are universal vaccination of children, selective vaccination of adolescent females, or a combination of these [2]. The universal vaccination of children with a two-dose measles, mumps and rubella (MMR) vaccine has been adopted in all countries of western Europe. However, a universal MMR immunisation programme has been implemented in only some of the other countries of the World Health Organization (WHO) European Region, and in many there is no rubella immunisation programme [3].

Serological surveillance is an important tool for the evaluation of vaccination programmes as it monitors immunity in the population, thus providing information with which to identify further control measures [4, 5]. Serological surveillance data are an important supplement to coverage data and avoid many of the limitations of pas-

sive disease reporting systems for rubella, which can be unreliable due to under-notification of clinical disease and under-diagnosis, as up to 50% of cases are estimated to be subclinical.

Serological surveillance data provides age-specific profiles that enable the identification of susceptible cohorts that can emerge following the implementation of vaccination programmes [6]. Furthermore, serological data are employed in mathematical models to simulate disease transmission within a population, thereby predicting the impact of public health interventions on future disease incidence [7, 8]. In particular, for vaccination programmes, mathematical models can provide important estimates of the proportion of the population needed to be immunised to attain herd immunity, the impact on disease incidence of not achieving these targets and the future emergence of susceptible cohorts. Such modelling estimates provide policy makers with important evidence with which to review the impact of possible options on disease incidence and burden [9].

The mathematical modelling of the impact of rubella immunisation programmes has demonstrated that if vaccine coverage falls below a threshold of approximately 80%, then there is an increase in congenital rubella syndrome (CRS), due to decreased circulation of the virus resulting in accumulation of adult female susceptibles [7]. The consequences of the introduction of a suboptimum rubella vaccination programmes have been observed in a number of European countries, where important numbers of CRS have been reported following outbreaks of rubella [10,11].

A coordinated vaccine policy within Europe is increasingly important as migration, especially within the European Union, means that outbreaks of diseases in one country can be exported to others. For example, an epidemic of rubella in Greece in the late 1990's was linked to a case of CRS in the United Kingdom [12]. Therefore, although individual vaccine schedules remain the responsibility of individual countries, there is a need that all populations in Europe have adequate levels of protection to prevent the occurrence of epidemics that could then be exported to other countries.

The European Sero-Epidemiology Network (ESEN2), based on the original ESEN project [13], was established in 2001 with funding from the Research Directorate of the European Commission. The aim of ESEN2 is to standardise the serological surveillance of eight vaccine preventable diseases (measles, mumps, rubella, diphtheria, pertussis, varicella zoster virus, hepatitis A and B virus), of which rubella is one, in twenty two European countries. By standardising both laboratory and epidemiological methodology, international comparisons can be made to allow the effectiveness of different immunisation programmes to be evaluated and to coordinate vaccine policy to ensure that adequate levels of immunity exist throughout Europe.

The ESEN2 project will achieve its objective by the following three main methods:

1. Standardisation of rubella assay results. A panel consisting of 150 samples including negative, equivocal and positive specimens was prepared and distributed to participant laboratories by the reference centre (Robert Koch-Institut, Berlin, Germany). Each participating national laboratory tests the reference panel and its results are regressed against those of the reference laboratory to obtain an equation for the line of best fit. The standardisation equation will convert each country's results to common ESEN2 units and the application of common cut-offs will control inter-assay variability, allowing comparison to be made.

2. Collection of national serum banks. These are both geographically representative and of an adequate size with a minimum total of 3500 specimens stratified by age and in equal numbers of males and females.

3. An organisational analysis questionnaire collects information on current and past rubella immunisation programmes in each of the participating countries. This provides valuable information with which to interpret the sero-profiles, but also a catalogue of different interventions. For rubella, of particular interest is the use of universal as opposed to selective vaccination programmes targeted at adolescent females.

The standardised rubella sero-profiles of twenty one European countries will be available this year, with a similar analysis as undertaken for the seven countries in the original ESEN project [14]. For some countries this will be the first time such a large scale serological surveillance will have been conducted in their own country and will provide invaluable data for each country to evaluate its own rubella immunisation programme. At a regional level, this will allow a mapping of each country's progress towards WHO targets for CRS control and their susceptibility to further rubella outbreaks. As part of a further EC Research Directorate funded project (POLYMOD), serological data will be used to model the epidemiological impact of different immunisation policies, thereby providing policy makers with an evaluation of the most cost-effective options.

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Acknowledgements

The European Sero-Epidemiology Network (ESEN2) is funded by a grant from DGXII of the European Union under project number QLK2-CT-2000-00542.

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ORIGINAL ARTICLES

Outbreak report

A LARGE RUBELLA OUTBREAK, ROMANIA - 2003

A Rafila[1], M Marin[2], A Pistol[1], D Nicolaiciuc[1], E Lupulescu[3], A Uzicanin[2], S Reef[2]

Romania experienced a large rubella outbreak in 2002-03, with more than 115 000 reported cases nationwide, and an incidence of 531 reported cases per 100 000 population. The incidence was highest in children of school age. The cohorts of adolescent girls vaccinated in 1998 and 2002 (when a rubella-containing vaccine was available) had significantly lower incidence rates ($p<0.001$) compared with those in boys in the same age groups who were not vaccinated. In 2003, of the 150 suspected congenital rubella syndrome (CRS) cases reported, seven (4.6%) were confirmed by positive rubella IgM antibodies. In the absence of available rubella containing vaccine for outbreak control, an outbreak response plan to improve the detection of cases and to limit rubella virus transmission was developed. The following activities were conducted: surveillance of pregnant women with suspected rubella or history of exposure to rubella virus was implemented, with follow up of pregnancy outcomes; surveillance for CRS was strengthened; existing infection control guidelines to prevent disease transmission within healthcare facilities were reinforced; and a communication plan was developed. In May 2004, Romania is introducing measles, mumps and rubella (MMR) vaccine for routine vaccination of children aged 12 to 15 months, while continuing vaccination of girls in the 8th grade of school (13-14 years of age) with rubella-only vaccine.

Euro Surveill 2004;9:7-9

Key words : Rubella, outbreak, Romania, congenital rubella syndrome, measles vaccine

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Introduction

Rubella is usually a mild rash illness in children and adults. However, its seriousness and public health importance stem from the ability of rubella virus to cross the placental barrier and infect fetal tissue, which may result in congenital rubella syndrome (CRS). Recognising that measles and rubella remain important causes of vaccine preventable morbidity and mortality in Europe, the World Health Organization (WHO) Regional Office for Europe has developed a Strategic Plan for Measles and Congenital Rubella Infection. The overall objectives are to interrupt the indigenous transmission of measles and reduce to very low levels the risk of congenital rubella infection (<1 case of CRS per 100 000 live births annually) by 2010. The strategy includes strengthening routine immunisation and surveillance programs throughout the Region [1].

The Romanian ministry of health (MoH) currently has no national childhood rubella vaccination program. However, rubella vaccine, in the form of measles-rubella vaccine, was first offered to girls aged 15-18 years (those born 1980-83) in 1998 as part of a measles vaccination campaign following a nationwide measles outbreak. In 2002, in Bucharest only, girls aged 14-18 years (born 1983-87) received rubella vaccine. In 2003, nationwide, all girls in the 8th grade (born 1987-1988) received rubella vaccine. In addition, in Bucharest only, 10% of girls in the 7th grade also received the vaccine in 2003.

Before the 2003 outbreak reported here, the last widespread rubella outbreak in Romania occurred in 1997, coincident with the measles outbreak, and had an incidence of 192 reported cases per 100 000 population. The average incidence in 1999-2001 was 26 reported cases per 100 000 population/year.

Methods

Case definitions

The following case definitions are used for surveillance:

- suspected rubella: any patient with fever and maculopapular rash and one of the following: cervical, suboccipital, or post-auricular adenopathy or arthralgia/arthritis.

-suspected CRS: any infant less than one year of age born to a mother with suspected or confirmed rubella during pregnancy or

any infant less than one year of age with one or more of the following: heart disease (complex, patent ductus arteriosus, pulmonary artery stenosis, ventricular septum defects), suspicion of deafness, or one or more of the following eye signs: cataract, congenital glaucoma, microphthalmia, nystagmus, diminished vision.

Description of the surveillance systems

Rubella has been reported in Romania since 1949. Currently, rubella cases are reported to MoH by family physicians, centers for diagnosis and treatment, and hospitals, on a quarterly basis, aggregated by sex, residence and in the following age groups: individual years of age 0-4 years, then in 5 year age groups from 5 to 24 years, in 10 year age groups from 25 to 84 years, and =85 years.

As part of the measles surveillance system, since December 2002, clusters with three or more cases of febrile rash illnesses are investigated by district public health directorates (DPHD) and data are reported to the regional institutes of public health. To confirm the clinical diagnosis, it is recommended that a sample of 5 to 10 cases in each cluster be investigated with serological testing for measles and, if the results are negative, for rubella. If rubella transmission is confirmed, pregnant women with suspected rubella or contacts of suspected rubella cases are given priority for testing.

National surveillance for CRS was initiated in 2000. Suspected cases are reported by the diagnosing physicians to DPHD, and from here, weekly, to MoH. Suspected CRS cases are investigated for rubella-specific IgM antibodies according to WHO methodology: a blood sample collected as soon after birth as possible; for infants with negative results and compelling clinical and/or epidemiological suspicion of CRS a second blood specimen is requested [2].

We analysed data reported by these surveillance systems during the 2003 rubella outbreak.

Results

The outbreak

During 2002-03, Romania experienced a large rubella outbreak with more than 115 000 reported cases nationwide, for an incidence of 531 reported cases per 100 000 population. More than 95% of the cases were reported in the first six months of 2003. The outbreak started in the second half of the last quarter of 2002, in the eastern part of the country, and spread towards south, then west, involving the entire country by June 2003. The incidence was highest among school-aged children (age-specific incidence 2564 per 100 000 population aged 5-9 years and 2446 per 100 000 population aged 10-14 years). Of the total number of cases, 27 614 (23.8%) occurred in persons aged = 15 years. At the national level there were no differences in incidences by sex; however, in Bucharest the cohorts of girls vaccinated in 1998 and 2002 (age groups 20-24 and 15-19 years, respectively) had a significantly lower incidence ($p<0.001$) compared with boys in the same age groups (208 per 100 000 versus 383 per 100 000 for ages 20-24 years and 640 per 100 000 versus 1569 per 100 000 for ages 15-19 years).

During 2003, more than 724 clusters of rubella cases were reported. The number of cases per cluster ranged from 3 to 278. At the national laboratory testing for rubella IgM antibodies was performed for 1252 specimens using Dade Behring kits. Of these, 626 (50%) were IgM positive. One specimen tested positive for measles. A total of 272 pregnant women with suspected rubella or contacts of rubella cases were tested; of these 29 (10.7%) were rubella IgM positive and IgG negative, consistent with an acute rubella infection in previously susceptible women.

Since surveillance for CRS was initiated in 2000, there have been 127 (2000), 123 (2001), and 124 (2002) suspected CRS cases reported, of which 20 (15.4%), five (4.1%), and five (4.1%) respectively were laboratory confirmed. In 2003, of 150 suspected CRS cases, seven (4.6%), were confirmed by positive rubella IgM antibodies. These cases were diagnosed in June (1), in September (1), in October (1), and in November (4). Of these, five had ocular abnormalities (cataracts (4) and microphthalmia (1)) and six had cardiac abnormalities (ventricular septum defects (2), complex congenital heart disease (2), atrial septum defects (1), patent ductus arteriosus (1)). The age of the mothers ranged from 16 to 36 years; four of them reported having a febrile rash illness during pregnancy (three during the first trimester and one during the second trimester of pregnancy). However, full assessment of CRS cases resulting from this outbreak will be done at nine months following the end of the outbreak. In 2004, preliminary results indicate that eight CRS cases were confirmed by April 15.

The response

In the absence of supply of rubella-containing vaccine for outbreak control, MoH developed an outbreak response plan to improve the detection of cases and to limit rubella virus transmission as much as possible. The following activities were conducted:

1. Surveillance of pregnant women with suspected rubella or history of exposure to rubella virus was implemented. A detailed set of guidelines was prepared and distributed to DPHD to:
   a. Detect, test and counsel pregnant women with suspected rubella or history of exposure to rubella virus
   b. Classify cases using WHO case classification
   c. Follow up these women for pregnancy outcomes. A pregnancy outcome registry was established at the district level

2. Surveillance for CRS was strengthened:
   a. CRS case definitions and classification were harmonised with the WHO regional case definitions
   b. In May 2003, active surveillance was introduced in maternity wards in the capital city, Bucharest. Public health directorate staff reviewed medical charts of newborns on a weekly basis to identify children with signs and symptoms consistent with CRS case definition

3. Existing general infection control guidelines to prevent disease transmission within healthcare facilities were reinforced.

4. A communication plan was developed to:
   a. Increase awareness among healthcare providers of the possibility of rubella and CRS and of the appropriate follow-up for pregnant women exposed to rubella virus
   b. Respond to inquiries from district epidemiologists, clinicians, and media regarding the rubella outbreak, detection, testing and counselling of pregnant women, and enhanced CRS surveillance.

Discussion

Key elements to prevent rubella outbreaks and occurrence of congenital rubella syndrome include ensuring high levels of rubella immunity through an ongoing childhood immunisation program, vaccinating susceptible adolescents and adults if necessary, and conducting rubella and CRS surveillance. Without a rubella vaccination program, periodic rubella outbreaks and subsequent CRS cases are expected. Two rubella immunisation strategies are currently available: selective vaccination of adolescent girls and/or women of childbearing age to protect those who have escaped natural infection, and comprehensive vaccination of all young children, (e.g., routine childhood immunisation) combined with vaccination

of susceptible women of childbearing age (1, 3-6). However, these two approaches are frequently combined. In Romania, the selective vaccination of only a few cohorts of adolescent girls implemented in 1998 and 2002 resulted in a significantly lower incidence among girls in the target age cohorts in Bucharest, compared to that among the boys of the same age group. In the light of the recent outbreak, the Romanian MoH is considering making a long term commitment to finance routine vaccination against rubella to prevent CRS. Beginning in May 2004, MoH will introduce combined measles-mumps-rubella (MMR) vaccine for routine vaccination of children aged 12 to 15 months and continue rubella vaccination of girls in the 8th grade (aged 13-14 years). Ongoing routine vaccination of all young children appears to be feasible in view of consistently high routine vaccination coverage with other antigens in Romania.

Acknowledgements

Our special thanks to healthcare providers, epidemiologists from DPHD and institutes of public health who investigated and reported CRS and rubella cases, Dr Nicoleta Teletin and other laboratory personnel from NIRDM "Cantacuzino" where testing was performed, WHO European Regional Office for providing technical and financial assistance to NIRDM "Cantacuzino", Peter Strebel, MBChB, MPH, who provided advice on methodological and scientific issues, and Mary McCauley, MS, for editorial assistance.

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ORIGINAL ARTICLES

Outbreak report

NEW FEATURES OF RUBELLA IN SPAIN: THE EVIDENCE OF AN OUTBREAK

C Lemos [1,2], R Ramirez[3], M Ordobas[3], DH Guibert [1,3], JC Sanz[4], L Garcia[3], F Martinez-Navarro[2]

In most of western Europe the rubella vaccine coverage is high. However, prior to the introduction of the vaccine in Latin America, rubella susceptibility in women of childbearing age was 10-25%. Forty one (93%) countries in Latin America have adopted the rubella vaccine since 2002. The adult immigrant population in Spain constitutes a group of susceptibles.
In February 2003, the Madrid Community Measles Elimination Plan detected an increase in rubella notifications in women who had been born in Latin America. A descriptive study was undertaken to characterise the outbreak. A confirmed case was a person with fever or rash and a positive IgM serology, and living in Madrid, between 1 December 2002 and 31 March 2003. The secondary attack rate (SAR) per household was calculated.
A total of 19 cases of rubella were identified, 15 were confirmed and four were probable cases. Fourteen (73.7%) cases were women at childbearing age. The mean age was 25.1 years. One pregnancy was diagnosed with a voluntary termination. Eleven (57.9%) cases were from Ecuador. The mean time of residence in Spain was 41 months. None of the cases or the 54 (78.3%) household contacts had been vaccinated against rubella. The SAR was 9.1%.
This study showed the spread of rubella in the susceptible Latin American Community that is resident in Madrid. The interventions proposed were a vaccination programme towards immigrants, a health education campaign to prevent congenital rubella, and a health professional training programme case management.

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4 Laboratorio Regional de Salud Publica del Instituto de Salud Publica de la Comunidad de Madrid, Spain.

Euro Surveill 2004;9:9-11
Key words : Rubella, Spain, Latin American community, pregnancy

Introduction

Immunisation strategy

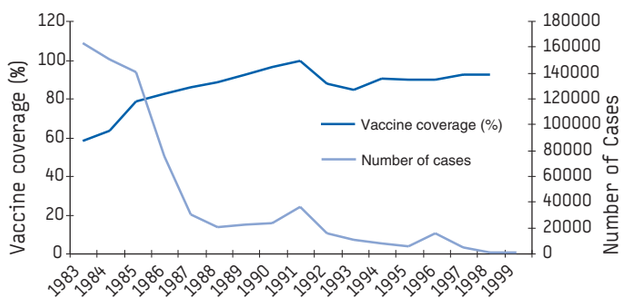
Rubella immunisation was introduced in Spain in 1979, and given to 11 year old girls. In 1981, the measles, mumps and rubella (MMR) vaccine was included in the national immunisation schedule for children of both sexes at 15 months of age. In 1995, a booster dose of MMR vaccine was introduced for both sexes at age 11 to 13 years.

In 1996, results of a serological survey suggested that antibody prevalence against rubella was higher than 95% [1]. Later, the MMR schedule was changed, and the booster dose was brought forward to pre-school age children (3 to 6 years old).

The MMR vaccine is currently part of the childhood immunisation programme, which includes a first dose at 12-15 months and a booster at 3-6 years. If a child has not received the second dose of rubella vaccine by the age of 11-13 years, a booster dose is offered. [FIGURE 1]

FIGURE 1

Number of reported cases of rubella and vaccine coverage - Spain, 1983-1999



Since 1985, high vaccine coverage has helped to achieve a dramatic drop in rubella incidence. In 1999 the annual incidence rate was 1.4 cases per 100 000 inhabitants. However, higher incidences still exist in some regions, such as the Canary Islands (10.8/100 000), Ceuta (26/100 000) and Melilla (54.2/100 000).

Incidence of congenital rubella syndrome

In 1998, there were seven cases of CRS detected in Spain (2 per 100 000 live births).

The Madrid Community serological survey carried out in 2000 indicated that 95% of all age groups were protected against rubella, and that 98.6% of women of childbearing age (16-45 years old) had protective antibodies [2]. Nevertheless, CRS cases were declared in Madrid in 1998, 1999 and 2001 [3].

Remaining susceptible individuals are probably the consequence of existing areas with low vaccine coverage and immunisation failures.

We describe here the latest rubella outbreak in Madrid in 2003, in which the population affected were unimmunised people living in Spain who had been born in Latin America.

In February 2003, the surveillance system for measles, within the framework of the Madrid community measles elimination plan [4], detected an increase in the notification of cases of rubella. Under the measles elimination plan protocol, all suspected patients presenting fever and exanthema must undergo a serologic screening for measles, rubella and parvovirus B19.

The affected population were mostly women of reproductive age who were born in Ecuador, Colombia, the Dominican Republic and Argentina.

We conducted a descriptive study to characterise the magnitude of the outbreak, define the transmission patterns and recommend control measures.

Methods

Applying the European case definition, the cases were classified as confirmed or probable. A confirmed case of rubella was defined as a person with rash and fever (more than 38.5ºC), who had been born in Latin America or was a family member of such a person, with a positive serology (IgM) confirmed by the regional public health laboratory, and who was resident or had visited Madrid, between 1 December 2002 and 31 March 2003. A probable case was a person with symptoms of rubella, and with an epidemiological link to a confirmed case but without laboratory confirmation.

A contact was defined as a person who was a family member of, working with, or had a social relationship with a case, and who was a resident of or visitor to Madrid during the same study period.

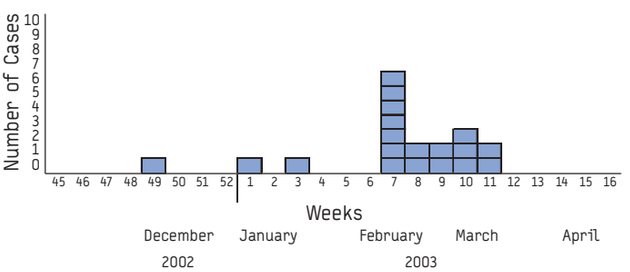
The household secondary attack rate (SAR) was defined as the number of secondary cases occurring in susceptible contacts of an index case in a family. A susceptible contact was someone with no history of rubella vaccination, who had not undergone a serologic test. A secondary case was a case occurring in the 21 days following contact with an index case.

Results

By active case finding, review of the notifiable disease register and by interviewing the cases, 19 cases of rubella were identified. Eleven cases suspected to have measles were found to have rubella by IgM serology. Three other suspected rubella cases were confirmed by positive IgM serology, and all 14 cases had low IgG avidity test [5]. Furthermore, during case finding, a probable case detected in January was confirmed by rubella IgG serology. The four remaining cases were classified as probable. The 19 cases were grouped within twelve household units: fourteen were considered to be primary cases and five were secondary. [FIGURE 2]

FIGURE 2

Distribution of reported cases of rubella per week, date of onset, Madrid - Spain, December 2002 to March 2003



Fourteen cases (74%) were in women of childbearing age (mean age 25 years, range 15 - 38 years). A pregnancy was diagnosed in one of the cases and a voluntary termination of the pregnancy was carried out. The health districts most affected were Centre West, South II, Southeast and North: 80% of the cases were found in these districts. Ecuador was the country of origin of 11 patients (58%); the other patients had been born in Argentina, Colombia and the Dominican Republic. The mean time of residence in Spain was 41 months (range 4-132 months). Previous rubella vaccination was not reported for any of the cases.

In the case-contact study, we identified a total of 93 contacts who had rubella infection during the period of infectiousness of the 19 rubella cases. Of those, 73 (78%) had not been vaccinated against rubella and 40 (43%) contacts were women of reproductive age. Overall, 69 contacts were considered to be household contacts. The SAR[h] was 9.3%.

Discussion

Our study suggests that the Latin American community in Madrid represents a new group which is susceptible to rubella infection. The resurgence of rubella infection in the population of people born outside Spain is a serious public health problem and a drawback to the measles elimination plan and the rubella control program.

The limitations of the outbreak study were possible misclassification bias introduced during ascertainment of cases and contacts, when some asymptomatic cases were considered to be susceptible contacts, and some immune contacts, due to previous asymptomatic infection, were classified as susceptible contacts. As a result of these misclassifications, the household SAR could be an underestimation of the reproductive rate of the disease. The SAR might have been much higher if all the asymptomatic cases had been identified, and all the immune contacts excluded.

If we accept a rubella reproductive rate (R_0) of 6 to 16 [6], and 40-50% of the cases to be asymptomatic, we can estimate that the magnitude of the outbreak was larger, and that the surveillance system network only detected a few symptomatic cases. Additionally, as most of the cases were in women of childbearing age, the surveillance of CRS should be strengthened.

In the framework of the national health system [7] in Spain, the principle of universal access to healthcare services ensures that those who migrate to Spain, whether they reside there legally or illegally, have the right to the same healthcare as the rest of the population of Spain. Several regional initiatives have been developed to ensure special healthcare programmes for migrants. One example is the Plan Integral para la Inmigración en Andalucía (Andalusia Immigrant Healthcare Programme) [8], which is developing a healthcare strategy that takes into account the epidemiological characteristics of the country of origin. In the adult healthcare programme, it is recommended that all women of childbearing age be vaccinated against rubella at their first visit to the healthcare services.

In the 1990s, in Spain as in other western European countries, a new population phenomenon occurred with the arrival of large numbers of people from other countries. In Spain, people who were born in Latin America have tended to settle in the province of Madrid. In 2001 [9], there were 210 000 Madrid residents who had been born in Latin America, representing 3% of the total population of Madrid.

To better understand this new public health problem, a serologic surveys panel, used by the Pan American Health Organization (PAHO) to estimate rubella susceptibility in women of childbearing age in Latin America countries, was reviewed prior to the introduction of rubella vaccine. The rubella susceptibility ranged from 10-25% [10], with large variability both between and within different countries.

Rubella vaccine has been progressively introduced in Latin America [11] since 1998. In 2002, 41 (93%) of the 44 countries and territories in the Americas Region had included MMR or measles-rubella (MR) vaccine in their childhood immunisation programmes. The remaining three countries, the Dominican Republic, Haiti, and Peru, plan to follow in 2003-2004 [12].

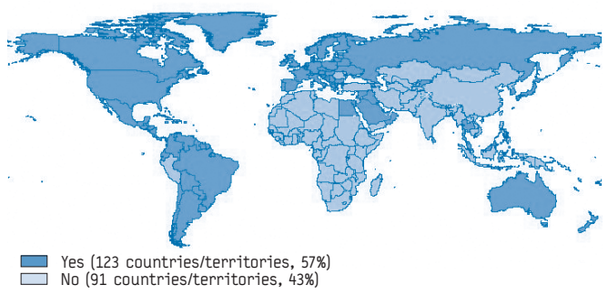
With reference to the previous information we can assume that a large proportion of the Latin American born adults in Madrid were not protected against rubella infection by natural or vaccine induced immunity.

Conclusion

We detected the spread of rubella infection in the susceptible Latin American community in Madrid. A large proportion of this community are women whose fetuses are at high risk of developing CRS if infected during pregnancy [FIGURE 3].

FIGURE 3

Countries/territories with rubella vaccine in the national immunization system, 2002



Source : WHO Department of Vaccines and Biologicals, December 2002

The measles elimination plan surveillance system was able to detect the occurrence of suspected cases of rash and fever in adults, which by differential diagnosis were found to be rubella infections.

In response to this emerging situation, the interventions proposed to prevent new outbreaks are the development of a combined immunisation programme aimed at the community of Latin American born people resident in Spain. The strategy rests on the creation of an adult immunisation programme, together with the MMR vaccine schedule in the childhood immunisation programme.

Additionally, as part of the CRS prevention strategy, all women of childbearing age who were born in Latin America should undergo rubella serology at their first visit to healthcare services. Women found to be susceptible to rubella infection should be systematically vaccinated.

These intervention activities should be carried out alongside a health education campaign to mobilise the participation of the Latin American community, through their associative organisations, such as the immigrant forum, NGOs, churches and sport clubs. Healthcare professionals should be trained in the measles elimination and rubella control protocol.

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ORIGINAL ARTICLES

Surveillance report

RUBELLA IN DENMARK

S Glismann*

An average of 20 000 rubella cases were recorded annually in Denmark until 1987. In 1989, however, only 1006 cases were reported, and the true current incidence of rubella infection in Denmark is unknown but considered to be very low and <1 per 100 000 population. The significant decrease in the incidence of rubella mirrors the success of vaccination of rubella seronegative women of childbearing age, which was initiated in Denmark in 1980. From 1982 and onwards the national health security scheme also refunded vaccination of children and the MMR vaccine was introduced in the Danish childhood vaccination program in 1987. The low incidence has been sustainable due to these interventions, and since 1994 congenital rubella syndrome and rubella in pregnancy have been listed as notifiable infectious diseases in Denmark. Nevertheless, in order to meet the WHO goal of control of rubella in the Region, the introduction of mandatory reporting of all laboratory diagnosed rubella cases is now being considered.

Euro Surveill 2004;9:12-3
Key words : Rubella, Denmark, vaccination programme

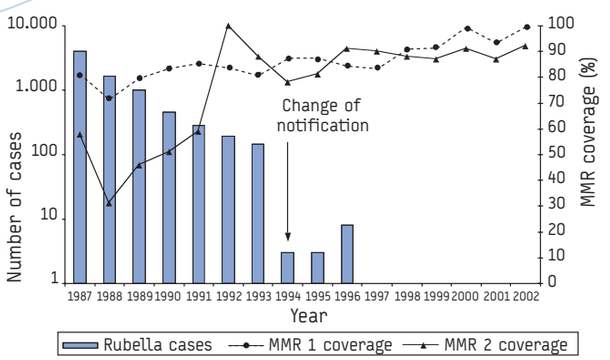
Introduction

Until 1987, an average of 20 000 rubella cases were recorded annually in the surveillance system, with most cases being in children. By 1989, however, only 1006 cases were reported, giving an incidence of 20 per 100 000 [1]. In 1994 the mandatory surveillance system was changed to include only congenital rubella syndrome (CRS) and rubella infection during pregnancy.

Vaccination of rubella sero-negative women of childbearing age was initiated in Denmark in 1980 and the National Health Security Scheme has refunded vaccination of children since 1982. The significant decrease in the incidence of rubella since 1985 mirrors the success of this intervention though early coverage data are not available. During the following years the low incidence has been sustainable due to the introduction of MMR vaccine in the Danish childhood vaccination programme in 1987.

FIGURE

Reported number of rubella cases and MMR coverage - Denmark, 1987 - 2002



Between 1975 and 1984 only 51 cases of CRS were reported. The reason for this relatively low number compared to the high incidence of rubella infection was primarily that most women chose legal abortion when they were diagnosed with rubella infection during the first 18 weeks of pregnancy. During the same period, a total of 726 women with clinical symptoms were diagnosed with rubella during the first 18 weeks of pregnancy. This number may not be exhaustive, however, as there was no policy of testing all pregnant women for rubella serology and most of these cases were probably tested because of known or suspected risk of infection.

From 1985 to 1989 a total of 200 rubella cases during pregnancy were diagnosed. Of these, 87 were diagnosed during the first 18 weeks of pregnancy and the remaining 113 were diagnosed later in pregnancy, when there is no risk of CRS and abortion is therefore not indicated. The incidence of rubella in the first 18 weeks of pregnancy decreased during the period and only one case was diagnosed in 1988-1989. From 1990 to 1997, when the most recent case was diagnosed in Denmark, 17 cases of rubella in pregnancy were diagnosed, and 11 of these 17 were diagnosed during the first 18 weeks of pregnancy.

During the five year period from 1985 to 1989, a total of seven CRS cases were reported, the last case being in 1988. Some of the manifestations of CRS will show only later in life, and therefore may not be diagnosed as relating to the mother having had a rubella infection during pregnancy. For this reason, when the MMR vaccine was introduced in 1987, it was assumed that the incidence of CRS in Denmark was about a minimum of 20 cases yearly [2]. The

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incidence of symptoms that may follow congenital rubella is another indicator of the incidence of disease. For example, it has been found that the incidence of severe congenital hearing disability caused by rubella infection has decreased significantly in some countries following the introduction of rubella vaccination. A similar trend was found in Denmark in 1994, when two 10 year cohorts of deaf children were compared, and the incidence of severe hearing disability caused by congenital rubella infection was found to have decreased from 13% to 5% [3].

The true incidence of rubella infection in Denmark is unknown at present but is considered to be very low and < 1 per 100 000 population. Nevertheless, in order to achieve the WHO goal of rubella control in the Region, there are plans to make reporting of laboratory diagnosed rubella mandatory in Denmark.

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ORIGINAL ARTICLES

Surveillance report

EPIDEMIOLOGY OF RUBELLA IN FINLAND

I Davidkin[1], H Peltola[2] and P Leinikki[1]

Before rubella vaccination programmes began, rubella infection was prevalent in Finnish children. The disease occurred as epidemics at intervals of a few years. Rubella infection was most often contracted between the ages of 2 and 12 years. Vaccinations specifically aimed at eradicating rubella were begun with monocomponent vaccine in the mid-1970s, and the measles, mumps and rubella (MMR) vaccination programme with two injections got underway in 1982. A clear reduction in rubella cases was evident a few years after the launch of the MMR programme. Owing to a sufficiently high vaccination coverage (>95% since 1987), circulation of the indigenous rubella virus in the Finnish population ceased in the late 1990s. Some rubella cases have been imported to Finland since elimination, but they have not caused any secondary cases. This shows unambiguously that protection against rubella continues to be effective, although our cohort studies imply that the vaccine induced antibody levels do decrease with time. The MMR programme has also eliminated congenital rubella syndrome (CRS) from the country. The last CRS case was recorded in 1986. As a result of the high coverage two dose MMR vaccination programme, rubella was successfully eliminated from Finland. How long the acquired protection will last remains to be seen.

Euro Surveill 2004;9:13-4

Key words : Rubella, Finland, MMR vaccination programme, elimination of rubella

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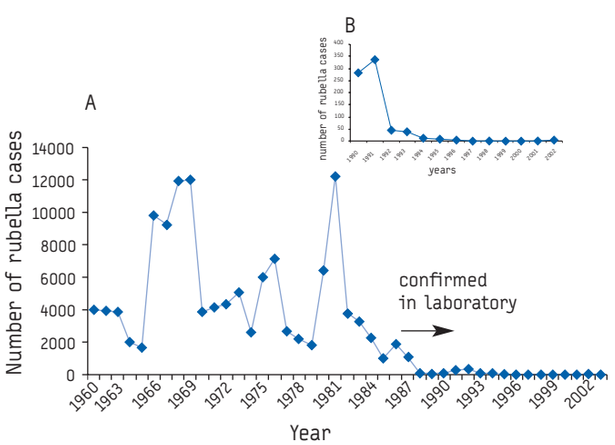
Rubella has been a notifiable disease in Finland for several decades. Before 1987, the notifications were based on the clinical picture, but since 1987, all cases reported to the National Infectious Disease Register have been laboratory confirmed before notification. In the pre-vaccination era, rubella was endemic in Finland, with large epidemics occurring every few years. The yearly incidence of notified rubella cases ranged from 33 to 249 per 100 000, with the majority of cases occurring in two to twelve year old children.

FIGURE

Number of notified rubella cases in Finland*.
A: 1960-2002, B: 1990-2002.



* Cases have been laboratory confirmed since 1997

The elimination of rubella in Finland was achieved over twenty years through two different vaccination strategies (Figure 1). Selective rubella vaccination with monocomponent vaccine was started in 1975. The programme targeted 11-13 year old girls and seronegative mothers after delivery. The vaccination coverage was 60-70%, which was not sufficient to eliminate rubella during pregnancy [1]. The rubella vaccine used in this programme until 1983 was Cendevax (SmithKline-RIT, Belgium) containing Cendehill rubella strain). Thereafter, Rubeaten vaccine (Berna, Swiss Serum and Vaccine Institut, Switzerland) containing RA 27/3 rubella strain was used until 1988 for adolescent girls and seronegative women in the postpartum period.

Monocomponent rubella vaccination had a very limited influence on the number of rubella cases between 1975-1982, probably because of low coverage and because it targeted only girls and seronegative mothers. Rubella cases continued to occur; for instance, the peak number of rubella cases since 1960 (245 per 100 000) was observed in 1980.

Consequently, a two dose nationwide measles, mumps and rubella (MMR) vaccination programme was launched in 1982, the two doses being given at the ages of 14-18 months and 6 years [2]. Catch up MMR vaccinations were given between 1983-1986 to children between 14-18 months and six years of age. The MMR vaccine was also used in the vaccination of military conscripts from 1986 to 1999. The vaccine was MMRII (Merck Co., United States) throughout the programme.

The vaccination coverage of the MMR was <90% during the first four years of the programme. By 1987, coverage of 97% was attained by means of a specific campaign [3]. Since then the coverage has remained >95% throughout the MMR programme, which is high enough to stop the circulation of rubella virus in population [4].

Concurrent with the MMR vaccination campaign, several specific studies were begun to evaluate the effectiveness of the programme. One was a study of suspected vaccine failures, which revealed that less than 1% of clinically suspected rubella cases could be laboratory confirmed between 1983-1995 [5], indicating the low positive predictive value of clinical diagnosis at this stage of control.

Soon after the start of the MMR programme, a large decline was seen, with the annual number of cases dropping from 3250 to 99 in five years [6], and a simultaneous transient increase in the age of acquisition to older and unvaccinated age groups [7].

The last two rubella outbreaks involved 200-300 cases each and occurred in 1990-1991. Any person having fever and maculopapular rash with rubella-specific IgM antibodies was considered as a rubella case. The cases appeared mostly at vocational schools in two cities in southwest Finland. Those infected were unvaccinated boys and young men aged between 15 and 21 years [8]. The girls of the same age at the same schools had apparently been protected because of vaccination with the monocomponent rubella vaccine. This epidemic rubella strain was found to belong to genotype 1, the most prevalent strain worldwide (unpublished data).

After this outbreak the number of cases continued to decline steadily. Since 1996 no indigenous rubella cases have occurred in Finland. Some imported cases are still diagnosed each year, with cases being imported from Russia, Estonia, Thailand and France over the past five years. No secondary cases have been observed in the Finnish population, indicating high herd immunity.

Rubella antibody screening of pregnant mothers during 1982-83 showed the prevalence of seronegative parturient women was 3.7% which was a half of that before selective vaccination [9]. A seroprevalence study performed as part of the ESEN (European Sero-Epidemiology Network) project from specimens collected from 0 to >65 year olds in 1997-98 revealed that the percentage of the population that was seronegative for rubella was less than 5% in all studied age groups for both sexes [10].

In spite of monocomponent rubella vaccinations, the number of congenital rubella syndrome (CRS) cases was high prior to the MMR vaccination programme. During a four year period (1979-1982) before the MMR campaign 22 cases of CRS were diagnosed. However, since 1983, the start of the MMR vaccination programme, CRS has been serologically confirmed in only five cases, the last of which occurred in 1986 [11].

A twenty year cohort study of MMR induced immunity suggests that serum antibody levels have waned substantially over time, even after two doses of rubella vaccine [12], so that a relatively large proportion of vaccinees had an antirubella antibody level of <15 IU/ml, a putative protective level (unpublished data). However, the decreased antibody levels still remain at a measurable level, i.e., all were seropositive.

Finland has now been free of indigenous rubella for eight years. Very high vaccination coverage has been the cornerstone for this state of affairs, and will be essential if it is to continue. It will be interesting to see how long the protection against rubella provided by our two dose MMR vaccination programme will last.

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ORIGINAL ARTICLES

Surveillance report

RUBELLA CONTROL IN FRANCE

D Lévy-Bruhl, C Six, I Parent*

In the pre-vaccination era, rubella was regarded as only a mild exanthematous acute viral infection of children. The devastating effects of the disease were first identified in the early 1940s by an Australian ophthalmologist, and further confirmed during the 1962-65 rubella pandemic in Europe and the United States. They result from the transmission of the virus by infected pregnant women to their fetus. The resulting congenital rubella syndrome (CRS) comprises a lengthy list of abnormalities. The most common ones are deafness, ocular and cardiac defects and mental retardation. The objective of rubella vaccination, to which France has subscribed, is the elimination of CRS [1].

Euro Surveill 2004;9:15-6
Key words : Rubella, France, vaccination coverage, pregnancy

History of immunisation strategy in France

Rubella vaccination was introduced in France in 1970 as a selective strategy for pre-adolescent girls. Epidemiological analysis, together with results from mathematical modelling, have shown that this strategy alone cannot eliminate CRS [2]. France, like other industrialised countries, therefore added rubella vaccination for young children of both sexes into the immunisation schedule first as measles-rubella vaccination in 1983, and since1986, as the measles, mumps, and rubella (MMR) vaccination. A second dose of MMR was introduced in the schedule in 1996, mainly as a catch-up for measles vaccination primary failures, in the context of the measles elimination objective. The current immunisation schedule for rubella includes two doses, the first of which is given from the age of 12 months and the second of which is given between the age of 3 and 6 years (with the possibility of earlier administration, provided that at least one month has elapsed since the first dose). It also includes a catch-up for all non-immunised children up to the age of 13 years with a MMR vaccine and for female adolescents and young women with the rubella vaccine alone. Non-immune women of childbearing age should also be vaccinated [3]. In addition, prenuptial and prenatal rubella testing are mandatory.

Measuring vaccine coverage

Childhood vaccine coverage is measured annually for children aged 2 years , by analysis of the health certificates that must be filled in for each child during the 24th month of its life. Until 2000, a school-based sample survey was performed bi-annually at 6 years of age [4]. Since 2001, this survey has been performed annually, on different school grades. In 2001, the study was carried out in children aged 14 to 17 years. There is no routine measurement of coverage for older age groups.

Rubella surveillance

Rubella is not a notifiable disease in France. Surveillance of rubella infections during pregnancy and of CRS has been carried out since 1976, based on the network of all laboratories, both private and public, performing rubella IgM testing. When the list of such laboratories was last updated in 2001, 278 laboratories were participating in the network. For each diagnosis of rubella infection during pregnancy or in a product of pregnancy termination or at birth, the clinician in charge (usually a gynaecologist or a paediatrician) is asked to fill in a questionnaire which includes demographic, biological and clinical data on the woman and/or either the fetus or the newborn [5].

Serologic surveillance

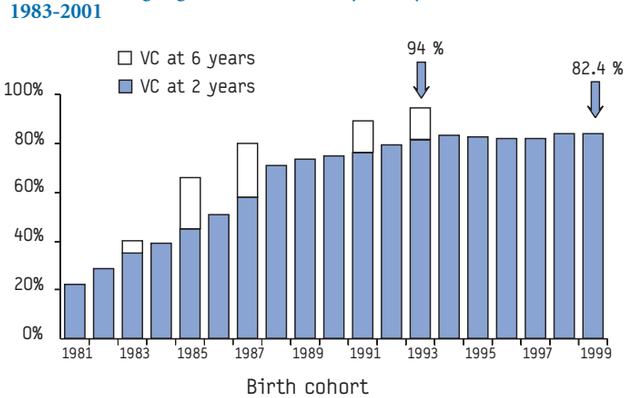
Through the European Sero-Epidemiology Network (ESEN), a nationwide sero-survey for various vaccine preventable diseases, including rubella, was carried out in 1998. About 3500 sera were collected, based on quota for age, sex and geographical location, yielding a reasonably representative sample of the general population. To allow inter-country comparisons, assay results were standardised [6].

Results

Figure 1 shows that vaccine coverage at 2 years of age has increased steadily during the eighties but has been levelling off in the last

FIGURE 1

Vaccine coverage against rubella* at 2 years by birth cohort - France 1983-2001



* Until 1989, measles coverage data, in the absence of specific data for rubella
Source : DREES (24 months old health certificates and school-based surveys)

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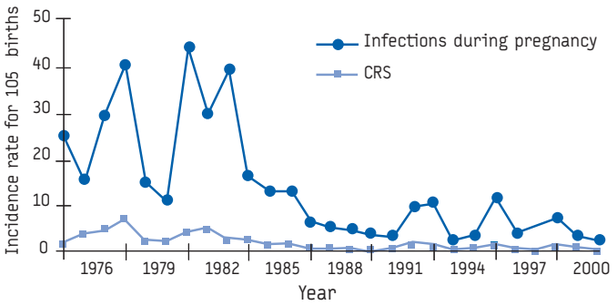
decade below 85 % (84.2% in 2001). The coverage at 6 years, measured in 1999-2000, shows an incomplete catching-up (94%).

FIGURE 2

Incidence of rubella infections during pregnancy and CRS in France from 1976 to 2002

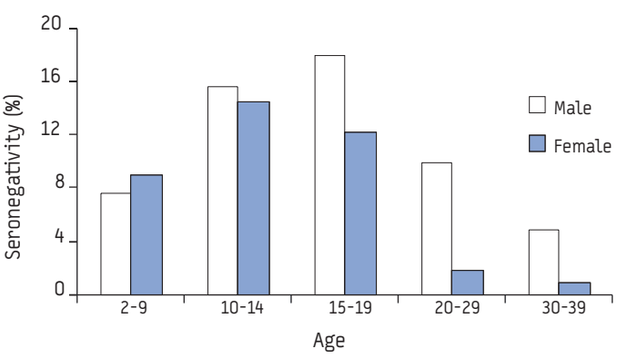


* Source : Renarub Network [5]

Figure 2 shows the dramatic impact on the incidence of rubella infections during pregnancy of the addition in 1983 of routine immunisation of children on the top of the selective pre-pubertal vaccination strategy. It also shows the persistence of rubella virus circulation in young adults with regular limited outbreaks. The last two peaks occurred in 1997 and 2000 with respectively 12 and 7.9 cases per 100 000 live births. The incidence of CRS for the period 1998-2000 has been 1 case per 100 000 live births or fewer, but each year at least one case has been notified.

FIGURE 3

Susceptibility to rubella according to age and sex - France (n= 2424)



Source : ESEN 1998 [6]

Figure 3 shows the results of the sero-survey according to age and sex. The lower susceptibility after 15 years of age for girls, compared with boys, reflects the impact of the selective sex-based vaccination strategy. However, the most striking finding is the high level of susceptibility in 15 to 19 year old girls (12%). This reflects the fact that these girls have grown up at a time when increasing vaccination activities for children were taking place, therefore reducing the risk of infection for those who had missed both the vaccination as a toddler and catch-up as an older child.

Even if it can be anticipated that some of these post-adolescent girls will benefit from natural infection or vaccination before their first pregnancy, it is most likely that, if vaccination activities remain at the 1998 level, periodic outbreaks of rubella infections during pregnancy may be predicted from this high susceptibility gap, when these cohorts become pregnant.

An intensified promotion of rubella vaccination has been undertaken since 1998. Vaccine sale data show a very significant increase in vaccination activity in children aged more than 6 years, but it is impossible to distinguish between late second dose administration and catch-up activities for the first dose in unvaccinated children. Preliminary results from the school-based survey performed in 2001 on cohorts born between 1984 and 1987 are encouraging, showing a rubella vaccination coverage close to 90% for girls. A new sero-survey is planned for 2005.

Conclusions

Even if the incidence of CRS has in recent years been below the World Health Organization European target for 2010 of less than 1 case per 100 000 live births, the past and current insufficient vaccination coverage at 2 years and the suboptimal catch-up of non-immune girls allow respectively the persistence of rubella transmission and the occurrence each year of several dozen rubella infections during pregnancy. This leads to spontaneous or induced early pregnancy terminations and the occurrence of a few cases of CRS. This situation is unacceptable, since rubella vaccination strategies, based on a very safe and widely available vaccine, and designed to protect women of childbearing age and to interrupt transmission through childhood vaccination, have been implemented for over 30 and 20 years respectively. Ongoing effort is needed to empty the reservoir of susceptible young women if future outbreaks, worse than those seen during the 1990, are to be avoided.

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ORIGINAL ARTICLES

Surveillance report

EPIDEMIOLOGY OF RUBELLA AND CONGENITAL RUBELLA SYNDROME IN GREECE, 1994-2003

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In 1993, there was a large epidemic of rubella and congenital rubella syndrome (CRS) in Greece. The epidemiology of rubella and CRS after 1993 is described in this paper using information from surveillance data and published studies and reports. The incidence of rubella fell sharply after 1993, but a smaller outbreak occurred in 1999, mainly in young adults, and four CRS cases (4.0 per 100 000 live births) were recorded. A very high proportion of the child population in Greece are currently vaccinated for rubella, while teenagers are inadequately covered (60-80% in different studies). A substantial proportion of women of childbearing age are susceptible to rubella (10-20% in urban areas). This could lead to local or more extended outbreaks. This situation shows that a comprehensive preventive policy should be implemented.

Euro Surveill 2004;9:17-9

Key words : Rubella, Greece, congenital rubella syndrome, outbreak

Introduction

Rubella is usually a mild disease, but infection during the first months of pregnancy can have severe consequences, which include spontaneous abortion, stillbirth and congenital rubella syndrome (CRS) [1]. Immunisation programmes to prevent CRS are implemented in many countries, and the World Health Organization Regional Office for Europe has designed a strategic plan aiming at controlling CRS in Europe by the year 2010 [2].

As described elsewhere, Greece experienced a large outbreak of CRS in 1993 [3]. There is evidence that this outbreak was the consequence of immunisation practices that had been followed. The measles, mumps and rubella vaccine (MMR) became commercially available in Greece around 1975, and started being administered to children of both sexes in their second year of life without adopting policies to protect adolescents and young women or policies to attain high immunisation coverage of children - until 1989 when the MMR vaccine was introduced in the national immunisation schedule. During the 1980s, immunisation coverage for rubella remained consistently below 50% and the proportion of pregnant women susceptible to rubella gradually increased to around 20-35% in the late 1980s and early 1990s in urban areas. In 1993, when a major rubella epidemic took place in Greece, a shift in the age distribution of rubella cases towards older ages was observed (64% of cases were 15 years old or more), and the incidence of the disease in persons of childbearing age was higher than in any previous epidemic year. The congenital rubella outbreak that followed, with 25 serologically confirmed cases recorded (24.6 per 100 000 live births), was probably the largest in the country after 1950 [3].

The epidemiology of rubella and CRS in Greece, and the immunisation policies adopted and implemented in the 10 year period after the 1993 epidemic are presented in this paper.

Methods

We used national surveillance data to describe the trend of rubella incidence over time, as rubella is a notifiable disease in Greece. We carried out a systematic review of the literature published in Greek and in English for information on the age distribution of rubella cases, on immunisation coverage and on serologically detected immunity in women of childbearing age.

We carried out an electronic search in the Athens Institute of Child Health database (http:// www.ich.gr) for publications in 1993-2003 on rubella / rubella vaccine / rubella virus, and a search in PubMed for similar publications referring to Greece. We also manually searched the major paediatric and other medical journals published in Greece, as well as the proceedings of the annual Panhellenic paediatric and the biannual Panhellenic microbiological and public health conferences (1993-2003).

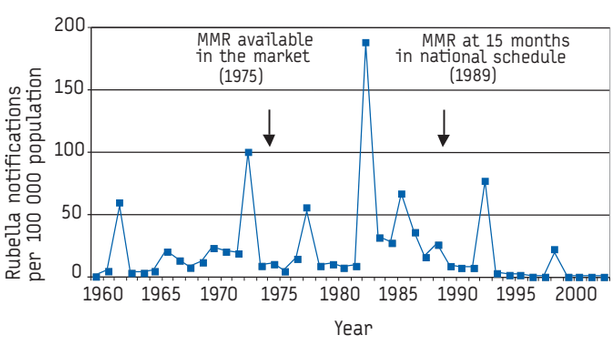
Results

Occurrence of rubella and congenital rubella syndrome

After the epidemic of 1993, the incidence of rubella in Greece decreased sharply, but in 1999 there was another epidemic of smaller magnitude (FIGURE 1). After this, an all-time low rubella incidence is observed. Four confirmed case of CRS were recorded after the epidemic of 1999 (corresponding to 4.0 per 100 000 population) and none in 1995-1999 and 2001-2003.

FIGURE 1

Notified cases of rubella in Greece, 1960 - 2003



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Age distribution of rubella cases

In 1999, 75% of notified cases with known age were in patients of 15 years or older, but only 18% of reports (259 of 1438 cases) included this information. Patients with rubella aged 15 years or older were estimated to be 74-93% and 67-94% in two studies of patients with rubella visiting the outpatient department of two large hospitals in 1999 (Athens area and Thessaloniki respectively) [4-5]. These figures compare with 64% estimated for the 1993 epidemic and 6-18% estimated for previous epidemics [3].

Immunisation coverage

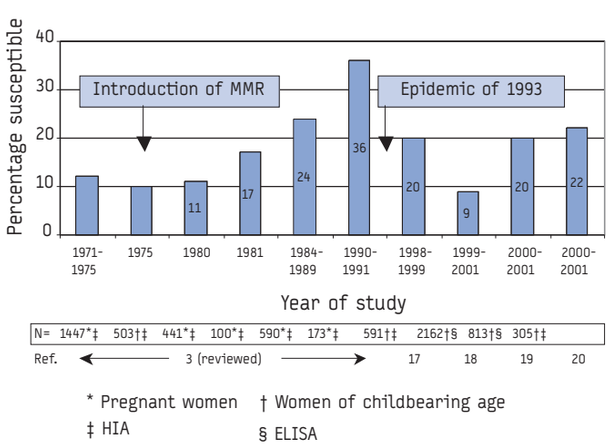
In a national study of immunisation coverage in Greece, carried out in 2001 in 2-3 year old children, it was found that 89% had been vaccinated by their 2nd birthday with at least one dose of rubella-containing vaccine [6]. We identified four local studies on immunisation coverage of children 2-12 years that were carried out in or after 2000; it was found that 94-98% of children were immunised for rubella [7-10]. We also identified four studies on coverage of children 12-18 years that were conducted in the same period; immunisation of teenagers for rubella ranged from 49% to 86% [10-13]. An earlier national study (1996-97) showed that 69% of 14 year old adolescents were vaccinated for rubella, ranging from 59% to 78% in the different regions of the country [14]. Studies of minority groups have shown that children in some Gypsy communities have low vaccination coverage for rubella (15-44% in two studies), and that vaccination of other minority groups are comparable to that of the general population [15-16].

Serologically detected immunity in women of childbearing age

Several hospital laboratories that routinely carry out serological tests for rubella antibodies in women of childbearing age occasionally report their results. We identified nine such published reports in the period 1994-2003, all referring to the period after the 1993 epidemic (another 17 reports, referring to the period before the 1993 epidemic, were previously reviewed [3]). The proportion of women of childbearing age susceptible to rubella ranges from 9.4% to 22.0%, without any clear geographical pattern or time trend in the period 1994-2003. Figure 2 shows the results of published studies in this and the previous review referring to women of childbearing age in Athens [3,17-20].

FIGURE 2

Women of childbearing age susceptible to rubella - Greece, 1971-2001



* Pregnant women † Women of childbearing age
‡ HIA § ELISA

Immunisation policies

The MMR vaccine became commercially available in Greece around 1975. In 1989 it was introduced into the national immunisation schedule for children aged 15 months, and in 1991 a second dose, at the age of 11-12 years, was also introduced. In 1999 the recommended age for the second MMR dose changed to 4-6 years. No active policy to immunise adults or susceptible women of childbearing age has been implemented to date.

Discussion

After the 1993 epidemic, rubella incidence decreased sharply, but in 1999, when rubella epidemics took place in some other European countries [2], a smaller epidemic occurred in Greece; there was a small increase in the interepidemic period to six years compared with 3-5 years in the pre-1993 period. During this, the age distribution of rubella cases shifted towards older ages more than it was observed in 1993. It has been reported that in 1999 the outbreak in the general population was in some instances preceded by outbreaks in army camps [21]. A link of the 1999 epidemic in Greece to outbreaks in at least four colleges and one CRS case in the United Kingdom has been reported [22].

Vaccination uptake has gradually increased during the 1990s: in the early 2000s about 90% of 2 year old children are vaccinated for rubella, and this proportion rises to >95% in school age. Nevertheless, the cohorts that were in their teens during the 1990s and early 2000s are inadequately vaccinated (coverage in the range of 60-80%). According to available evidence, a substantial proportion of women of childbearing age are susceptible to rubella: 10-20% in urban areas compared with about 10% in the pre-vaccination era.

This review has several limitations. There is substantial underreporting in the mandatory notification system and age is recorded for only a small proportion of reported cases, local studies on vaccination coverage give a partial picture and often have methodological problems, serological studies on rubella immunity are local and hospital based. Nevertheless, all these studies as a whole, together with the studies reviewed previously [3], probably give an accurate description of time trends. We used published studies as a source of information on rubella epidemiology, because a comprehensive surveillance system was not in place during the period studied; such a system is designed in the framework of a major revision of the surveillance system of infectious diseases in Greece, which is currently (2003-2004) being instituted.

In conclusion, a very high proportion of the child population in Greece is presently vaccinated for rubella, which contributes importantly to the reduction of viral circulation in the population. Nevertheless, teenagers are inadequately covered and there is evidence that a substantial proportion of young adults / women of childbearing age are susceptible to rubella. This can lead to local or more extended outbreaks in which young adults would be predominantly affected, and CRS cases could appear. There is a need for the implementation of a comprehensive preventive policy, which should probably include catch-up vaccination of young adults / women of childbearing age.

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ORIGINAL ARTICLES

Surveillance report

RUBELLA CONTROL IN ITALY

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In Italy, rubella vaccination has been recommended since 1972 for pre-adolescent girls, and since the early 1990s for all children in the second year of life. Nevertheless, coverage in children from 12 to 24 months of age is suboptimal (i.e., 56% in 1998, 78% in 2003), with wide variations among regions.
As a result, rubella is still circulating in Italy, and in 1996 the percentage of women susceptible to rubella between 15 and 39 years of age was >5%.
Congenital rubella syndrome (CRS) was a notifiable disease between 1987 and 1991, with a range of 8-76 cases reported annually. Since 1992, national incidence data are no longer available, but local reports show that CRS cases are still occurring. Nationwide, coordinated and uniform actions are needed to control CRS effectively. For this reason, the National Plan for the Elimination of Measles and of Congenital Rubella has recently been launched. This plan includes strategies aimed at increasing MMR vaccination coverage in children and specific control measures for congenital rubella control, i.e., improving the vaccination of susceptible women of childbearing age, and reintroducing national surveillance of CRS.

Euro Surveill 2004;9:19-21
Key words : Rubella, Italy, congenital rubella syndrome

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Introduction

In Italy, rubella vaccination has been recommended since 1972 and was initially targeted at pre-adolescent girls. Following the introduction of the combined measles, mumps and rubella (MMR) vaccine in the early 1990s, a universal vaccination strategy targeting 15 month old children was adopted. Since 1999, the national immunisation schedule has recommended that the first dose of MMR vaccine be given at 12 to15 months old, and a second dose at 5 to 6 or 11 to 12 years of age [1]. Immunisation of pre-adolescent girls will continue to be recommended until high levels of coverage in the second year of life are achieved.

Rubella immunisation coverage is not routinely assessed, but studies in the 1990s have shown that measles immunisation of children in their second year of life is achieved in over 90% of cases, through the use of the combined MMR vaccine [2]. Coverage of rubella vaccine in children from 12 to 24 months old is therefore similar to that of measles. Results from national EPI (Expanded Programme on Immunization) cluster sampling surveys showed coverage rates of 56% in 1998 [2], and 78% in 2003 [3]. In 2003, regional coverage rates ranged from 55% to 90%, being generally lower in southern Italy than in northern Italy.

As a result of suboptimal vaccination coverage, a high proportion of individuals remain susceptible to rubella. A serosurvey in Italy in 1996 showed that over 30% of children aged 2 to 14 and 9% of subjects over age 14, were seronegative [4]. In adolescents and adults, higher susceptibility rates were reported in males than in females (40% versus 26% in the 10-14 year age group; 21% versus 10% in the 15-19 year age group; 10% versus 7% in the 20-39 age group), as a consequence of the selective immunisation programme aimed at pre-adolescent girls. Mean susceptibility rates among women of childbearing age were higher in southern than in northern Italy (12% versus 6% of women aged 15-39 years respectively).

Surveillance data

Systems for monitoring rubella incidence in Italy include statutory notifications and the paediatric sentinel surveillance system (SPES) [5]. In both systems, case definition is based on clinical criteria.

Rubella has been a notifiable disease since 1970; the figure shows the number of cases reported annually from 1970 to 2001. Epidemics occurred approximately every four to five years until 1997, which was the last epidemic year of the 1990s, when approximately 35 000 cases were reported. Between 1998 and 2001, disease incidence declined, with a maximum of 5500 reported cases per year. Approximately 70% of cases occurred in children under 15 years of age, with a mean annual incidence in this age group of 25 per 100 000.

According to statutory notifications, the mean age of reported cases has shifted upwards, from 9.5 years between 1976 and 1980, to 11.7 years between 1991 and 1996. Nevertheless, the incidence in women of childbearing age has slightly decreased (from 14.1/100 000 in 1976 to 1980, to 10.5 per 100 000 in 1991 to 1996), probably because of the selective immunisation programme.

The paediatric sentinel surveillance system was launched in 2000, covering approximately 4% of the national population aged <15 years. It consists of a network of national health system primary care paediatricians who participate on a voluntary basis, and aims to monitor the incidence of several vaccine preventable diseases in a timely way. Each month, participating physicians report cases of vaccine preventable diseases seen in their practices.

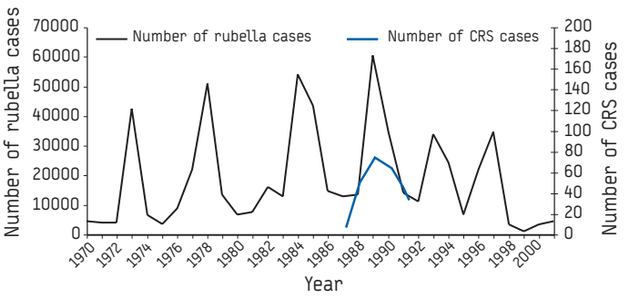
SPES surveillance is considerably more sensitive than the statutory notification system: estimated incidence of rubella in children in the year 2000 was found to be 5 to 6 times higher than that estimated by statutory notifications [5].

According to SPES, the incidence of rubella was low between 2000 and 2001 but increased in 2002 when it reached an incidence of approximately 300 cases per 100 000 children. In the years 2000 to 2002, the incidence of rubella was consistently higher in central and southern Italy than in northern Italy. Most cases occurred in children between 10 and 14 years of age. However, since SPES is limited to children <15 years old, it does not provide information about rubella incidence in adults.

Congenital rubella syndrome (CRS) was reportable only between 1987 and 1991 (FIGURE). During that period, the number of reported cases ranged from a minimum of 8 cases in 1987 to a maximum of 76 cases in 1989. Since 1992, national incidence data are no longer available, nevertheless, two recent local reports confirmed the presence of congenital rubella cases in Italy. The first report was from Campania, a region in southern Italy where a registry of CRS and other perinatal infections was established in 1997 [6]. A network of maternity wards, where 89% of regional births take place, participate in the registration. Between 1997 and 2002, 18 children with CRS were identified. Two incidence peaks were observed: one in 1997 (5 cases) and another between 2001 and 2002 (4 and 3 cases respectively). Approximately 70 000 children are born each year in the Campania region; the annual incidence rate of CRS has thus always been above 1/100 000 live births, and was 6/100 000 in 2001.

FIGURE

Cases of rubella and Congenital Rubella Syndrome - Italy, 1970-2001



The second report is from the San Matteo Hospital in Pavia, a third level hospital in Lombardia, a region in northern Italy [7]. In 2002, 11 primary, laboratory confirmed rubella infections occurred in pregnant women and were prospectively followed. Only four of the eleven pregnancies resulted in non-infected live newborns. In all four cases, the women had acquired rubella in a period of low risk of maternal-fetal transmission (i.e., between 7 to 11 days after the last menstrual period in 3 cases, and at 28 weeks of gestation in one case). The remaining seven pregnancies (one of which was a twin pregnancy) resulted in four elective terminations, two in uterus deaths of infected fetuses, and two live births of infants with congenital infection. One of the two liveborn infants presented clinical symptoms compatible with CRS, while the other was still asymptomatic at 1 year old.

The medical histories of the 11 women revealed that, for seven women this was a first pregnancy, while four women had had previous pregnancies. Only one of the nulliparous women had been screened for rubella immunity before pregnancy and, though found to be seronegative, had not subsequently been vaccinated.

Furthermore, the pluriparous women had all been found to be susceptible in previous pregnancies but had not been vaccinated after delivery.

Conclusions

To prevent CRS, high levels of immunity must be ensured among women of childbearing age, and uniformly high levels of coverage at 2 years of age must be achieved and sustained to interrupt transmission.

Serological and surveillance data indicate that rubella transmission is continuing in Italy. Although there is limited data on the incidence of CRS, the available data does indicate that it is still present.

Screening for rubella immunity is recommended and free of charge both before conception and during pregnancy, as is vaccination of women found to be susceptible. Nevertheless, our data indicate that screening and vaccination programs targeting women of childbearing age have so far been inadequate.

Nationwide, coordinated and uniform actions are needed to reduce and maintain the incidence of CRS at less than 1 case per 100 000 live births. For this reason, the national plan for the elimination of measles and of congenital rubella has recently been developed by the regional health authorities, the Istituto Superiore di Sanità (national institute of health) and the ministry of health [8].

This plan includes strategies aimed at increasing MMR vaccination coverage in children (i.e. increasing routine coverage with one dose of MMR vaccine for children aged 24 months to >95%; conducting a national catch-up vaccination campaign for children aged 6 to 13 years; achieving and sustaining a high second dose routine coverage among children aged 5 to 6 years), as well as specific control measures for congenital rubella. These include:

· evaluation of the susceptibility status of women of childbearing age at every opportunity, and their vaccination if necessary

· evaluation of the susceptibility status of all pregnant women and post partum vaccination of all women found to be susceptible;

· reintroducing national surveillance of CRS, by including it among the statutory reportable diseases.

The participation of various health providers, such as general practitioners, gynaecologists, paediatricians and public health physicians is crucial to effectively perform these activities. For this reason, the plan includes also a coordinated educational training program targeting the above mentioned professionals.

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ORIGINAL ARTICLES

Surveillance report

RUBELLA IN ENGLAND, SCOTLAND AND WALES

P Tookey*

Rubella vaccine was offered to schoolgirls in the United Kingdom (UK) from 1970, with antenatal testing and postpartum vaccination for susceptible women introduced during the 1970s. Mass vaccination with MMR of children aged 12-15 months was introduced in 1988; schoolgirl vaccination was discontinued in 1996 and replaced by a second dose of MMR for pre-school children; postpartum vaccination of susceptible women identified through antenatal testing continues. Rubella was made a notifiable disease in 1988, and is monitored through clinical and laboratory reports; data are available on rubella associated terminations and congenital rubella syndrome(CRS) births, rubella susceptibility in population subgroups, and vaccine uptake. Reported cases of CRS declined from about 50 a year 1971-75 to just over 20 a year 1986-90, and rubella associated terminations from an average of 750 to 50 a year. About 40 infants with CRS have been reported since 1991; about a third of their mothers were infected abroad, most in their country of origin (imported infections), a third were born abroad but acquired infection in the UK, and a third were UK-born. Women living in the UK who were born abroad have much higher rubella susceptibility rates than UK-born women. Although there is currently very little rubella infection circulating, uptake

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of MMR has dropped by over 10% since 1995. If rubella starts to circulate again, immigrant women will be at increased risk of acquiring infection in pregnancy.

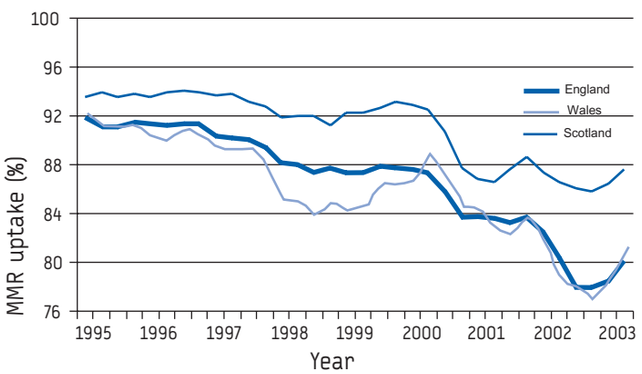
Euro Surveill 2004;9:21-3
Key words : Rubella, England and Wales, Scotland, vaccination, imported infections

Introduction

Before the introduction of rubella vaccine in 1970, British children usually acquired infection sometime between the ages of 4 and 9 years. Nevertheless, about 18% of women of childbearing age were susceptible to rubella infection, and congenital rubella (CR) was a significant problem, with about 200-300 CR births in non-epidemic years, and many more during epidemics. Since 1970, the incidence of CR has slowly declined, and in recent years, the very few reported births have mainly been associated with infection acquired abroad. However, although rubella infection is currently rare, it is possible that it could re-emerge. As shown in figure 1, uptake of the combined measles, mumps and rubella (MMR) vaccine in two year olds has declined in all three parts of Britain [1]. Outbreaks of measles and mumps have already occurred, particularly in student and travelling communities. Although rubella susceptibility rates are probably only about 2% overall for pregnant women [2], they are much higher among some minority ethnic groups which could be hit hard if rubella outbreaks occur [3].

FIGURE 1

Percentage of MMR uptake by 24 months - England, Scotland and Wales, 1995-2003



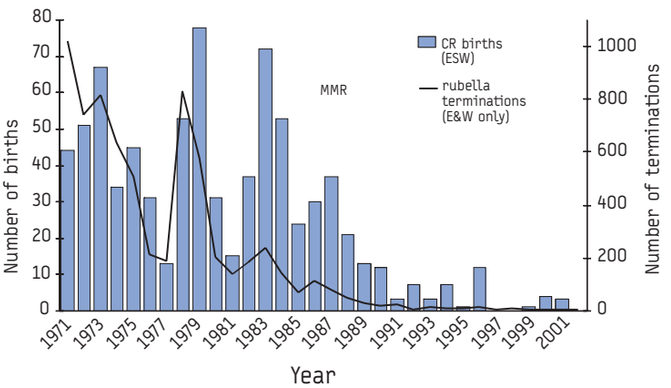
* Cover data from HPA and SCIEH [1]

Development and impact of vaccination strategy

Selective rubella immunisation for schoolgirls, health care workers, and susceptible adult women (mainly identified through antenatal testing) was first introduced in the United Kingdom (UK) in 1970. The National Congenital Rubella Surveillance Programme (NCRSP) was established in 1971 to monitor the effect of this strategy on CR incidence in England, Scotland and Wales [4]. As shown in figure 2, diagnosed reported cases of CR declined over the next 20 years from an average of about 50 a year (1971-75) to just over 20 a year (1986-90). Terminations of pregnancy carried out because of rubella disease or contact in pregnancy, monitored by the Office for National Statistics (ONS, previously OPCS), declined even more dramatically over the same time span, from an average of 750 a year to about 50 [5].

FIGURE 2

Congenital rubella births* and rubella associated terminations 1971-2002**



* National Congenital Rubella Surveillance Programme (NCRSP)
** Office for National Statistics (ONS)

In 1988, MMR vaccine was introduced for all children at the age of 12-15 months, with the aim of eliminating all three diseases. Uptake soon exceeded 90% by the age of 24 months, and rubella infection became rare, although there were small increases in notifications in 1993 and 1996, mainly affecting young men who had never been offered single rubella vaccine, and were too old to have been offered MMR [6]. In 1994, all schoolchildren were offered combined measles and rubella vaccine in a one-off attempt to avert a predicted measles epidemic and to reduce the number of rubella-susceptible young men who could facilitate transmission of rubella. After this, the schoolgirl programme was discontinued, and a second dose of MMR was introduced for all four year olds in 1996.

Since 1990, the number of CR births has declined further, with only 40 reported for the period 1991-2002 (FIGURE 2), along with about 60 rubella-associated terminations. Three notifications of infants born in 2003 are also under investigation. Almost all infants had typical CR signs at birth. It is possible that since the introduction of MMR, children with isolated sensorineural hearing loss due to CR have not been identified and reported, because by the time hearing loss is investigated, many children have already been vaccinated, and diagnosis is then less straightforward. Furthermore, since rubella is now so rare, health professionals might not consider CR as a possible diagnosis in infants with non-specific or atypical signs.

In recent years, mothers of babies diagnosed with CR have fallen into three roughly equal groups: those who acquired infection abroad in early pregnancy, most in Africa or Asia (imported infections); those who were born abroad but acquired infection in the UK, many within two years of arrival; and UK-born women, all but one of whom acquired their infection in the UK [7]. Among the UK-born women, five reported prior immunisation, although independent confirmation of this was only available for two women with confirmed reinfection in pregnancy; five had not been immunised, and the immunisation status of the others was unknown. Only one of the women born abroad reported having been previously immunised. Most of the 12 births reported in 1996 occurred in the late summer or autumn, and were associated with the outbreak of infection earlier in the year [4].

Current issues

The current low level of circulating infection depends on a high immunity level in the population as a whole. However, MMR uptake has declined over time, because of adverse publicity in the UK suggesting a link between MMR, autism and bowel disease [8] (FIGURE 2). Despite a consensus among most experts that no such link exists, and that the triple vaccine is the most effective way to control all three diseases [9-12], parental anxiety persists. MMR vaccine uptake was only 82% overall in England in 2002-3, with considerable local variation and some parts of London reporting uptake of less than 60% [13]. During 2003, English and Welsh uptake dipped below 80%, although Scottish uptake remains in excess of 85% [1]. Uptake of one dose of MMR by age five is currently about 90%, but it is unclear whether parents who decline the triple vaccine for their young children accept it when it is offered again pre-school. There are no data available for uptake of the single rubella vaccine among those rejecting MMR, and it is likely to be the least demanded of the three separate vaccines, since parents are generally more concerned about measles and mumps than about rubella. To further complicate the issue, single rubella vaccine is no longer available, and even susceptible women are now being offered MMR vaccine post partum [14].

Outbreaks of rubella infection abroad have the potential to cause outbreaks in the UK. This was demonstrated in early 1999 following the Greek outbreak, when infected Greek students attending British universities triggered a number of small UK outbreaks, including one in Aberdeen (Scotland). The only infant reported with congenital rubella in the UK in 1999 was born there, six months after this outbreak, to a woman who was subsequently diagnosed as having had rubella reinfection [15].

It has long been recognised that ethnic minority women have higher rubella susceptibility rates than white women in the UK, and this has led to their babies being disproportionately represented in congenital rubella births [16-18]. An analysis of rubella susceptibility rates in women in North London revealed high rates in some minority ethnic groups [3]. While less than 2% of British-born pregnant women were susceptible, between 4% and 8% of women originating from the Mediterranean region, Asia and Africa were susceptible. Within these groups women in their first pregnancy had particularly high susceptibility rates. The most vulnerable group identified were Sri Lankan women, 15% of whom were susceptible overall, including 23% of those in their first pregnancy. Where areas of low vaccine uptake are also those with a diverse ethnic mix, there is considerable potential for the importation and spread of rubella infection, with potentially disastrous consequences.

Antenatal rubella testing

A rubella immunity test is still routinely offered to pregnant women, usually at their first antenatal visit, and acceptance is high. This policy was recently reviewed by the National Screening Committee, which concluded that in view of the continuing inadequate uptake of MMR vaccine, and the presence of minority groups in the antenatal population with high levels of rubella, susceptibility screening should continue. In common with other programmes, this is subject to a three year review period [19]. The review group also recommended the following: better monitoring of the offer and uptake of a rubella-containing vaccine in the postpartum period; the development and implementation of strategies to protect susceptible women before they become pregnant, with particular emphasis placed on the needs of recent immigrants and asylum seekers and consideration of an offer of MMR vaccine to school leavers. Those caring for pregnant women should be aware that the rubella immunity test is not a diagnostic test, and cannot exclude the possibility of recent or current primary infection: guidelines are available for the management of rash illness or contact in pregnancy [20].

Surveillance methods

Surveillance of rubella in England, Scotland and Wales is carried out through a combination of methods providing data on uptake of vaccine, clinical and laboratory confirmed cases of rubella and congenital rubella, rubella susceptibility in population subgroups, and rubella-associated terminations [18]. Regional monitoring of the uptake of routine antenatal tests, including the rubella immunity test, is currently being developed. These data are reported mainly to the national communicable disease surveillance centres (the Health Protection Agency (HPA) and Scottish Centre for Infection and Environmental Health (SCIEH)), the Office of National Statistics (ONS), and the National Congenital Rubella Surveillance Programme (NCRSP) at the Institute of Child Health. A comprehensive review of the evolution of measles, mumps and rubella surveillance in England and Wales was recently published (2).

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STRENGTHENING EARLY WARNING FUNCTION OF SURVEILLANCE IN THE REPUBLIC OF SERBIA: LESSONS LEARNED AFTER A YEAR OF IMPLEMENTATION

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The Republic of Serbia, with WHO support, has implemented an early warning system (ALERT) for priority communicable diseases, to complement the routine surveillance system which notifies individual confirmed cases.

The results of its evaluation, conducted one year after implementation is presented here. ALERT relies on notification of 11 syndromes by primary care facilities. Data is analysed weekly at district level and transmitted to national epidemiologists. ALERT is perceived to be a simple and flexible tool. Acceptability is higher at national level than at district level. Some districts perceive ALERT as a parallel system poorly connected to control measures. Sensitivity of ALERT in detecting cases of meningitis is 93%, and 37% for cases of hepatitis. Retrospective analysis of ALERT data identified nine outbreaks, five of which had been recognized by epidemiologists. ALERT was the timeliest system for detecting four outbreaks identified by both systems. ALERT was useful for triggering timely investigation and control of outbreaks of hantavirus and salmonellosis and for detecting the start of the influenza season.

However, ALERT did not detect clusters of brucellosis and tularaemia targeted by the unexplained fever syndrome. This evaluation underlined the need for a global review of surveillance activities when implementing new components such as ALERT. While control measures based on notification of individual confirmed cases are well understood and implemented, the investigation and verification process that should result from an increase in ALERT syndromes is not fully understood.

Field epidemiology training programmes, such as the EPIET programme, are best suited to bring about this change of perspective.

Euro Surveill 2004;9:24-6
Key words : Serbia, WHO, surveillance, early warning, ALERT

Introduction

The timely detection of outbreaks at district, regional and national level is a priority function of communicable disease surveillance systems for countries. The World Health Organization (WHO) Headquarters Department of Communicable Diseases Surveillance and Response (CSR) is in the process of revising the International Health Regulations (IHR) to include the requirement for member states to maintain an adequate core capacity in detecting and responding to significant public health threats [1]. This requires that member states develop effective early warning systems (EWARS) and strengthen their investigation and response capacities.

Since December 2000, central and eastern Europe, and the Baltic countries (CCEE-Baltic) have worked together to strengthen surveillance and early warning and response systems [2-4]. In this context, some of the countries, like Albania [5], Serbia, and the Former Yugoslav Republic of Macedonia have developed or are developing EWARS with WHO support.

After describing the system, we present the results of the evaluation of the EWARS in Serbia, one year after its implementation, and discuss methodological issues to be considered when developing EWARS in eastern Europe.

Background

With a population of 8.7 million inhabitants, the Republic of Serbia, excluding Kosovo, is divided into 25 districts and 167 municipalities. Since the end of the war in 1999, the country has facing a period of instability and political crisis.

In 2001, the Serbian Republic Institute of Public Health (RIPH), in collaboration with WHO/Emergency and Humanitarian Action Office in Belgrade carried out an assessment of the routine surveillance system, which includes 70 diseases. The assessment underlined the absence of case definitions, a lack of laboratory confirmation, significant delays in reporting between surveillance levels, delayed and inadequate outbreak response, lack of feedback to reporting level, lack of training, lack of analysis at peripheral level, under-reporting of unconfirmed cases or outbreaks, and poor motivation of healthcare staff.

In 2002, following the assessment recommendations, the RIPH, with WHO support, developed a syndromic EWARS called ALERT, to strengthen early detection of outbreaks of epidemic prone and emerging infectious diseases.

TABLE

List of health events under surveillance in ALERT, Serbia, 2002-2003

Health events
Upper respiratory tract infection
Lower respiratory tract infection
Rash with fever
Meningo-encephalitis
Acute watery diarrhoea
Acute bloody diarrhoea
Acute gastro-intestinal disease without diarrhoea
Acute jaundice
Acute haemorrhagic fever
Fever of unknown origin
Other infections (*)

* *Other infections* category was added to allow an estimation of the burden of infectious diseases

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2. Nisaviski Institute of Public Health, Nis, Serbia
3. Republic Institute of Public Health, Belgrade, Serbia

A panel of Serbian experts defined the list of the 11 health events to be included in ALERT [TABLE]. The data sources are all primary healthcare facilities (PHCF). Syndromic case definitions are used to ensure that PHCF can make notifications, even in the absence of capacity for laboratory confirmation at their level.

Through a standardised surveillance form, PHCFs report weekly the aggregated number of new cases in four age groups to the corresponding Municipal Health House.

The Health house epidemiologist aggregates data and sends it by mail or fax to the district Institute of Public Health (IPH). Data are computerised at district IPH and transmitted electronically to the RIPH in Belgrade. Feedback is sent electronically from the RIPH to the IPHs. Districts prepare a report for the Health houses. In addition, some Health houses prepare feedback reports for primary care facilities.

A software has been developed using public domain software for relational data-entry (EpiData, http://www.epidata.dk) and production of interactive reports (Epi Info, http://www.cdc.gov). It includes features for data entry (with quality checks) at IPH level and electronic transfer of records to RIPH. It provides links with Excel and Word. The application produces a weekly epidemiological bulletin in Word and allows interactive browsing of tables, charts and maps in HTML format. The system generates alert reports based on disease specific thresholds (one case for haemorrhagic fever and relative increase compared to the three previous weeks for other syndromes).

In September 2003, ALERT was evaluated to document the implementation process and to identify its strengths and weaknesses, in order to adapt the system if necessary.

Methods for evaluation

The evaluation team included epidemiologists from RIPH, the Institute of Public Health of Nis, and WHO/CSR/Epidemiology Support team. The team analysed the ALERT database, revised ALERT documents and reports, conducted structured interviews with key informants at all surveillance levels (republic, district, municipal and health facility level) and held a one day evaluation workshop with all district epidemiologists. We evaluated attributes such as flexibility, acceptability, simplicity, sensitivity and usefulness as defined by the Centers for Disease Control and Prevention guidelines for evaluating public health surveillance systems [6].

To evaluate the sensitivity of the EWARS, we compared the number of cases of meningoencephalitis, jaundice and rash with fever reported through ALERT with the corresponding ICD10 coded cases reported in the routine system

To evaluate outbreak detection, we analysed the ALERT database and defined a potential outbreak as an increase in reported cases in the database compared to previous weeks. For each potential outbreak identified in our analysis we asked epidemiologists if they had noted and reacted to this increase.

Results of the evaluation

ALERT started in four pilot districts and expanded to the whole country over a six month period. All 25 districts and 156 municipalities (98%) are currently participating.

Acceptability, flexibility, simplicity

The system is considered simple and flexible. Interviewees underlined that ALERT has improved communication between all surveillance actors and strengthened the surveillance network.

Although the process for implementing the EWARS was piloted by the ministry of health, the EWARS reporting procedures were not incorporated in the public health laws and regulations for Serbia, which has hampered its acceptability. Some of the surveillance actors perceive ALERT as a parallel surveillance system with no connection with the routine system, thus resulting in a duplication of activities.

The acceptability is higher at republic level mainly because data from ALERT is received in a timely fashion and allows the surveillance department at RIPH to monitor potential outbreaks at republic level. Using syndromic case definitions allows remote areas that do not usually report, because of lack of confirmation capacity, to report, thereby providing valuable early warning information. Moreover, for some rare and serious diseases like those targeted by the haemorrhagic fever syndrome, ALERT is used as zero reporting.

Epidemiologists at municipal level are responsible for implementing control measures based on detection, laboratory confirmation and tracing of individual cases. ALERT aggregated syndromic data cannot trigger these control measures for cases and is therefore considered as not useful in some districts. Surveillance procedures for district epidemiologists are regulated by law and do not mention the necessity of conducting an investigation in the event of an increase in the notified syndromic cases.

Therefore, the lack of connection of ALERT with individual control measures and the absence of guidance on investigation and control measures resulting from an increase in cases reported through ALERT affects its acceptability.

As far as the software is concerned, epidemiologists evaluate positively the automated reports and underlined the importance of having standardised data at republic level.

Data entry is perceived to be simple and takes on average about one minute per week. Most district epidemiologists look only at the the automatically generated text-only epidemiological bulletin, however, and do not browse through the detailed tables, charts and maps.

Although the software for data entry, transmission and report generation is user friendly, all the epidemiologists reported that they would like more training so that they can use all the software options.

Sensitivity

The ratio of meningitis cases detected through ALERT over meningitis cases reported through the routine system was 0.93, suggesting a sensitivity of 93%. Fewer cases of meningitis are reported through ALERT because severely ill patients go directly to hospital emergency departments. For jaundice, we compared the cases of jaundice reported though ALERT to the total number of all hepatitis cases reported in the routine system (ratio = 0.37). General practitioners usually refer patients presenting with jaundice to infectious disease clinics without registering them in PHCF. On the other hand, cases of asymptomatic hepatitis detected through serological studies are also included in the routine system.

Nine potential outbreaks were identified in our analysis of the ALERT database.The epidemiologists only noticed and verified five. One of them (cases of haemorrhagic fever) was a false alert due to a reporting error. For the four outbreaks reflected in ALERT and in the routine system, ALERT was the most timely source of detection.

The routine system identified six additional outbreaks that were not detected by ALERT.

Usefulness

Three cases of haemorrhagic fever reported in the same week were investigated and confirmed as a cluster of hantavirus infection among women collecting fruit in a forest.

The increase in cases of acute respiratory infection meant that the start of the influenza season could be identified, and a public health response triggered (virological identification, dissemination of public health messages, and information to general practitioners).

An increase in cases of acute watery diarrhoea was confirmed to be salmonellosis in one district and control actions were launched as stated in the procedures recommended by the Serbian Commission of Infectious Diseases (e.g. environmental and contact sampling).

However, ALERT failed to detect clusters of brucellosis and tularaemia targeted by the 'unexplained fever' syndrome. Those clusters were detected by the routine surveillance system through hospital notification, weeks or months after their occurrence.

Besides its use for outbreak detection, ALERT has enabled IPHs and

RIPH to interact with the media in a timely fashion and to communicate with the Ministry of Health. It has improved feedback and communication at republic and district level, strengthening the surveillance network.

The introduction of ALERT has increased the awareness and visibility of surveillance activities in Serbia. A year after the introduction of the EWARS, all surveillance actors perceive the need for an in-depth revision of surveillance activities in Serbia.

Discussion

One year after its implementation, ALERT is operational in most of Serbia's districts. It has complemented the existing routine surveillance system with an early warning module, based on the weekly reporting of aggregated syndromes by the PHCF.

A total of 14 potential outbreaks have been detected retrospectively during the study period: four by epidemiologists through ALERT, four in our retrospective analysis of ALERT database, and six by the routine surveillance system.

We cannot make any conclusions about the sensitivity or the positive predictive value of ALERT because we could not verify whether the alerts detected retrospectively during the evaluation were true outbreaks. However, detection was more timely in ALERT for the outbreaks detected by both systems.

Syndromic surveillance is simple and often the only available surveillance tool at primary healthcare level, when laboratory confirmation of disease is not possible. It allows detection of potential outbreaks of targeted diseases earlier than with the diagnosis based routine surveillance system and leads to field investigations for confirmation and control.

The experience in Serbia has shown that PHCF are not the most appropriate source of notification for early detection of some epidemic prone diseases. Some specific syndromes may be seen first in emergency departments, private clinics, or pharmacies.

Syndromes such as haemorrhagic fever, as an indicator for hantavirus or Crimean-Congo haemorrhagic fever, are sensitive and specific enough to detect outbreaks. As it is a serious and uncommon syndrome, each individual case reported is an alert and triggers an action. For other diseases such as influenza, targeted by acute respiratory illness, the alert for action is a rise in the reported syndrome cases indicating the onset of the influenza season. ALERT was able to detect this increase during the 2003 season.

However, other categories of syndromes have not been sensitive or specific enough to detect outbreaks in a timely fashion. Those are syndromes targeting serious uncommon diseases but with a clinical presentation similar to common diseases that will be reported in the same category. This is the case with unexplained fever, which targets severe diseases such as brucellosis or typhoid fever but also includes other common non-severe diseases such as the prodromic phase of most viral diseases. A small number of these severe diseases may not yield a noticeable increase in cases because of their dilution in a greater number of less severe diseases.

Timely detection of public health threats relies on proper analysis of early warning data at each level. Surveillance data analysis is often restricted to tabulating data. Even though the ALERT software produces automated tables charts and maps highlighting increases, epidemiologists are not inclined to consult them since they are used to trigger actions when individual confirmed cases are reported. The routine surveillance and response system in Serbia is based primarily on control measures targeting patients and their immediate environment. Surveillance data are analysed at patient level and not at community level. Therefore, syndromic approach and aggregated data are not fully accepted since they do not correlate with the interventions defined by laws and regulations.

The routine surveillance system in Serbia, as in many countries from the CCEE-Baltic Network, is well designed to identify individual cases of infectious agents with potential spread resulting in case management and control measures around the case. It should, however, be complemented by an early warning system to detect changes in trends or clustering of cases potentially related to an outbreak to trigger community investigations. Both systems should be complementary. ALERT was not implemented as part of a global strategy for strengthening surveillance. This created a perception of duplication of systems and lack of integration.

The evaluation resulted in recommendations to increase the sensitivity and usefulness of ALERT in Serbia, such as adding emergency departments as notification sources for some syndromes, better defining the role of the laboratory to confirm the suspicion of outbreaks, revising the list and definition of syndromes to adjust their sensitivity and specificity for detecting the targeted diseases, strengthening data analysis through training.

However, the strengthening of the early warning function in Serbia should be included in a broader evaluation process covering all functions of surveillance. In particular, we recommend that a communicable disease risk assessment is conducted in order to revise the list of 70 diseases under surveillance, and set the priorities for communicable disease surveillance. This would allow defining the appropriate data sources (e.g. hospitals, PHCF, laboratories), the type of case definitions (e.g. syndromic versus disease specific), and the data to be collected (e.g. aggregated versus individual) for each disease.

Development of the early warning function of surveillance is a priority in many countries. Our experience shows that this priority can only be addressed through an integrated approach covering all the national surveillance functions.

In countries where epidemiological surveillance and response are focused on identification of individual patients (hygienic approach), bringing a community perspective (risk containment approach) implies a profound change of perspective for public health officers.

Our experience shows that the role of training should not be overlooked. It is a change of paradigm which is impossible to induce by simply implementing new surveillance tools, difficult to induce by short training, and best induced by coaching programmes such as field epidemiology training programmes. Epidemiologists from some of the eastern European countries have been trained in international courses such as the European Programme for Intervention Epidemiology Training (EPIET) [7], or the Epidemic Intelligence Service [8]. In addition, short field epidemiology courses have been conducted or are planned (e.g. Romania, Former Yugoslav Republic of Macedonia, Albania, and Poland). In November 2003, the WHO Regional Office for Europe organised a training of trainers workshop on intervention epidemiology with the participation of senior epidemiologists from 20 Baltic and central, southern and eastern European countries [9]. As in other regions of the world, national and regional field epidemiology training courses should be promoted in eastern Europe as a key element to strengthen epidemiology capacity at national and regional level.

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SENTINEL SURVEILLANCE OF HIV INFECTION IN HIV TEST CLINICS, SPAIN 1992-2002

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HIV infection in Spain was monitored in persons undergoing voluntary HIV testing in ten sentinel clinics between 1992 and 2002. Only patients on their first visit were considered for inclusion, and their numbers rose from 4426 in 1992 to 6649 in 2002. Most of them recognised their risk exposure as heterosexual. The proportion of injecting drug users decreased from 19% to 2% of the study population, and the proportion of female sex workers increased from 6% to 26%. The number of patients diagnosed with HIV infection declined from 604 in 1992 to 153 in 2002, and HIV prevalence fell from 13.6% to 2.3% in the same period. In all risk exposure categories, a decrease in HIV prevalence was observed, more pronounced during the first few years and stabilised in the later years. In 2002, the highest HIV prevalence was found in injecting drug users (IDUs) (14.2%), homo/bisexual men (7.5%) and individuals who had an HIV infected heterosexual partner (10.2%).

Euro Surveill 2004;9:27-9
Key words : Spain, HIV, sentinel surveillance, risk exposure

Introduction

In European countries, the epidemiological surveillance of HIV infection combines population based reporting systems and seroprevalence monitoring in specific population groups. The countries most affected by HIV infection have had difficulties in extending reporting systems within their respective territories. Epidemiological surveillance of HIV prevalence in specific groups provides useful information for the planning and evaluation of the preventive activities [1].

In Spain, HIV infection diagnosis is performed in a wide variety of healthcare centres, which has made it difficult to introduce an HIV reporting system to cover the general population. In the major cities there are HIV counselling and testing clinics that perform a large number of HIV tests and diagnoses. Because they are easy to access, these clinics have become the standard providers of this service for specific groups with HIV risk practices, which has consequently permitted very efficient monitoring of the evolution of the infection in these groups [2].

This paper presents HIV surveillance data based on voluntary tests performed in a network of sentinel clinics in Spain between 1992 and 2002.

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Methods

The present study is based on a sentinel network of ten sexually transmitted diseases and HIV testing clinics in the following cities: Seville, Granada, Malaga, Gijón, Tenerife, Madrid (two centres), Murcia, Cartagena and Vitoria. All of them offer voluntary, anonymous and free HIV testing, and have been operating without major changes during the period of this study. Epidemiological information was collected by healthcare workers before the HIV test was performed, using a brief questionnaire. Patients were grouped in exposure categories according to self-reported risk situations, and in the following priority order: injecting drug users (IDUs), homo/bisexual men, female sex workers, heterosexual men, other heterosexual women, and other risk exposure groups. Blood specimens were tested for HIV by the ELISA method, and reactive sera were confirmed by western blotting or immunofluorescence.

Only patients on their first visit to a particular clinic between 1992 and 2002 were included in this study.

Results

Time trends in the number and characteristics of persons having an HIV test

The total number of patients undergoing their first HIV test in these clinics increased from 4426 in 1992 to 6649 in 2002. The proportion of women rose from 37% to 51% ($p<0.001$) and the average age remained about 29 years. The mean age only increased in IDUs, rising from 26.8 to 32.3 years ($p<0.001$).

Throughout the entire period of this study, the majority of patients underwent an HIV test following heterosexual risk exposure. Between 1992 and 2002, the annual number of IDUs who underwent HIV testing dropped by 85%, the number of female sex workers tested increased by a factor of six, the number of heterosexual men tested almost doubled, and the number of homo/bisexual men remained more or less constant [TABLE].

Patients diagnosed with HIV infection

In 2000, despite the increase in the number of patients who took the test, the percentage of individuals diagnosed with HIV had fallen by 75%, and since then has remained relatively stable. Seventy eight percent of patients diagnosed with HIV were men, and their average age was 29 years; these figures did not vary noticeably with year of test.

The annual number of HIV infection diagnoses decreased in all categories mentioned except for female sex workers and heterosexual men. The greatest decrease was found in IDUs, who represented 53% of the HIV diagnoses in 1992 but only 12% in 2002 ($p<0.001$). The HIV infection diagnoses in homo/bisexual men decreased less spectacularly, and by 2002 they represented approximately one half of newly detected HIV infections.

Time trends in HIV prevalence

The HIV seroprevalence in the tested population decreased from 13.6% in 1992 to 2.3% in 2002 ($p<0.001$); however, in the final few

TABLE

Time trends of number of new voluntary testers, diagnoses and prevalence of HIV infection by exposure category. Spain, 1992-2002

Year	Injecting drug users			Homo/bisexual men			Female sex workers			Heterosexual men			Heterosexual women			TOTAL*		
	Testers No.	HIV+ No.	%	Testers No.	HIV+ No.	%	Testers No.	HIV+ No.	%	Testers No.	HIV+ No.	%	Testers No.	HIV+ No.	%	Testers No.	HIV+ No.	%
1992	830	319	38.4	1039	204	19.6	281	7	2.5	1073	25	2.3	999	40	4.0	4426	604	13.6
1993	608	201	33.1	1150	179	15.6	353	5	1.4	1268	21	1.7	1304	41	3.1	4991	456	9.1
1994	538	156	29.0	1106	123	11.1	385	5	1.3	1444	23	1.6	1325	36	2.7	5080	360	7.1
1995	365	102	27.9	1096	142	13.0	397	4	1.0	1387	20	1.4	1278	29	2.3	4859	304	6.3
1996	326	92	28.2	979	98	10.0	608	8	1.3	1584	28	1.8	1330	25	1.9	5084	257	5.1
1997	255	61	23.9	959	99	10.3	638	2	0.3	1745	19	1.1	1444	32	2.2	5301	215	4.1
1998	184	46	25.0	970	86	8.9	710	9	1.3	1800	28	1.6	1508	20	1.3	5454	193	3.5
1999	153	47	30.7	946	99	10.5	1037	9	0.9	1919	27	1.4	1497	18	1.2	5737	204	3.6
2000	91	21	23.1	992	82	8.3	1428	10	0.7	1774	19	1.1	1523	16	1.1	5995	150	2.5
2001	92	19	20.7	1102	83	7.5	1733	13	0.8	1977	19	1.0	1581	16	1.0	6706	152	2.3
2002	127	18	14.2	1022	77	7.5	1708	11	0.6	2083	29	1.4	1548	15	1.0	6649	153	2.3

* Including patients with other or unknown exposure category.

years of the study period, the figure became stable.

In IDUs, HIV seroprevalence descended from 38.4% to 14.2% (p<0.001) [FIGURE 1], but still remains the highest percentage of all considered risk categories. In the homo/bisexual men category, prevalence descended from 19.6% to 7.5% (p<0.001), this reduction was steeper during the first years. In female sex workers, HIV prevalence dropped from 8.4% in 1992 to 0.8% in 2002 (p<0.001). This decrease is primarily due to the reduction in the number of IDU female sex workers; as a matter of fact, they previously accounted for 15.4% of total female sex workers analysed in 1992, but they only represented 0.5% in 2002. However, a reduction in the HIV prevalence in non-IDU female sex workers was also observed from 2.5% to 0.6% (p=0.008) [FIGURE 2].

The HIV prevalence in the heterosexual category was initially higher in women (4.0%) than in men (2.3%), however the heterosexual women category had a greater prevalence decrease during the study period, which resulted in a lower prevalence than in men by 2002 [TABLE]. The seroprevalence in sexual partners of HIV infected persons remained about 10%; it is the only exposure category, which did not show a clear trend of reduction [FIGURE 1].

FIGURE 1

HIV prevalence among new female sex workers voluntarily tested by exposure categories. Spain, 1992-2002

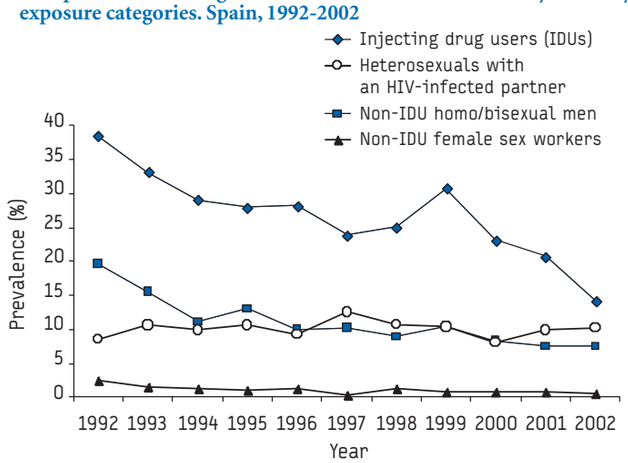
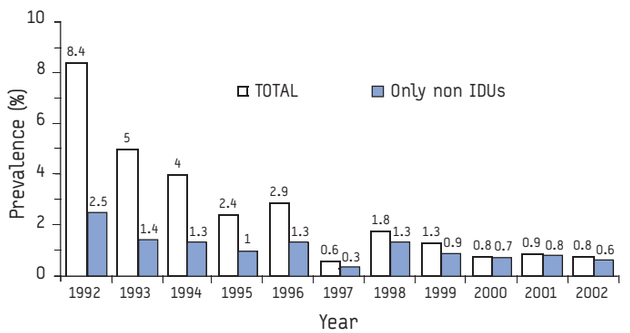


FIGURE 2

HIV seroprevalence among female sex workers who were new voluntarily tested. Spain 1992-2002



Discussion

These results draw a favourable time trend in HIV infection between 1992 and 2002 in all of the exposure categories used for analysis. The reductions in prevalences were, in general, more significant at the beginning of the 1990s, and have tended to become stable in the past few years. These trends contrast with the rise in risk behaviours and HIV transmission that have been reported in some studies following the introduction of combination antiretroviral therapies [3,4].

One of the most important findings of this study is the decrease in the proportion of IDUs in new testers; this is due to changes in drug administration routes and to the decreased tendency for young people in Spain to become IDUs [5]. The progressively smaller number of IDUs, which is associated with the highest prevalences, contributes to reduce the overall prevalence of HIV infection in this population of clinic attendees.

We did not have information on the patients' nationality, although other studies centred on female sex workers in Spain have shown that there has been a change in their nationality composition, with a pronounced increase of patients who were not born in Spain, and a lower proportion of IDUs [6]. Nevertheless, the increase in the number of tested female sex workers may in part be due to improvements in the clinics' ability to attract members from this category.

Homo/bisexual men represent a large and stable component of these clinics' users. Their HIV prevalence decreased during the first years of the study, but subsequently stabilised at rates that can still be considered high, indicating the persistence of high risk behaviour in sexual relations between men [7].

These results, collected in nine cities, are a good reference for the situation and evolution of HIV infection in high risk populations in Spain. This information is of great practical value for the planning and evaluation of preventive actions for these groups. The epidemiological characteristics of HIV-diagnosed patients in these clinics probably do not coincide with the general epidemic pattern in Spain, on account of the over-representation of homosexual men and female sex workers. The HIV prevalences of voluntary testers may be biased; nevertheless,

due to the way in which this bias was maintained throughout the study period, the changes in prevalence that have been detected probably indicate true changes in HIV infection in the respective population groups. The characteristics and working methods of these clinics were constant throughout the study period, allowing valid comparisons to be made. Only patients who attended for the first time have been considered in this study. This prevents multiple inclusion of any individual and may improve sensitivity for the detection of recent changes in HIV transmission, as well as helping comparison across different years. The problem of interpreting prevalence in those undergoing repeated HIV tests are made more difficult due to progressive ageing, and the effects of preventive counselling. Of course for those undergoing a first HIV test, we cannot exclude the possibility that some patients had previously been diagnosed elsewhere.

HIV seroprevalence monitoring using voluntary testers complements other surveillance systems and provides interesting information for preventive programmes [1,2]. To interpret the results, however, it is important to monitor the changes in the number of testers.

Acknowledgements

This work was partly funded by FIPSE (Foundation formed by the Spanish Ministry of Health and Consumer Affairs, Abbott Laboratories, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme, and Roche, exp. 3076/99 and 36303/02) and by the Spanish Red de Investigación en Sida - RIS (Network for Research on AIDS) and the Spanish Red de Centros de Investigación Cooperativa en Epidemiología y Salud Pública - RCESP (Network for cooperative research in Epidemiology and Public Health).

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ORIGINAL ARTICLES

Surveillance report

INTERRUPTION OF MEASLES TRANSMISSION IN GIPUZKOA (BASQUE COUNTRY), SPAIN

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Measles vaccine was introduced in Gipuzkoa (Basque Country, Spain) in 1978 and was replaced by the measles, mumps, and rubella (MMR) vaccine for children aged 12-15 months in 1981. A second dose of the MMR vaccine was introduced in 1992. Both doses of the MMR vaccine were well accepted by the population and high coverage was achieved (95% and 91% for the first and second doses respectively for the period 1993-2002). Measles virus circulation was interrupted in the second half of the 1990s: no cases of indigenous measles were notified between 1998 and 2003, and only imported cases have been confirmed during this period. These data indicate that the measles vaccination programme implemented has been effective. Nevertheless, to avoid measles outbreaks following viral introduction, high MMR vaccine coverage levels for the two doses have to be maintained (>95%).

Euro Surveill 2004;9:29-31
Key words : Measles, Spain, Basque Country, MMR vaccine

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Introduction

The World Health Organization (WHO) has made the interruption of indigenous measles transmission by 2010 a target for its European Region [1]. However, the epidemiology of this infection in European countries currently shows considerable differences, mainly due to different immunisation strategies and targets, their time of implementation, their degree of acceptance in the population, and therefore the levels of immunisation coverage achieved [2]. In Spain, measles vaccination (Schwartz strain) was included in the vaccination

calendar in 1978, producing a marked decrease of the incidence of measles infection. The present study describes changing patterns of measles in Gipuzkoa since 1984, a region in which no indigenous cases of measles have been notified for the past six years (1998-2003).

Methods

Gipuzkoa is one of the three regions of the Basque Autonomous Community (northern Spain), with 676 208 inhabitants. Measles vaccination of children aged 9 months was introduced in 1978 and was replaced by the measles, mumps, and rubella (MMR) vaccine in children aged 12-15 months in 1981. In the Basque Autonomous Community, a second dose of this vaccine was introduced for children aged 11 years in the 1991-92 academic year. In 2000, the age of administration of the second dose was brought forward to 4 years and a vaccination catch-up campaign was carried out for children aged 5-11 years.

The vaccine coverage achieved was calculated by considering the number of children and adolescents vaccinated in the public health services, where each vaccination is documented, and the total number of subjects to undergo vaccination, obtained from the corresponding population census (Euskal Estatistika Erakundea (Basque Statistics Office)). We did not consider the doses of the MMR vaccine delivered through the private sector, as these represent <1% of all doses administered in the region. The annual incidence of measles was obtained from the mandatory notification system (weekly notifications of suspected cases of measles by paediatricians and general practitioners). The definition of a suspected case of measles was: generalised rash lasting longer than 3 days, fever higher than 38.3°C and cough, coryza or conjunctivitis. We considered as confirmed cases those which had a positive IgM against measles (laboratory confirmed cases) and those suspected cases epidemiologically linked to a laboratory confirmed case.

Since 1986, serological investigation of measles cases in Gipuzkoa has been performed by the microbiology laboratory of the Hospital Donostia in San Sebastián. IgM against measles was requested to confirm suspected cases of measles and also for other patients for whom a physician considered it convenient to exclude a measles virus infection, that is, encephalitis, other exanthemal diseases, etc. Detection of IgM antibodies to measles was performed with an enzyme-linked immunosorbent assay (Dade Behring, Germany) on previously treated sera to eliminate rheumatoid factors.

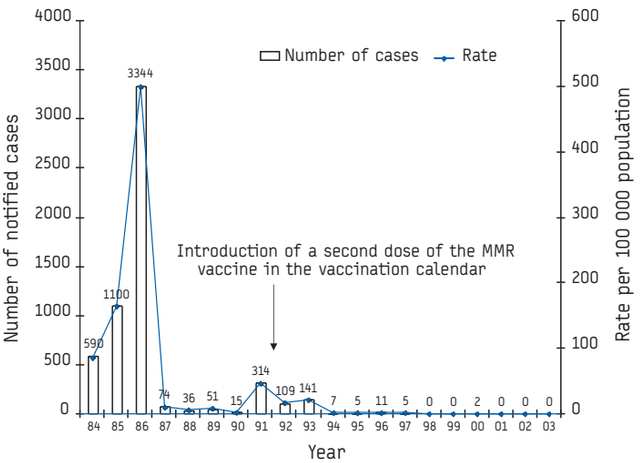
Results

The first dose of the MMR vaccine presented a vaccine coverage of >90% from 1987, with the exception of 1992 (87%); the mean annual coverage was 95.1% for 1993-2002. The vaccine coverage of the second dose of the MMR vaccine was >88% from 1993, with the exception of 2000, when it was 83.4%, rising to 93.0% in 2002 (a mean annual coverage of 90.6% for 1993-2002). The coverage obtained in the vaccination catch-up campaign was 92.4%. About 98% of children received the first dose of the MMR vaccine in their second year of life showing a good compliance with the immunisation schedule.

The number of notified measles cases decreased considerably after an epidemic with an incidence of 480.1 cases per 100 000 inhabitants in 1986 [FIGURE]. Incidence rates oscillated between 10.2 and 2.2 cases per 100 000 inhabitants between 1987 and 1990. Between 1991 and 1993 measles outbreaks occurred in several regions of Gipuzkoa (an incidence of 45.6 cases per 100 000 inhabitants in 1991). Since 1994, the number of notified cases has been very low: two cases were notified in the period 1998-2003, both of which occurred in 2000. The first case was a 31 year old man from Gipuzkoa who had spent the incubation period in London (laboratory confirmed case) and the second case was the result of transmission from this man to his sister (epidemiologically confirmed case). Neither of these two individuals had been vaccinated. A third imported case was detected in 2000 and serologically confirmed. This case was not notified because it occurred in a 12 year old Irish boy who was in Spain temporarily.

FIGURE

Number of notified cases of measles and incidence rates per 100 000. Gipuzkoa, Spain, 1984-2003



Source: weekly notifications by paediatricians and general practitioners

Since 1987, samples from 1218 patients were processed for serological investigation of measles, detecting specific IgM in 174 patients [TABLE]. The proportion of cases aged more than 10 years rose from 4.3% for the 1986-1989 period (1/23 cases of known age) to 45.7% for the 1990-1993 period (48/105 of known age).

TABLE

Number of cases in which detection of IgM against measles was requested in Gipuzkoa and number of IgM positive cases between 1986 and 2003

Period	1986-89	1990-93	1994-97	1998-2003
Investigated cases	60	430	366	362
IgM Positive (%)	27 (45.0)	139 (32.3)	6 (1.6)	2* (0.6)

* Cases imported from the United Kingdom and Ireland respectively (see Results section).

Discussion

Both epidemiological (notifications) and microbiological data (serologically confirmed cases) indicate that measles virus circulation was interrupted in Gipuzkoa in the second half of the 1990s; no cases of autochthonous measles have been notified in the past six years, and only imported cases were confirmed during this period. These data indicate that the measles vaccination programme implemented has been effective. The introduction of a single dose MMR vaccine was well accepted by the population and high vaccine coverage was achieved from 1987. This, and the fact that measles was highly endemic in the years immediately before implementation of the programme, produced a considerable reduction in the incidence of the disease, which was below 11 cases per 100 000 inhabitants between 1987 and 1990. However, important outbreaks of measles in 1991 prompted the decision that same year to introduce a second dose to interrupt measles virus circulation. In 1995 and 1997 the incidence was already lower than 1 case per 100 000 inhabitants, and the important outbreak of rubella in Gipuzkoa in 1996 [3] was probably the cause of the slight increase in measles notifications observed that year. In countries approaching the interruption of indigenous measles transmission, cases of rubella are not infrequently mistaken for measles [1]. A few years after the introduction of the second dose, which also achieved high coverage, circulation of indigenous measles virus was interrupted and no autochthonous cases were notified in 1998-2003.

Despite of these favourable results, the administration of the second dose of the MMR vaccine must be strengthened to achieve the very high levels of coverage recommended by the WHO in each of the two doses (>95%), and to avoid the accumulation of susceptible people and the threat of future outbreaks [1].

The changes produced in Gipuzkoa are probably representative of the progress toward measles control obtained in Spain in the last two decades. In Spain, each autonomous community has the power to decide its vaccination policy. Overall, the trend in Spain is towards a reduction: the incidence of measles since 1999 has been <1 case per 100 000 inhabitants and in 2002 only 64 cases were confirmed by laboratory analysis or epidemiological link [4]. In Catalonia, interruption of indigenous measles transmission was confirmed between June 1999 and July 2000 [5]. Indeed, the prevalence of immunity to measles in the Spanish population in 1996 was encouraging, with the percentage of immune individuals in almost all age groups above the levels recommended by the WHO for interruption of viral transmission; only the 1977-81 cohort, composed of individuals born prior to or at the time when vaccination was being introduced, failed to reach these levels [6]. Nevertheless, measles outbreaks still occur in Spain [4], indicating that there are still groups within the Spanish population whose level of immunity allows viral circulation.

Decreases in vaccine coverage have also been observed throughout these years in Gipuzkoa, when changes in the vaccination strategy were implemented (1992 and 2000). Measles is one of the most infectious diseases known to man, and consequently decreases in vaccine coverage should be detected and corrected as soon as possible. Reintroductions are frequent in Spain [4,5], a finding confirmed in the present study. It is therefore essential that surveillance systems be kept active and that all physicians suspecting a case of measles contact the relevant health authorities as soon as possible for laboratory confirmation [1].

The results obtained in the present study confirm that the two dose MMR vaccine strategy introduced in our region has been effective. This strategy, which has achieved high coverage, can interrupt indigenous viral circulation within a few years. Nevertheless, given that measles virus is highly contagious and continues to be endemic in many regions throughout the world, it is essential to maintain high vaccine coverage in the two doses of the MMR vaccine (>95%) so that the percentage of susceptible individuals in the population remains very low.

Acknowledgements

We thank Rosa Sancho for her helpful data on vaccination coverage.

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ORIGINAL ARTICLES

Euroroundup

CURRENT SITUATION OF HUMAN DIPHYLLOBOTHRIASIS IN EUROPE

J Dupouy-Camet[1], R Peduzzi[2]

Diphyllobothriasis, a parasitosis caused by the flatworm *Diphyllobothrium latum*, is contracted by consuming raw or undercooked freshwater fish. The aim of this study was to evaluate the situation of this parasitosis during the past 20 years in Europe through the analysis of databases and search engines (Medline, CABI Helminthological abstracts,Yahoo, Google), and through a questionnaire sent to a network of European parasitologists and to microbiological laboratories located on the shores of the large Alpine lakes. This study has shown that several dozen cases have been reported each year in Finland and Sweden, that there have been numerous cases in the French or Italian speaking areas of subalpine lakes, and that sporadic cases only have been observed in Austria, Spain, Greece, Romania, Poland and Norway. Over 30 cases have been identified on the Swiss shores of Lake Maggiore since 1990, and 70 cases on the Swiss and French shores of Lake Léman between 1993 and 2002. Eight to 12% of perch fillets from Lake Leman and 7.8 % of perch from Lake Maggiore were infested with larvae. Contamination sources include marinated fish fillets in northern Europe, 'carpaccio di persico' in northern Italy, and perch and charr consumed raw or undercooked around Lake Léman. Factors allowing the continuation of the parasitic cycle include the continued dumping of wastewater into lakes, yachtsmen who also fish, and a possible animal reservoir.

Euro Surveill 2004;9:31-5

Key words : Diphyllobothriasis, parasitosis, lake fish, Europe

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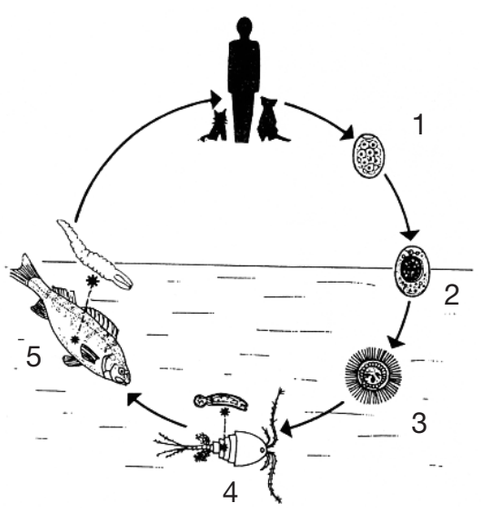
Introduction

Diphyllobothriasis is an intestinal parasitosis caused by the ingestion of mostly raw freshwater fish containing infectious larvae of the *Diphyllobothrium latum (D. latum)* cestode worm. The cycle of this

parasite is complex and involves several hosts [1,2]. Released in water, the eggs mature within eight to 12 days at a water temperature of 16-20°C, and yield a procercoid larva that is ingested by a zooplanktonic copepod crustacean [FIGURE 1]. About 40 copepod species of the Eudiaptomus or Cyclops genus are likely to be the first intermediate hosts. This larva develops into a procercoid larva within the general cavity of the copepod. When carnivore fish ingest planktonic crustaceans, the larva develops into a plerocercoid larva a few millimetres long. It migrates into the fish musculature or viscera where it can remain inactive for several years, but can re-encyst several times in other predatory fish. In Europe, the types of fish susceptible to host the larvae are perch (Perca fluviatilis), pike (Esox lucius), charr (Salvelinus alpinus), and burbot (Lota lota). The Coregonidae (feras) and probably the Salmonidae of Salmo genus (except for the Canadian Salmonidae of the genus Onchorynchus) do not host *D. latum* larvae (TABLE 1). Man and other ichtyophagous mammals become contaminated by ingesting this undercooked fish. The plerocercoid larva can grow between 5 and 20 cm a day [2], and develops into an adult that yields its first eggs about one month after infestation. *D. latum* is the longest human parasite known (about 10 metres long) and can live for several years. Its symptomatology, although limited, is polymorphous: manifestations may include abdominal discomfort (abdominal pain, diarrhoea), weight loss, asthenia, and vertigo. Anaemia due to vitamin B-12 deficiency has been described in case of prolonged infestation [1]. Human experimental infestations have been practised [4]. Three volunteers, infected by two to three plerocercoid larvae, did not present any obvious clinical symptoms except for the release of proglottis. The two non-treated subjects dewormed spontaneously seven months (in the first case), and four years and six months (in the second case) after being infected. The parasite is sensitive to praziquantel (15 mg/ kg/ day in one dose) and to niclosamide (2 g on an empty stomach in two doses an hour apart). In 1999, the world prevalence of diphyllobothriasis was estimated at 9 million cases [3], despite the difficulty of making precise evaluations because of the existence of other species either morphologically close or undistinguishable, such as *D. pacificum* in Peru, and D. nihonkaiense in Asia [4]. The earliest description of diphyllobothriasis prevalence in western Europe goes back to Von Bonsdorff's monograph of 1977 [1]. The objective of our study is to report the current situation of diphyllobothriasis in western European countries.

FIGURE 1

***Diphyllobothrium latum* Cycle**



1: egg, 2: embryonated egg, 3: coracidium, 4: procercoid larva in a copepod, 5: plerocercoid larva in fish

TABLE 1

Name of fish species in some European languages

Latin name	French	English	German	Italian
Perca fluviatilis	perche	perch	Egli/Barsch	persico
Esox lucius	brochet	pike	Hecht	luccio
Lota lota	lotte	burbot	Trüsche	bottatrice
Coregonus fera	féra	big whitefish	Felchen	coregone
Salvelinus alpinus	omble chevalier	charr	Seesaibling	salmerino alpino
Salmo trutta lacustris	truite de lac	lake trout	Seeforelle	trota di lago
Onchorynchus mykiss	truite arc en ciel	rainbow trout	Regenbogenforelle	trota iridea

Material and methods

The analysis was carried out with data from literature published since 1980 using the following databases : Medline, CABI Helminthological abstract, INIST Pascal, and the Yahoo and Google internet search engines. Information was collected for each of the 25 countries of the European Union (with the exception of Malta and Cyprus), and some adjacent European countries (Switzerland, Hungary, Croatia and Yugoslavia). In March 2003, we also contacted or sent a questionnaire to a network of European parasitologists (specialising mainly in food safety), to microbiological laboratories (those located near lakes and identified through professional directories) in Savoie, Isère, and Haute-Savoie (France), and Switzerland, and to university hospital parasitology laboratories in Besançon, Lyons and Grenoble. The questionnaire concerned the number of human cases observed in the course of the past 20 years as well as possible veterinary data (fish and mammal), either personal or published data.

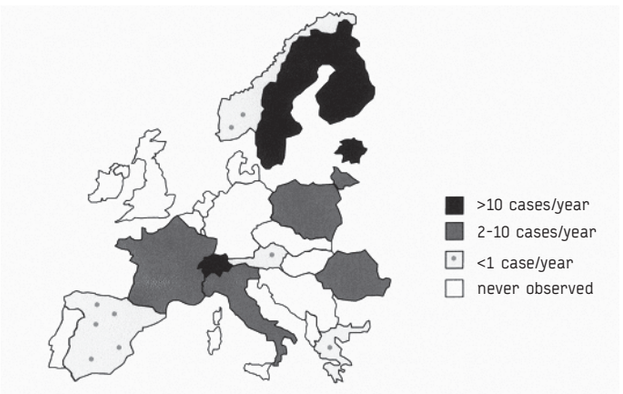
Results

Information was obtained from a network of parasitologists, and from databases from 23 European countries. For France and Switzerland, data was completed by the network of laboratories that were contacted. There are three types of epidemiological situation in Europe: areas where parasitosis is frequent or relatively frequent, areas where sporadic or imported cases have been observed, and areas where no parasitosis was reported [FIGURE 2]. Specific surveillance of diphyllobothriasis exists only in Estonia, Lithuania, and Poland. In Finland, at least 20 cases are reported each year [S Meri, personal communication]. A study carried out between 1978-1989 by hospital practitioners showed that prevalence varied between 0.3 and 3.8% of patients [5]. In Sweden, 10 to 50 cases are observed each year [D Christensson, personal communication]. In Estonia, 440 cases were reported in 1997, compared with 715 cases in 1990 [6]. Cases are numerous in French and Italian speaking areas surrounding the Swiss, Italo-Swiss, and Franco-Swiss Alpine lakes. In 1990, one of the authors reported 18 cases on the Swiss shores of Lake Maggiore [7], bringing the total to 33 cases over the last 20 years [8]. Golay and Mariaux retrospectively identified seventy three cases around Lakes Léman, Bienne, and Morat between 1980 and 1994 [9]. Alpine lakes in northern Italy are subject to frequent contamination: in 1987, Magatelli [10] described eight cases on Lake Iseo [10], and in 2000, Terramocci et al [11] reported six cases on Lake Como [11]. Several further cases were reported on Lakes Como and Iseo in 2003 [A Raglio, E Pozio, personal communication]. On the French shores of Lake Léman, Gregory et al [12] diagnosed two cases in St Julien en Genevois and, in 2001, the authors published 22 cases diagnosed between 1993-2000 following a survey carried out in 50 laboratories located in Haute-Savoie [13]. Lake Léman seems to be particularly affected, with 48 cases identified on its shores in 2001 and 2002. The parasitosis is absent in Lake du Bourget, and the last case observed was in a professional fisherman six years ago [C Bernot, personal communication], Lake d'Annecy, Lake d'Aiguebelette and Lake de Paladru. Rare studies published on the

prevalence of fish infection [7,9,14] have concerned only the Swiss and Italian Alpine lakes (TABLE 2), and showed a sometimes high infestation of pikes and perch. In other European countries, parasitosis is reported less frequently. In Romania, the historical foci of the Danube delta were subject to massive treatment campaigns, although cases continue to be reported [CM Cretu, personal communication]. A few cases are reported each year in Poland [15] and in Lithuania [V Jasulaitene, personal communication]. Five cases were observed in Vienna between 1991 and 2003 [H Aspock and H Auer, personal communication, [6]]. Two cases were reported in Spain, one caused by imported salmon from an unknown country [17,18]. Three cases were reported in Greece [19]. Cases have also been reported infrequently in Slovakia [20] and in Norway [L Robertson, personal communication]. An imported case was reported in the Czech Republic [21]. In addition to the foci of Lake Léman, at least six imported cases have been described in France since 1980 (A Cazin, ME Bougnoux, M Deniau, H Pelloux, P Marty, and C Tourte-Schaefer, personal communication). To our knowledge, no autochthonous human case was reported in Denmark, Croatia, Belgium, the United Kingdom, the Netherlands, Yugoslavia, Macedonia, Hungary or Germany.

FIGURE 2

Distribution of human diphyllobothriasis in Europe (since 1980)



Discussion

The methodology used in this study, without being exhaustive, is original and could be used as a basis for further studies to evaluate evolution trends. Human diphyllobothriasis is still present in western Europe, but when compared with previous studies [1,5,6], can be seen to be decreasing in Baltic and Scandinavian countries. It seems to be either emerging or better diagnosed in the French and Italian speaking areas around Alpine lakes, as shown by the more than 200 cases that have been reported or published around Lake Léman, Lake de Morat, Lake de Bienne, Lake Maggiore, Lake Como, Lake Iseo, and Lake Gardia since 1987. German speaking areas around Alpine lakes did not seem to be affected: Golay and Mariaux [7] identified only rare cases in the cantons of Freiburg and Bern compared with around 30 cases in the cantons of Geneva and Vaud. In 1963 [22], human diphyllobothriasis was rare around Lake Léman: no cases had been reported for five years at the Lausanne Institute of Hygiene (Institut d'hygiène de Lausanne), four cases reported in nine years at the Lausanne Badoux, Bauer and Rochat Laboratory, one case in four years at the Geneva University Polyclinic (Polyclinique Universitaire de Genève).

Diphyllobothriasis is associated with ancestral eating habits: consumption of raw salted or marinated fish fillets in Baltic or Scandinavian countries, 'carpaccio di persico' in northern Italy, 'carpaccio d'omble chevalier' and 'poissons du lac façon nordique' in French-speaking areas. Faddish and extreme food choices such as

TABLE 2

Recent data (since 1980) available on human cases and fish infestation in sub-alpine lakes from Italy, Switzerland and France

Lake	Country	Presence of human cases	Prevalence in fish [ref]	Fish species
Lake Gardia	Italy	+	No data	
Lake Iseo	Italy	+	No data	
Lake Como	Italie	+	No data	
Lake Maggiore	Italy Switzerland	+	7.8 % [8]	*Perca fluviatilis*
Lake Lugano	Italy Switzerland	0	0 [8]	*Perca fluviatilis*
Lake Varese	Italy	?	0 [8]	*Perca fluviatilis*
Lake Orta	Italy	?	33.3 % [8]	*Perca fluviatilis*
Lake Morat	Switzerland	+	12.5% [9] 5.2 % [9]	*Esox lucius*, *Perca fluviatilis*
Lake Neuchatel	Switzerland	0	0 [9] 0 [9] 0 [9]	*Esox lucius*, *Perca fluviatilis* *Lotta lotta*
Lake Bienne	Switzerland	+	14.2 % [9] 3.7 % [9] 0 [9]	*Esox lucius*, *Perca fluviatilis* *Lotta lotta*
Lake Léman	Switzerland France	+	8-12 % *	*Perca fluviatilis*
Lake Annecy	France	0	No data	
Lake Bourget	France	+ **	No data	

* Analysis of 50 fillets in November 2003 and February 2004, Dupouy-Camet J unpublished data

** One case at the end of the 1990s

"instinctotherapy" (a type of raw food diet) and the increasing popularity of sushi could also be contributory factors. The prevalence of fish infestation in the Alpine lakes is between 3.7% and 33% (TABLE 2).

The continuation of the diphyllobothriasis cycle is an indicator of the faecal pollution of lakeside environment. The complex cycle is compensated by the prolificness of the parasite: one worm alone can yield between one and several million eggs a day that can infest zooplanktonic crustaceans, the first intermediary host. No data was found on zooplanktonic species involved in the transmission or on their level of infestation. Building waste water treatment plants contributes to fighting the parasitosis [6] but there are other unrelated habitats. For instance, around Lake Léman, 89% to 98.6% (according to sources) of the inhabitants of the drainage basin are connected to 159 wastewater treatment plants [23,24]. These treatment plants purify only between 95% and 99% of eggs. The eggs not caught are viable, and the treatment plants may overflow during storms [1,2].

There is professional and leisure fishing on and around lakes. There are about 150 professional fishermen and 5000 fishermen on Lake Léman, who caught around 1000 tons of fish in 1999, of which 47% was perch and 6.5% was charr [25]. The fish is consumed directly by fishermen, or sold to fishmongers or to the many restaurants located on the shores of the lakes, which sometimes offer dishes made with raw fish. Veterinary data on fish infestation in Lake Léman is scarce and very old: 58% of perch and 95% of burbot were carriers of plerocercoid larvae in 1909 versus 12.5% of burbot in 1963 [22]. In 2003-2004, we found plerocercoid larvae in 8% to 12% of perch fillets analysed and the precise identification of the larvae was carried out with molecular biology techniques (polymerase chain reaction and sequencing). Faecal pollution of lakes by the many yachts that sail there can also be considered in the continuation of the cycle although regulations require that faecal matter is disposed of in appropriate sanitary facilities [26]. There is also the issue of faecal pollution of shores by fishermen or by wild or domesticated carnivores that are numerous on those shores. Cases of infestation of dogs have been reported in the Geneva area [B Gottstein, personal communication]. In 1963, around Lake Léman, Bouvier et al [22] found only two infected dogs out of the 259 one they had examined. No infestation was found in 179 cats and 31 foxes examined, but the incidence of

parasitosis in man was low at that time. Some cases of fox infestation have recently been reported in the Tessin, Grisons and Geneva areas [Deplazes, personal communication]. A wild cycle would be ensured by trouts and foxes [D Gerdeaux and M Morand, personal communication]; the latter consuming dead genitors on spawning grounds. Elsewhere, diphyllobothriasis was found in 0.5% of foxes captured in Karlsruhe in Germany [27] and in 0.2% of dogs captured in Finland [28]. However, it seems that the parasite does not develop very well in those carnivores who, unlike man, may only play a minor role in the continuation of the cycle [1,2].

Our study has also shown the relative frequency of imported cases (contracted during travel abroad or after consumption of imported fish) that could in certain cases help to maintain the parasite, or to reintroduce it in areas it had previously disappeared from. This survey is certainly limited since we can not pretend to have made an exhaustive collection of cases. In fact, some laboratories from German speaking Switzerland did not respond to the invitation to participate in the survey. Moreover, many cases are likely to be treated by general practitioners either for diphyllobothriasis or for Taenia saginata taeniasis considering the relative similarity of the proglottis of both species. An in-depth study of eight clinical cases has shown that severe clinical symptoms can lead to specialised consultations and expensive complementary analyses, resulting in an average cost of 400 for the management of a single diphyllobothriasis case [13]. Finally, comparing the incidence of different countries is difficult since it would be necessary to know the size of the exposed populations to calculate the risk. For example, in France and Italy, exposed populations are limited to the shores of the lakes, whereas in Finland, the entire population is at risk of exposure. Consumption studies could be carried out in each of the countries to learn about eating habits and therefore evaluate a possible risk behaviour.

Conclusion

Diphyllobothriasis is decreasing in Baltic and Scandinavian countries, but is emerging in French and Italian speaking Alpine areas. The fashion for carpaccio, sushi and recipes based on raw fish, as well as the proliferation of restaurants serving these kinds of dishes, will certainly not slow down this emergence. Work towards ending the disposal of waste water in lakes has been done, but the imperfect efficiency of waste water treatment plants, and the many yachtsmen who also fish explain the continuation of the parasitic cycle. It is therefore necessary to inform consumers of the risks linked to the consumption of raw or undercooked fish as well as prophylactic methods. Cooking fish at a temperature of 55°C kills the plerocercoid larvae in five minutes, and freezing it at -10°C kills the larvae within 8 to 72 hours, depending on the thickness of the fish [29]. Smoking fish does not kill the parasite [30]. Changing food habits is illusory especially when such habits are ancestral as shown by the discovery of diphyllobothriasis eggs in the archaeological sediments of neolithic lakeside villages of these areas [31]. Finally, it would be interesting to monitor the infestation in man and in fish with regular prevalence surveys to study the evolutive nature of diphyllobothriasis.

Acknowledgements

We wish to thank the numerous French medical analysis laboratories of Haute-Savoie, Savoie and Isère, and the Riotton Bioanalytical Laboratory (Geneva), for their collaboration. We also thank those in France for their help in this survey: Alain Gregory (Saint Julien en Genevois), Catherine Bernot (Aix les Bains), Daniel Gerdeaux (Station d'Hydrobiologie lacustre, INRA, Thonon les Bains), Michel Morand (LDA 39, Lons le Saunier), Hervé Pelloux (CHU Grenoble), François Peyron (CHU Lyon), Renaud Piarroux (CHU Besançon), Laurent Desvois and Claire Dupouy-Camet. finally, we thank the informal network of European parasitologists who participated in this survey: Seppo Meri (Finland), Pavol Dubinski (Slovakia), Christian Kapel (Denmark), Dan Christensson (Sweden), Bretislav Koudela and Tolarova Vira (Czech Republic), Dragutin Golubic (Croatia), Antonio Martinez-Fernandez, Guillermo Esteban, Antonio Clavel and Santiago Mas-Coma (Spain), Georgios Theodoropoulos (Greece), Bruno Gottstein, Peter Deplazes, Madeleine Van-Saanen and Floriane de Marval (Switzerland), Lucy Robertson (Norway), Stanny Geerts (Belgium), Peter Chiodini (UK), Zbigniew Pawlowski (Poland), Nino Ioli, Massimo Scaglia, Eduardo Pozio and Annibale Raglio (Italy), Joke van der Giessen (The Netherlands), Carmen Micaela Cretu (Romania), Karsten Noeckler (Germany), Viktorija Jasulaitene (Lithuania), Horst Aspock and Herbert Auer (Austria), Liliana Sofronic (Yougoslavia), Tibor Kassai (Hungary). This work was made possible thanks to a grant from ADERMEPT (Association pour le Développement Et la Recherche en Médecine Parasitaire et Tropicale).

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ORIGINAL ARTICLES

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PROPOSED RECOMMENDATIONS FOR THE MANAGEMENT OF HIV POST-EXPOSURE PROPHYLAXIS AFTER SEXUAL, INJECTING DRUG OR OTHER EXPOSURES IN EUROPE

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Post-exposure prophylaxis (PEP) is the standard of care for a healthcare worker (HCW) accidentally exposed to an HIV infected source person (occupational exposure), but this is not the case for non-occupational exposures. Very few national guidelines exist for the management of non-occupational exposures to HIV in Europe, contrarily to the occupational ones. The administration of non-occupational post-exposure prophylaxis (NONOPEP) for HIV may be justified by: a biological plausibility, the effectiveness of PEP in animal studies and occupational exposures in humans, efficacy in the prevention of mother to child HIV transmission, and cost effectiveness studies. These evidences, the similar risk of HIV transmission for certain non-occupational exposures to occupational ones, and the conflicting information about attitudes and practices among physicians on NONOPEP led to the proposal of these European recommendations.

Participant members of the European project on HIV NONOPEP, funded by the European Commission, and acknowledged as experts in bloodborne pathogen transmission and prevention, met from December 2000 to December 2002 at three formal meetings and a two day workshop for a literature review on risk exposure assessment and the development of the European recommendations for the management of HIV NONOPEP.

NONOPEP is recommended in unprotected receptive anal sex and needle or syringe exchange when the source person is known as HIV positive or from a population group with high HIV prevalence. Any combination of drugs available for HIV infected patients can be used as PEP and the simplest and least toxic regimens are to be preferred.

PEP should be given within 72 hours from the time of exposure, starting as early as possible and lasting four weeks. All patients should receive medical evaluation including HIV antibody tests, drug toxicity monitoring and counseling periodically for at least 6 months after the exposure.

NONOPEP seems to be a both feasible and frequent clinical practice in Europe. Recommendations for its management have been achieved by consensus, but some remain controversial, and they should be updated periodically. NONOPEP should never be considered as a primary prevention strategy and the final decision for prescription must be made on the basis of the patient-physician relationship. Finally, a surveillance system for these cases will be useful to monitor NONOPEP practices in Europe.

Euro Surveill 2004;9:35-40

Key words : Europe, HIV, Post exposure prophylaxis, non occupational exposure, recommendations

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Introduction

Post-exposure prophylaxis (PEP) is now the standard of care when a healthcare worker (HCW) is accidentally exposed to a source person known to be infected with HIV (occupational exposure), but this is not the case for non-occupational exposures.

We considered as non-occupational exposure all accidental and sporadic incidents in which contact with blood or other body fluids (semen, vaginal secretions, etc.) that pose a potential risk for HIV infection occurred, excluding exposures of HCWs in a healthcare or laboratory setting. Non-occupational exposure includes unprotected sexual exposure, sexual exposure involving a broken or slipped condom, injecting drug users (IDUs) sharing equipment, accidental needlestick injuries, bite wounds, mucosal exposure, etc. Exposure to tears or sweat is not considered to be a risk for HIV transmission.

Although there have been no prospective controlled trials or retrospective case-control studies to support its potential efficacy, non-occupational post-exposure prophylaxis (NONOPEP) is used increasingly frequently. Faced with a request for NONOPEP for HIV, physicians must deal with several questions such as the magnitude of the risk of the exposure or whether or not to prescribe antiretroviral therapy (ART). NONOPEP demand is not negligible in Europe [1-3], nor is it in other parts of the world [4-8]. Several questions regarding the prescription of NONOPEP remain unanswered, however, including which combination of antiretrovirals to choose, the duration of the follow up, and which laboratory tests are necessary.

Curiously, guidelines for the management of occupational HIV exposures exist in the United States and in most European countries; yet very few national guidelines for the management of possible sexual, injecting drug use, or other non-occupational exposures to HIV have been developed in Europe [9].

Background

Several factors justify the administration of NONOPEP:

1- The biological plausibility of NONOPEP for preventing HIV infection.
2- Scientific literature on the effectiveness of the ART used for post-exposure prophylaxis in animals and occupational exposures in humans.
3- Efficacy studies on the prevention of mother to child HIV transmission.
4- Studies on cost effectiveness and cost benefit of HIV post-exposure prophylaxis.

1. One of the characteristics regarding the pathogenesis of HIV infection is the period of time between the HIV exposure and the replication of the virus in the lymph nodes [10]. Immediately after HIV exposure, there is an infection of dendritic cells at the site of the inoculation. These infected cells will migrate to the regional lymph nodes during the first 24-48 hours [11]. The beginning of HIV systemic infection is marked by the settlement of the infected dendritic cells in the lymph nodes. In theory, administering ART as a prophylaxis during this period and before the lymph node settlement could prevent the establishment of a systemic infection.

2. The results of different animal studies have shown plausibility in preventing HIV infection, by administering ART after an exposure to HIV [12]. In 1995, the results of a study showing the prevention of SIV infection in macaques were published. Administering an antiretroviral compound (PMPA (tenofovir)) 24 hours after virus inoculation, for four weeks, prevented SIV infection in all of the macaques. Protection was incomplete if tenofovir was administered at 48 or 72 hours after the exposure, or if the duration of treatment was 3 or 10 days only. This suggests that the earlier ART is given, the more effective the prevention [13]. In 2000, Otten et al published data from a study in which macaques received an atraumatic intravaginal inoculum of HIV-2. One group of macaques did not receive ART, the second group received tenofovir 12 hours after the exposure, the third at 36 hours, and the fourth at 72 hours. In the first group, all but one of the macaques became infected. None of the macaques from the second and third group became infected, and one in three macaques in the fourth group became infected after 16 weeks. These data confirm that the time elapse between the exposure and the beginning of ART is an important factor which can affect NONOPEP efficacy, and support the need for an adequate follow up period after NONOPEP to monitor for delayed seroconversions [14].

In a retrospective case-control study, AZT given after an occupational percutaneous exposure to a HCW was associated with an 81% decrease in the risk of HIV infection. Another issue raised by this study was the increase in the risk of acquiring HIV when some enhancing factor existed, such as the depth or extent of the injury, the presence of visible blood on the device, or an advanced stage of HIV disease in the source person [15].

3. Data from human studies regarding the prevention of mother to child HIV transmission also support the probability of the efficacy of an HIV post-exposure prophylaxis. In a randomised trial, the administration of AZT to HIV infected pregnant women was associated with a 2/3rd reduction in HIV infections in babies whose mothers had been given AZT pre and intra partum (and who themselves had received AZT post partum) versus those randomised to placebo [16]. Despite contact between the child's blood and the HIV status of its mother, AZT prevented infection in the majority of cases.

4. In 1997, an article was published describing the cost effectiveness of tritherapy with zidovudine, lamivudine and indinavir following moderate to high risk occupational exposure [17]. Another cost effectiveness study on post-exposure prophylaxis following potential sexual HIV exposure in humans concluded that in the following cases PEP is cost effective: receptive anal sex when it is almost certain that the source person is infected, and receptive vaginal sex only when the source person is know to be HIV positive [18]. Assuming that it is not only cost effectiveness that can predominate in a public health decision, further studies are necessary.

The above mentioned studies encouraged us to propose and standardise this prophylaxis for non-occupational exposure, despite some difficulties, including the extrapolation of animal study data to humans, the specificity of the mother to child transmission, the difference between occupational and non occupational exposures, the difficulty of the risk assessment in non occupational exposure, the reports of PEP failures to prevent HIV infection after occupational exposure in at least 21 instances with different ART [19-23].

Another argument for introducing NONOPEP guidelines is the results of a French study in which the existence of NONOPEP recommendations at national level had an impact on physicians' behaviour, improving their acceptance of and attitude towards NONOPEP [24] and probably on their risk assessment. Furthermore, a survey about knowledge of, attitudes towards and practices of NONOPEP for HIV has been conducted among European physicians, as part of the same project that led to the present recommendations [25]. The results clearly showed that in the countries with national guidelines there were significantly more prescriptions made following requests for NONOPEP (76% versus 61%, $p=0.007$), as well as more antiretroviral emergency starter kits available (92% versus 44%, $p<0.001$). Similarly, the exposure risk assessment and the management of NONOPEP requests improved among this group of physicians in comparison with the group without national guidelines.

Finally, the probability of HIV transmission by certain non-occupational exposures is estimated to be higher than the risk of percutaneous occupational exposure. Furthermore, the characteristics of both situations – occupational and non-occupational - are different. In the case of occupational exposures, it is possible to start ART earlier, the HIV status of the source is usually known, and the follow up of the exposed person is more feasible. In the case of a non-occupational exposure, however, the time delay between exposure and ART initiation is frequently longer, the possibility of knowing the HIV status of the source person is lower, and the rate of lost-to-follow-up is higher, hence the need for specific guidelines for these non-occupational exposure situations.

Methods

In September 2001, the European Commission (Directorate-General for Health and Consumer Protection, (DG-SANCO)) funded a project

on non-occupational post-exposure prophylaxis to HIV (Euro-NONOPEP Project - project number 2000CVG4-022), coordinated by the Centre d'Estudis Epidemiològics sobre la Sida de Catalunya (Center for Epidemiological Studies on HIV/AIDS of Catalonia, CEESCAT), with the participation of 14 European countries. One of the main objectives of this project was the development of the European recommendations regarding the management of HIV NONOPEP. In this perspective, the national representatives from each participant country were contacted and integrated into the project, on the basis that they were responsible for the national registry or multicentre group, or had been designated by national healthcare agencies. The representatives of participating member countries were acknowledged to be experts in the field of bloodborne pathogen transmission prevention and PEP.

A steering committee was established to take responsibility for the logistic and scientific aspects of the project, with participation of members from five of the participating countries (Spain, France, the United Kingdom, Italy and Belgium). Concerning the development of the European recommendations, the steering committee members reviewed previous recommendations, risk assessment, possible prophylaxis regimens and their cost effectiveness, and shared and updated information at three meetings, in December 2000, June 2001 and December 2002. For this review, data from the published literature and abstracts from recent scientific conferences were taken into consideration.

Reviewed data were presented and discussed by representatives of all participant countries in the project during the first of a two day workshop on 19-20 October 2001. The national representatives were divided into two working groups, one to achieve consensus on the risk assessment of non-occupational post-exposure prophylaxis, and the other to achieve consensus on the treatment and clinical follow up protocols for non-occupational post-exposure prophylaxis. The results are presented in this paper.

Results and discussion

Literature review on risk exposure assessment.-

Table 1 shows the different risk estimates of HIV transmission by non-occupational exposures, according to a literature review. It is important to remember that these estimates of transmission are not absolute. Every risk exposure depends on the type of exposure, but also on cofactors such as follows: a) infectivity of the source, taken as a high plasma viral load, increases the risk of transmission in all cases [37]; b) genito-oral ulcers, sexually transmitted infections or bleeding increase the risk of transmission for a sexual exposure [34], and c) for accidental needlestick exposures, fresh blood, a deep injury or intravenous injection all increase the risk of HIV transmission [15].

The figures of risk for the first type of accidental exposure in table 1 refer to accidental needlestick injuries in healthcare workers or healthcare setting, and can not be directly applied to accidents with abandoned needles.

Some of the reviewed articles in the literature about estimates on transmission risk of insertive vaginal and anal sex come from North America, where a high proportion of men are circumcised. Therefore the risk for uncircumcised men may be underestimated.

When the HIV status of the source person is unknown, the risk assessment is usually based on the type of exposure, on the estimated HIV prevalence in the source HIV group and/or the HIV prevalence in the source person's country of origin.

Recommendations

In general, physicians facing a request for non-occupational post-exposure prophylaxis to HIV should take the following steps:

1- Evaluate of HIV status and risk behaviour history of reported source of HIV exposure (person belonging to a high risk group for HIV or coming from a country with high HIV prevalence) and, if possible, test the source person for HIV antibodies.

2- Evaluate the risk for HIV transmission regarding the type of exposure, as well as the presence of factors that would increase the risk (e.g., use or non-use of a condom, details of the exposure as receptive or insertive intercourse, anal or vaginal intercourse, presence of visible genital ulcers for a sexual exposure; number of persons sharing equipment for IDU; and depth of injury for any other needlestick exposure).

3- Determine the time elapsed between the exposure and the presentation for medical care before deciding to prescribe an antiretroviral therapy. PEP should be given within 72 hours from the time of exposure.

4- All patients should receive medical evaluation including testing for HIV antibodies at baseline and periodically for at least 6 months after the exposure, as well as testing for other bloodborne pathogens such as HBV and HCV, and for sexually transmitted infections (STIs) if indicated.

5- In the case of prescribing ART, treatment must start as early as possible. Drug toxicity monitoring should include a complete blood count, renal and hepatic chemical function tests at baseline, and again at least 6 weeks after the exposure.

6- For women sexually exposed to HIV, a pregnancy test must be undertaken, and the result taken into account before any prescription. Consult obstetricians or other experts in the care of HIV infection during pregnancy. Similarly, for children, consult specialist paediatrician in the care of HIV infection.

7- The exposed individual should be counselled to prevent additional exposure, and to improve ART adherence in the case of prescription.

8- NONOPEP should never be considered as a primary prevention strategy.

The indications of NONOPEP for sexual, IDU, needlestick and other exposures are shown in boxes 1 to 4 respectively, according to the criteria expressed by the consensus group. It should be stated that at-risk sexual exposures are 'unprotected intercourse', either without condom or with broken or slipped condom.

The drug selection was based on the antiretroviral drugs approved by the United States Food and Drug Administration [38], and the belief that a combination of drugs with activity at different stages in the viral replication cycle have proved to be superior to monotherapy regimens, and a three drug regimen (tritherapy) superior to bitherapy.

Guidelines for the treatment of HIV infection recommend the use of three drugs [39]. It is supposed that a three drug therapy will also be the most effective in the case of NONOPEP, when there is a real risk of HIV transmission. Any complete treatment has to take four weeks duration.

TABLE 1

Summary of HIV transmission risk by type of non-occupational exposure

Type of exposure (from a source known to be HIV positive)	Risk of HIV transmission per exposure	Ref.
Accidental needlestick injury	0.2%-0.4%	[15]
Mucosal membrane exposure	0.1%	[26]
Receptive oral sex	From 0 to 0.04%	[27,28]
Insertive vaginal sex	≤ 0.1%	[29-32]
Insertive anal sex	≤ 0.1%	[29-32]
Receptive vaginal sex	0.01%-0.15 %	[29,31,33,34]
Receptive anal sex	≤ 3%	[28,32,34]
IDUs sharing needle	0.7%	[35]
Transfusion	90-100%	[36]

Looking at the treatment combination, tritherapy (treatment with a combination of three drugs belonging to two different classes) is recommended; bitherapy (treatment with two nucleoside reverse transcriptase inhibitors (NRTI)) may also be an option. In general, any combination of drugs available for HIV infected patients can be used as PEP and the simplest and least toxic regimens are to be preferred.

When the source person has unknown HIV status, or is HIV positive but not treated, or HIV positive with an efficient first line therapy, the NONOPEP treatment recommended for the patient as first line treatment is 2 NRTI (a) + 1 protease inhibitor (PI) (b) or efavirenz, being the NRTI combinations zidovudine + lamivudine; or stavudine + lamivudine; and the PI, nelfinavir; or indinavir; or lopinavir/ritonavir combination.

Several remarks were made with respect to the NONOPEP:

- When there are several possibilities for the same active principle, the simplest pharmaceutical form must be used.
- Dual PI treatment is less appropriate.
- Indinavir and nelfinavir are frequently associated with side effects and intolerance.
- Do not use abacavir or nevirapine in a four week regimen, because of potential severe adverse events [40,41]. Only a single initial dose should be used, if necessary.

For a second line of prophylaxis, two possibilities arise: if the source person is HIV positive and has been treated by ART with any failure of treatment in his/her history (actual or previous), the NONOPEP must be adapted to the drug history and/or to resistance testing if

Box 1

Indications of NONOPEP for sexual exposures

1. HIV source person known as HIV positive

• Receptive anal sex	PEP is Recommended
• Insertive anal sex	PEP is Considered
• Receptive vaginal sex	PEP is Considered
• Insertive vaginal sex	PEP is Considered
• Receptive oral sex with ejaculation	PEP is Considered
• Splash of sperm into eye	PEP is Considered
• Receptive oral sex without ejaculation	PEP is Discouraged
• Female to female sex	PEP is Discouraged

In the case of rape or the existence of any **high risk factors** (for both, source person or exposed individual): high viral load of the source partner, menstruations, other bleeding during intercourse, genital ulcer, STI.

• Insertive anal sex	PEP is Recommended
• Insertive vaginal sex	PEP is Recommended
• Receptive vaginal sex	PEP is Recommended
• Receptive Oral sex with ejaculation	PEP is Recommended
• Female to female vaginal-oral sex	PEP is Considered

2. Unknown HIV status of the source person

A - The source person is from a group or from an area of **high** HIV prevalence (at least 15%).

• Receptive anal sex	PEP is Recommended
• Receptive vaginal sex	PEP is Considered
• Insertive anal sex	PEP is Considered
• Insertive vaginal sex	PEP is Considered
• Receptive oral sex with ejaculation	PEP is Considered
• Other situations	PEP is Discouraged

In the case of rape or the existence of any **high risk factors** (for both: source person or exposed individual): menstruations, other bleeding during intercourse, genital ulcer, STD.

• Insertive anal sex	PEP is Recommended
• Insertive vaginal sex	PEP is Recommended
• Receptive vaginal sex	PEP is Recommended
• Receptive oral sex with ejaculation	PEP is Recommended

B - The source person does **not** belong to a group with high risk activities or is from an area of **low** HIV prevalence.

• Receptive anal sex	PEP is Considered
• All other situations	PEP is Discouraged

In the case of rape or the existence of any **high risk factors** (for source person or exposed individual): menstruations, other bleeding during intercourse, genital ulcer, STD.

• Receptive anal sex	PEP is Considered
• Receptive vaginal sex	PEP is Considered
• Insertive anal sex	PEP is Considered
• Insertive vaginal sex	PEP is Considered
• Receptive oral sex with ejaculation	PEP is Considered
• All other situations	PEP is Discouraged

* Such as cookers to melt the drug, cotton used as filter, or water to rinse the syringe

Box 2

Indications of NONOPEP for IDU exposures

1. Source person known to be HIV positive

• Needle or syringe exchange	PEP is Recommended
• Any equipment* sharing within IDU group	PEP is Considered

2. Source person HIV status is unknown

• Needle or syringe exchange	PEP is Discouraged
• Any equipment* sharing within IDU group	PEP is Discouraged

In case of the prevalence of HIV infection in concerned IDU population >15%

• Needle, syringe or any equipment* exchange	PEP is Considered

* Such as cookers to melt the drug, cotton used as filter, or water to rinse the syringe

Box 3

Indications of NONOPEP for other needle exposures

• Needlestick from abandoned needle	PEP is Discouraged
• Aggression with a needle	PEP is Discouraged

If extreme factors exist: needle of someone known to be HIV positive, or in 'high risk area' (prevalence of HIV infection in the IDU population concerned >15%), injection of blood or deep injury, fresh blood in syringe, etc.

• Aggression with a needle	PEP is Considered
• Needlestick from abandoned needle with visible fresh blood	PEP is Considered

Box 4

Indications of NONOPEP for other exposures: non-intact skin, mucosal, bite, etc.

• Source person is HIV positive, or is from a group or from an area with **high** HIV prevalence (at least 20%)	PEP is Considered
• HIV source person status unknown, or is **not** from a group or from an area with **high** HIV prevalence	PEP is Discouraged

available, and abacavir may be an option in this case. However, if the source person is HIV positive and has been treated by ART without treatment failure, and has an undetectable viral load, the same ART as that of the source person can be used.

TABLE 2

Patient follow-up schedule

Laboratory tests recommended	Baseline	Week 2	Weeks 4-6	Months 3 and 6
HIV antibody tests	Yes		Yes	Yes
Haematological tests	Yes	Yes	Yes	
Creatininaemia, Transaminases, Glycaemia, Amylasaemia	Yes	Yes	Yes	
Pregnancy test (if patient is female)	Yes			
Medical visit (counselling, compliance assessment, adverse events, clinical seroconversion)	Yes	Yes	Yes	Yes

Table 2 shows the patient follow up schedule established by consensus, but some remarks were made with respect to follow up:

- The assessment of other STIs (syphilis, gonorrhoea, chlamydia infection) and hepatitis B and C infections must always be considered.
- Viral load or p24 antigen tests in exposed person are not recommended, except in case of suspected primary HIV infection (fourth generation antibody/antigen tests are an option).
- If possible, deliver drugs for no longer than a 2 week period, to maximize likelihood of patient follow up.
- In case of ART prescribed, written informed consent is recommended.
- For pregnant women, efavirenz and amprenavir are contraindicated [39,42]. In any case, decisions should be made on a case by case basis and we recommend consulting an experienced specialist.

Conclusion

According to the consensus process presented, the risk assessment and prescription of antiretroviral post-exposure prophylaxis can be made and prescribed in specific non-occupational situations of risk for HIV transmission that seem to be frequent in clinical practice.

Most of the points and agreements expressed in these recommendations have been achieved by consensus, on the basis of indirect evidence, and some remain controversial; the maximum time elapsed from exposure to prescription may be reduced to 36 hours; the prevalence limit for unknown HIV status of source person may vary; biotherapy regimens should be considered more frequently, follow up schedule may be varied or shortened, etc. For this reason, the working group thinks that these recommendations should be reviewed and updated periodically according to new knowledge and evidence, if any.

Standardised recommendations have proved useful for improving counselling and care to HIV exposed individuals. However, every country is free to adapt these recommendations to its own HIV infection epidemiological situation, and its own NONOPEP policies, especially regarding the indications named as 'PEP is considered'. In fact several national recommendations for NONOPEP issued by ministries of health in Greece, Italy, Portugal and Spain were promoted following these European recommendations, adding to other previous and updated ones (Austria, France, Germany, Luxembourg, Sweden).

In any case, the final decision for NONOPEP prescription must be made on the basis of the patient-physician relationship, bearing in mind that NONOPEP should never be considered as a primary prevention strategy.

Finally, although it will be difficult to assess the NONOPEP effectiveness, a surveillance system for these cases will be useful to describe and to monitor NONOPEP practices in Europe.

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ORIGINAL ARTICLES

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TOWARDS A STANDARD HIV POST EXPOSURE PROPHYLAXIS FOR HEALTHCARE WORKERS IN EUROPE

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Antiretroviral prophylaxis (PEP) after occupational exposure to HIV in healthcare workers (HCWs) is used across Europe, but not in a consistent manner. A panel of experts, funded by the European Commission, formulated a set of recommendations.
When it has been decided that the characteristics of the exposure indicate the initiation of PEP, PEP should be started as soon as possible; initiation is discouraged after 72 hours. PEP should be initiated routinely with any triple combination of antiretrovirals approved for the treatment of HIV-infected patients; a two class regimen is to be preferred. The source patient's treatment history should be sought. Counselling, psychological support, HIV testing and clinical evaluation should be performed at baseline, at 6-8 weeks, and at least six months post exposure. Additional clinical and laboratory monitoring at one and two weeks should be considered, as adherence with and tolerance of the regimen can highlight adverse reactions and potential toxicity. Routine HIV resistance tests in the source patient, and direct virus assays in the exposed HCW are not recommended.

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Euro Surveill 2004;9:40-3
Key words : Europe, HIV, Post exposure prophylaxis, non occupational exposure, recommendations

Introduction

In September 2001, the European Commission funded a project for a standardised management of healthcare worker (HCW) occupational exposures to HIV and other bloodborne infections in European countries, including antiretroviral post-exposure prophylaxis (PEP). The main objective of the project was to develop a set of common recommendations, based on a review of the literature and of national management strategies.

Nine European countries participated in the project: Croatia, Denmark, France, Germany, Portugal, Spain, Switzerland, the United Kingdom, and Italy (as coordinating centre).

The recommendations that follow were discussed during 2002 with representatives of participating countries, and approved. The final consensus document therefore represents the opinion of experts in the field of bloodborne pathogens transmission prevention and PEP. Scientific evidences appearing in the literature after the consensus meeting were included in this document.

The complete rationale and a full list of references used to support the present recommendations can be consulted at http://europa.eu.-int/comm/health/ph_projects/2000/com_diseases/comdiseases_project_2000_sum_en.htm.

Recommendations

All preventive efforts should be made to reduce the risk of occupational exposures (i.e. development of educational programs, implementation of standard precautions and safer procedures, provision of safety devices and personal protective equipment).

All HCWs should be made aware of how to report an exposure. The availability of PEP should be publicly advertised so that it is immediately and readily accessible 24 hours/day and initiated as soon as possible following an occupational exposure.

WHEN TO OFFER OCCUPATIONAL PEP?

The application of PEP should be evaluated following an occupational exposure with the potential for HIV transmission, based on the route of exposure, the materials involved, and the evaluation of the source patient (TABLE).

TABLE

Recommendations for post-exposure prophylaxis against HIV infection in healthcare workers

1. According to exposure	
- Percutaneous injury	Recommended
- Exposure of mucous membrane or non intact skin	Considered
- Exposure of intact skin	Discouraged
2. According to material	
- Blood, body materials containing visible blood, cerebrospinal fluid, concentrated virus in a research laboratory or production facility	Recommended
- Semen; vaginal secretions; synovial, pleural, peritoneal, pericardial, or amniotic fluid, and tissues	Considered
- Urine, vomit, saliva, faeces, tears, sweat, sputum	Discouraged
3. According to source patient	
- Known to be HIV infected	Recommended
- Serostatus unknown, consent refusal, not available	Considered
- HIV seronegative	Discouraged

Efforts should be made to assure 'immediate' results in order to prevent unnecessary initiation of PEP. Rapid HIV-antibody testing could be useful for the diagnosis of HIV infection in the source patient, facilitating the prompt beginning of PEP in the exposed HCW and limiting unnecessary treatment [1-3].

The possibility of 'serologic window' of infection in the source patient should be considered on individual case assessment.

TIMING OF STARTING PEP AND DURATION

PEP should be initiated as soon as possible following an occupational exposure and administered for 4 weeks [4-6].

PEP should be discouraged more than 72 hours after exposure [7, 8].

CHOICE OF REGIMEN

- Any combination of antiretrovirals approved for the treatment of HIV-infected patients can be used in PEP regimens at the recommended dose.
- Triple combination, two class regimen is recommended as first line PEP.
- Nevirapine (NVP) is not indicated for a full course of PEP because of the reported severe hepatotoxicity [9].
- Dual Nucleoside Reverse Transcriptase Inhibitor (NRTI) combination therapy could be considered an option on a case by case evaluation (i.e. pregnancy).

Available clinical information about stage of infection, CD4+ T cell count, viral load testing, current and previous antiretroviral therapy, and results of any previously available genotypic or phenotypic viral resistance testing should be collected for consideration in choosing the most appropriate PEP regimen [10]. If this information is not immediately available, initiation of PEP, if indicated, should not be delayed; changes in the PEP regimen can be made after PEP has been started, as appropriate.

Ad hoc genotypic and/or phenotypic resistance tests are not recommended [11].

Check for any existing medical conditions and any medications that an exposed HCW may be taking, in order to prevent toxicity and drug interactions.

A simplified regimen should be used whenever possible to increase adherence by reducing number of pills and frequency of dosing.

If reported constitutional adverse reactions can be controlled through the administration of symptomatic drugs, this could enhance adherence to the prescribed regimen with the ultimate goal of achieving treatment completion in the exposed HCW.

PEP IN PREGNANCY

Pregnancy per se should not preclude the use of HIV PEP. However, the decision to use any antiretroviral drug during pregnancy should involve discussion with the exposed HCW regarding the potential benefits and risks to her and her baby, to help her to make an informed decision about the use of PEP.

Women should be asked about the possibility of pregnancy. If pregnancy cannot be excluded, a pregnancy test should be performed.

- The use of efavirenz should be avoided in pregnant women.
- The need for a combination of d4T and ddI should be carefully evaluated.
- Because of the observed association with hyperbilirubinaemia, indinavir should not be administered shortly before delivery.

FOLLOW UP SCHEDULE

All HCWs occupationally exposed to HIV should receive appropriate counselling and clinical follow up regardless of whether or not they have received PEP. A first HIV test should be performed within a few days after exposure.

Psychological support should be offered at any time during follow up [12].

HCWs should be strongly encouraged to report signs and symptoms promptly, and should be counselled in order to prevent secondary transmission during the follow up period.

Follow up visits and HIV testing are recommended at 6-8 weeks and three months post exposure [3]. The routine use of direct virus assay (HIV p24 antigen or tests for HIV-RNA) to detect infection in exposed HCW is not recommended [13].

Adherence to PEP and tolerance must be monitored. Complete blood cell count, ALT, AST, creatinine, glucose, amylase blood levels and urine test at baseline and at 15 days can be performed on a case by case basis, and according to the toxicity profiles of the drugs included in the PEP regimen.

The HCW should be tested for HIV at least once more, 6 months post exposure. Testing the HCW at one year post exposure should be considered in cases when the source patient is coinfected with HIV and HCV [14].

Conclusions

About 100 documented and 200 possible cases of HIV infection in HCWs have been reported worldwide [15]. The risk of transmission has been estimated on average to be 0.3% after a percutaneous exposure to HIV infected blood, and 0.09% after a mucous membrane exposure; the risk can be higher following an exposure to a large volume of blood or to a high titre of HIV [14].

A convergence of indirect evidence suggests that PEP administered soon after occupational exposure to HIV in HCWs decreases the risk of infection. Most information derives from animal experiments [4-6] and studies on vertical transmission of HIV infection [7,8]; additional data derives from studies in exposed persons.

Although recommendations on the use of PEP have been issued in a number of European and non-European countries [14,16], differences exist and several issues remain controversial. The present document aims to harmonise the recommendations at the European level, and must be considered as being dynamic: recommendations may change in the future with further research and scientific information. Updated information on available combinations of antiretrovirals, and on their pattern of resistance, interactions and toxicity profiles, including their use in pregnancy, are available at http://www.aidsinfo.nih.gov-/guidelines/default_db2.asp?id.

Currently, the main issues on the agenda are represented by the increasing prevalence of HIV strains resistant to antiretroviral drugs and PEP toxicity concerns. Both these issues relate to the choice of an appropriate regimen.

Indeed, recent studies have demonstrated the emergence of HIV mutations associated with resistance to antiretroviral agents from source patients involved in occupational exposure [10,11]. Moreover, the more recent cases of PEP failure reported in the literature occurred after exposure to source patients harbouring resistant HIV strains. [17,18].

In fact, the ideal regimen for PEP is not fully defined. When it has been decided that the characteristics of the exposure indicate the initiation of PEP, clinicians should choose the drug combination only after careful assessment of source patient's characteristics, including treatment history. When available, data from genotyping or phenotyping resistance tests should be considered. However, because of the time needed to perform drug resistance tests and the necessity of a prompt initiation of PEP, ad hoc testing for antiretroviral resistance mutations is not applicable in this setting [12,13].

Others have supported the HIV fusion inhibitor enfuvirtide for post-exposure prophylaxis (PEP) [19], but the complex modality of administration and the frequent local injection site reactions could make enfuvirtide poorly acceptable for PEP [20].

Furthermore, clinicians should choose the drug combination after a careful assessment of the HCW's characteristics, including existing medical conditions and medications. For example, since hepatotoxicity may be more common in persons with chronic viral hepatitis, caution should be used in the choice of the regimen when the healthcare worker is chronically infected with hepatitis B or hepatitis C virus. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors interact with oral contraceptives, so that alternative or additional methods should be used to avoid pregnancy. Several antihistamine, cardiac or psychotropic drugs should not be used with these antiretrovirals, and plasma concentrations of anticoagulants and anticonvulsants might be decreased by coadministration with ritonavir.

Drug intolerance and regimen complexity are factors affecting adherence to PEP and causing interruption in approximately 50% of HCWs. For example, simplicity and tolerability of the regimen induced the New York State Department of Health to recommend zidovudine, lamivudine and tenofovir as a first line PEP regimen [21]. Although the use of regimens easier to assume and proven to be well tolerated is obviously recommended, further information should be gathered on the efficacy of a one class regimen. For example, disappointing data about the efficacy of all-nucleoside regimens were recently presented [22].

Concerns about PEP safety arise because of its wide and increasing use following occupational and non-occupational exposures. Many adverse effects of PEP, most frequently gastrointestinal symptoms, can be controlled by symptomatic interventions, but in case of severe toxicity it could be necessary to stop one or all the drugs of a combination regimen. Toxicity usually has an early onset and promptly reverses when the drugs are stopped. Some antiretroviral drugs can cause alterations of the glucidic and/or lipidic metabolism, even if it seems unlikely that these alterations could lead to irreversible consequences during PEP. Cases of PEP-associated ototoxicity, galactorrhoea and hyperprolactinemia, acute cholestatic hepatitis have been described anecdotally. More recently, a case of rapid development of central adiposity [23], and a case of reversible multiorgan failure have been reported [24].

ARV-induced hepatotoxicity seems rare, often mild to moderate, and always reversible [25].

However, nevirapine (NVP) during PEP was associated with cases of life-threatening hypersensitivity (Stevens-Johnson syndrome), myositis, and hepatitis, mostly rash-associated [26]. Efavirenz could also determine increased transaminase levels and rash, though usually milder; however, severe rashes (Stevens-Johnson syndrome) have been reported [27]. Hypersensitivity reactions which could be fatal have been reported following the use of abacavir [28].

Some studies suggest that adverse effects and discontinuation of PEP are more common among persons taking protease inhibitor containing PEP regimens, compared with those taking two NRTI [14]. Other

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studies seem to demonstrate that the difference in the proportion of individuals developing adverse effects and discontinuing PEP between the two regimens is not very significant [29].

Although the incremental benefit of a triple, two class combination of drugs active at different stages of the viral replication cycle as PEP is speculative at present, neither the prevalence of resistant strains in the sources nor the rate of side effects and PEP discontinuation seem to justify per se the initial use of a potentially less potent regimen.

Acknowledgements

The European Occupational Post-Exposure Prophylaxis Study Group wishes to thank the personnel working at the Coordinating Centre: Francesca Mattioli and Zlatan Lazarevic for data collection and management, Yohanka Alfonso Contreras for secretarial support, Lorena Fiorentini for administrative support.

Funded by the European Commission Directorate-General for Health and Consumer Protection. Unit F4. Project 2000/SID/107, grant no. SI2.322294. Supported in part by the Italian Ministry of Health- AIDS Research ISS grant 30D.66, and Ricerca Corrente IRCCS.

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INCREASE IN HEPATITIS A IN MSM IN DENMARK

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Published online 27 May 2004
(http://www.eurosurveillance.org/ew/2004/040527.asp)

A review of notifications to the Department of Epidemiology in the Statens Serum Institut (http://www.ssi.dk/sw379.asp) has revealed a cluster of cases of hepatitis A acquired in Denmark among men aged 18 years or older [1]. Twenty eight cases in men have been notified so far in 2004. Of the 20 patients from the greater Copenhagen area, at least 16 are men who have sex with men (MSM). At least five Swedish men have also been infected with hepatitis A in Copenhagen.

In the past five years, the median number of notified cases of hepatitis A acquired in Denmark each year among men aged 18 years or over was eight (range 6-11). Because of missing or delayed notifications, a full overview of the current outbreak has not yet been achieved. An increased incidence of syphilis has also been observed among MSM in Copenhagen [2], but a possible association between these two outbreaks has not yet been established.

Close contacts of infected cases, primarily household members and sexual partners, should receive immunoglobulin or hepatitis A vaccine as quickly as possible. Non-immune MSM who are not in a monogamous relationship should receive vaccination against hepatitis A, preferably together with hepatitis B vaccination. To prevent further spread, it is important that the MSM community is made aware of this outbreak and of routes of infection.

Outbreaks of hepatitis A among MSM have previously been reported both in Copenhagen and abroad, acquired in places such as saunas [3-5]. The most recently described outbreak in Denmark was in 1991 [6]. Studies have established risk factors for infection with hepatitis A among MSM. Examples of these risk factors are recent anonymous sexual partners, oral-anal sex or digital-anal sex, as well as visiting certain bars or saunas. Social contact of a non-sexual nature and secondarily contaminated foodstuffs may also contribute to infection. In the current outbreak, no particular risk factors have so far been found. Danish HIV/AIDS organisations are currently launching a nationwide information campaign about sexually transmitted infections, which includes hepatitis A.

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INCREASE IN HEPATITIS A IN MSM IN THE NETHERLANDS

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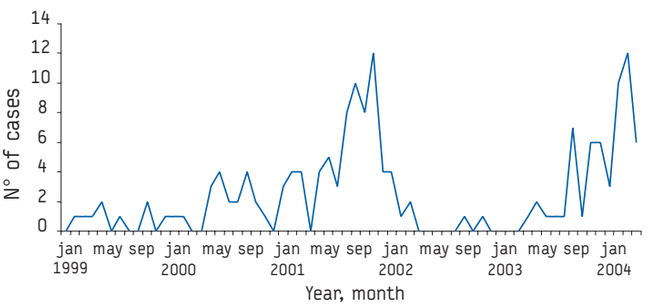
Published online 27 May 2004
(http://www.eurosurveillance.org/ew/2004/040527.asp)

It is unusual for an upsurge in hepatitis A incidence to be seen in spring or early summer in the Netherlands. A recent increase in the number of notifications of hepatitis A has, however, been detected through the Dutch data collection system for notifiable diseases (FIGURE). Men who have sex with men (MSM) appear to be particularly affected.

FIGURE

Number of notifications of hepatitis A among MSM in the Netherlands. 1999 -2004



In 2004, there have so far been 99 notifications of hepatitis A acquired by men aged 18 years or older, compared with 37 during the same period in 2003. Among the notifications in 2004, 31 reported homosexual sex as a risk factor for hepatitis A. Information about patients' sexual behaviour is not yet a standard requirement of notification of hepatitis A across the country and therefore hepatitis A cases acquired by this route of infection could be underestimated at present.

In 2003, there was just one notification with sex between men as a risk factor over the same period of time. However, the current outbreak is not unusual; a similar increase in hepatitis A infections in MSM was seen in 2001.

The recent outbreak of lymphogranuloma venereum in MSM [1] has increased awareness of sexually transmitted infections in the MSM community, and so sex between men may now be being recorded more often as a risk factor for transmission.

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Legionnaires' disease associated with whirlpools at an exhibition - Austria, March 2004

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Published online 8 April 2004

(http://www.eurosurveillance.org/ew/2004/040408.asp)

Three cases of legionnaires' disease have been confirmed in Austria's central Oberösterreich province. Three men, aged between 42 and 65 years, were admitted to hospital in the cities of Ried im Innkreis and Linz on 16, 17, and 19 March respectively. This temporal and spatial cluster prompted an epidemiological investigation, performed by the Österreichische Agentur für Gesundheit und Ernährungssicherheit (Austrian Agency for Health and Food Safety, http://www.ages.at). For all reported cases, the date of onset of clinical symptoms was between 10 and 13 March. All patients had attended a trade fair for energy-saving products in Wels (Ried im Innkreis and Linz are both approximately 100 km from Wels), from 5 to 7 March 2004. The trade fair included a whirlpool display stand. All three patients, when questioned, reported that they had visited the whirlpool stand at the exhibition at approximately the same time. For this reason, and because whirlpools can be very effective at propagating *Legionella*, the whirlpools at the fair are currently under suspicion as the source of this outbreak.

No additional cases have been detected since 31 March, when the Bundesministerium für Frauen und Gesundheit (Federal Ministry for Women and Health, http://www.bmgf.gv.at) announced the oubreak in a press statement [1]. All three cases were initially diagnosed by urinary antigen detection. *Legionella pneumophila* serogroup 1 was detected using a direct immunofluorescence test performed on a tracheal secretion specimen from the 65 year old patient, who developed multiorgan failure and required mechanical ventilation and haemodialysis for 11 days. All three patients are currently in a stable condition. Environmental samples taken from the whirlpools exhibited at the fair are being tested.

Previous cases of legionnaires' disease linked to whirlpool baths at public events have been reported. An outbreak at the Westfriese Flora, a flower and consumer products show, in the Netherlands in 1999, affected 188 people [2,3]. Two whirlpool spas on display at the show were implicated. Another outbreak of legionnaires' disease occurred in Belgium in 1999, which affected 93 visitors to a trade fair in Kapellan. A whirlpool and a fountain at that exhibition were found to be contaminated with *Legionella* [4].

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Legionella infections from a private whirlpool in Sweden

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Published online 20 May 2004

(http://www.eurosurveillance.org/ew/2004/040520.asp)

In mid-February, a middle aged Swedish man fell severely ill with legionellosis. The cultivation of his sputum sample showed growth of *Legionella bozemanii*, an unusual species in Sweden [1].

Since the patient had not recently travelled abroad, an investigation to find the source of infection was initiated by the department of communicable disease control and prevention in Stockholm County. The man was staying at his summer cottage during the incubation time. The water supply to his cottage is delivered through a long pipe via his neighbour's property. This water in the pipe was suspected to be the source of infection and so the water was sampled and analysed for the presence of *Legionella*, but this was not detected. On further questioning, the patient recalled that he had visited a friend and they had bathed in the friend's whirlpool bath.

The owner of the whirlpool was contacted and was found to be suffering from protracted symptoms of a respiratory tract infection. He had taken a course of penicillin for about two months, which had had no effect on his symptoms. Serological results later showed raised titres of antibodies to *Legionella bozemanii*.

At the end of April, samples were taken from the whirlpool and very high amounts of *Legionella bozemanii/anisa* were detected in the whirlpool water (3 600 000/ litre). The bacteriological analysis also showed high numbers of *Pseudomonas aeruginosa* and very high numbers of heterotrophic bacteria, (> 30 000/ml). These results indicated that the whirlpool had not been maintained correctly.

The owner of the whirlpool stated that he had maintained the whirlpool in accordance with the manufacturer's maintenance instructions, although he had changed the filter more often than was recommended. The whirlpool has a volume of about 3 m^3 and the water was changed every second week. Chlorine was used as disinfectant and was added manually. The owner of the whirlpool contacted people who had visited him previously and had bathed in the whirlpool. He reported that about 40 people had developed mild respiratory symptoms after their visit.

The growth of the unusual *Legionella bozemanii/anisa* could be due to the fact that the water used in the household is a mixture of well water and water from a nearby lake. Outbreaks caused by whirlpools distributing *Legionella* are becoming more frequent [2]. Outbreaks of Pontiac fever with high attack rate are more common [3] but legionellosis outbreaks also occur.

Whirlpools are commonly installed in public places such as hotels, gyms or spas and bad or non-existent maintenance of the whirlpools is common. This is the first time that a private whirlpool has been found to be the vehicle of legionella infection in Sweden, but it is likely that the number of people contracting an infection with milder symptoms from their private whirlpools is underestimated.

Guidelines have been produced for hotels and public places where whirlpools are installed to help the organisations reduce the risk of whirlpools becoming distributors of *Legionella* [4].

→ → →

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Community outbreak of hepatitis A in southern Italy – Campania, January-May 2004

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Published online 3 June 2004

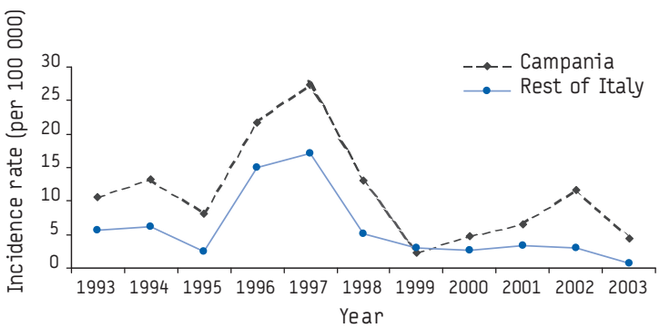
(http://www.eurosurveillance.org/ew/2004/040603.asp)

Introduction

Campania, a region in southern Italy (5 700 000 inhabitants, regional capital Naples), is one of the 20 political regions in Italy. Hepatitis A (HAV) is an endemic disease here, with an annual incidence rate often twice as high as the total rate for the rest of Italy (Figure 1). Typically the seasonal pattern shows an increase during summer and in the first quarter of the year, after Christmas. During the last decade, the largest epidemic of HAV occurred in 1996 and 1997 in Puglia, south-east Italy [1].

Figure 1

Annual incidence rates (per 100 000 inhabitants) of HAV in Campania and the rest of Italy (1993-2003)



Around the end of March 2004, the main hospitals treating communicable diseases in Campania reported an increasing number of admissions of patients with HAV. This was confirmed by the number of statutory notifications received by the Osservatorio Epidemiologico Regionale (OER), the regional epidemiological unit.

A review of the number of notifications received in the same three month period in previous years for this region showed that the number of cases observed in 2004 vastly exceeded the expected cases for the same period.

Due to the high number of cases involved, the OER requested assistance from the communicable disease epidemiology unit at the National Centre for Epidemiology, Surveillance and Health Promotion at the National Public Health Institute (Istituto Superiore di Sanità) in Rome. The aims were then to reinforce local surveillance of the occurrence of cases, to investigate the outbreak in order to identify the most probable route of transmission, and to implement appropriate control measures.

Methods

According to the criteria for statutory notification of HAV in Campania, a case of HAV is defined as any person resident in Campania with a clinical presentation of acute hepatitis (one of the following: jaundice, fever, nausea, dark brown urine) and a positive serological result for IgM-HAV. Using this description, cases with an onset from 1 January 2004 onwards are being examined.

An additional enhanced surveillance system with rapid reporting through an ad hoc on-line system (EPOS) has been implemented. Cases with pending serological results have also been recorded. Hospitals have been asked to collect serum samples from patients admitted with a diagnosis of HAV diseases for further virus characterisation.

A descriptive analysis of reported cases was undertaken, so that hypotheses about the source of the infection, and possible modes and vehicles of transmission could be formulated. Following this, an environmental investigation was launched to collect and test samples of seafood products from local outlets and the main seafood providers in the region, as these are known to be the most common vehicles for endemic cases.

Preliminary results

Descriptive results presented here are preliminary and refer to any reported case (either confirmed or suspected) from 1 January until 21 May 2004. Up to 21 May 2004, 615 confirmed and suspected cases of HAV had been notified. Among them, 58% are males. The median age is 20 years (range: 1-76 years) and 9% were less than 5 years of age (Table).

Table

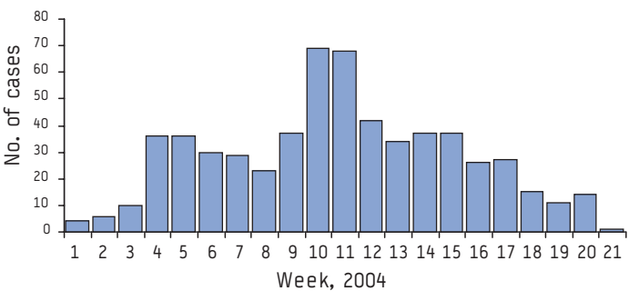
Age distribution of cases of HAV, Campania, Italy, 2004

Age group	Number of cases	%
0 to 5	54	8.7
6 to 10	70	11.4
11 to 20	183	30
21 to 30	209	34
31 to 40	74	12
41+	19	3.1
Missing	6	0.9
Total	615	100

The date of onset of symptoms was available for 592 cases (96%). The first cases in the current epidemic were reported in one particular district – district A. The epidemic curve, drawn by week of onset, shows two peaks around weeks 4-5 and 10-11 of 2004 (Figure 2).

Figure 2

HAV cases by week of onset, Campania, Italy, 2004



Over 60% of the cases were clustered in two out of 16 districts in Campania (112 and 265 cases). Most of the cases were reported in district A: about 60% of them were males. The median age was 16 years (range: 1-52). When cases in this district were compared to those in other districts, no significant difference was found in sex distribution (57.4% of males to 58.3%, p = 0.7). However, the median age of cases from district A was significantly lower than the median age of cases from other districts (16 to 23, p<0.001).

Case distribution by date of onset in district A showed a similar pattern compared to cases in the other districts. Preliminary interviews with patients suggested that shellfish was a popular food item. Further results of the case control study, microbiological and environmental investigations are pending.

Discussion

Most of the cases occurred in one densely populated district on the coast, south of Naples. Patients from this area were younger than patients from the rest of the region suggesting a different pattern in susceptibility to HAV of the local population or a different mode of transmission.

The epidemic curve profile is compatible with two waves of transmission. After an initial point source of infection around New Year's Eve, the epidemic is thought to have amplified locally and was sustained through person to person transmission. As the average incubation period for HAV is 28-30 days, the period of exposure for most cases can be traced back to early January and mid February 2004. Seafood is suspected to have been the initial exposure source in both waves of HAV cases in the area but also contributed to the continuation of the outbreak. The seafood is believed to have been locally contaminated through incorrect handling or storage. These hypotheses are being tested on the field in a case-control study currently in progress.

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Outbreak of Vero cytotoxin-producing E.coli O157 linked to milk in Denmark

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Published online 13 May 2004
(http://www.eurosurveillance.org/ew/2004/040513.asp)

In an outbreak which lasted from September 2003 to March 2004 in Denmark, 25 people became ill with disease caused by Vero cytotoxin-producing E.coli (VTEC) O157 [1-2]. The outbreak was limited to the Greater Copenhagen area. A total of 18 children and seven adults were registered: six males and 19 females. The dominant symptoms experienced were abdominal cramps and diarrhoea: there were no cases with renal failure. The isolates cultured from stool samples had the same unique genetic fingerprint.

Eleven patients who became ill after 15 January 2004 and 55 controls were interviewed. Eight of the 11 patients were probably primary cases, while three might have been secondary cases. Of the eight primary patients, seven had bought goods from a certain supermarket chain (matched odds ratio (mOR) 7.7; 95% Confidence Interval (CI): 0.9-65). No other chain of shops was associated with increased risk of infection. On the basis of the interviews, milk from a certain dairy was the only foodstuff that was linked with an increased risk of infection. Five of the eight primary patients had drunk milk from the dairy in question, compared with five of 39 control persons, (mOR 8.7; 95% CI: 1.6-48). The last three primary patients did not remember that they had drunk milk from this dairy.

The outbreak was likely to have been caused by a foodstuff that was sold in a certain supermarket chain, which sells a large amount of milk products from the dairy mentioned. It is suspected that the milk from this dairy was contaminated with very low levels of VTEC O157. Following a press release by the Danish Veterinary and Food Administration (http://www.uk.foedevaredirektoratet.dk/forside.htm, [3] on 26 March, the production of milk from the dairy mentioned was temporarily stopped, the plant was cleaned and the pasteurisation temperature raised. Since then, there have been no further cases. The dairy has been investigated for VTEC O157 contamination, but these results have been negative. A further investigation of the herds supplying the dairy is planned [4].

Physicians in the Copenhagen area are still being officially advised to request a laboratory investigation for VTEC O157 when requesting cultures of stool samples for enteropathogenic bacteria from patients presenting with abdominal cramps and diarrhoea.

This outbreak caused by VTEC O157 is the first general one recorded in Denmark. Previous outbreaks of VTEC O157 linked to milk and dairy products have been reported in the United Kingdom [5,6].

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Short reports

Measles outbreak in Norway in children adopted from China

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Published online 20 May 2004
(http://www.eurosurveillance.org/ew/2004/040520.asp)

Of a group of eight adoptees from China who came to Norway at the end of March 2004, four children developed a rash on the journey or shortly after arriving in Norway. In all four cases, measles was confirmed by laboratory results.

The Nasjonalt Folkehelseinstitut (Norwegian Institute of Public Health, http://www.fhi.no/) was alerted to this outbreak in early April by the mother of one of the sick children. A few days later, we became aware of a similar outbreak of six confirmed and three possible cases among adoptees from China who were taken to the United States

(US) in March 2004 [1]. Due to the international character of the outbreak and because we assumed that some of the children had been infectious during their journey from China to Norway, an early warning was issued through European Union Public Health Information Network Health Surveillance System for Communicable Diseases (EUPHIN HSSCD) on 14 April. A response from Spain reported one possible case of measles in an adoptee from Hunan province in China.

Our epidemiological investigation, which included an internet search and contact with the parents of the adoptees, found that the Norwegian adoptees came from the same orphanage in Hunan province as the American adoptees with measles.

The children were all 11-12 months old at the time of the outbreak, with the exception of one who was 16 months old. The orphanage staff had informed the adopting parents that the children had not been vaccinated against measles. The parents were not officially informed, but some of them reported having heard rumours, of an outbreak in the orphanage (there are around 400 children in the orphanage, of all ages).

The Norwegian parents travelled to China as a single group. They collected their children from the orphanage on 22 March, and left Beijing by plane, arriving in Norway via Copenhagen on 31 March. Before the flight, one child was admitted to hospital in Beijing due to illness with a rash and her journey to Norway was delayed by a few days. The hospital diagnosed pneumonia, but measles was not confirmed.

Three children came down with fever and a rash shortly after their arrival in Norway and two of them were admitted to hospital. One case was laboratory confirmed as measles in the hospital, one was clinically diagnosed as a typical case of measles, and the third was initially regarded as not measles. Later, laboratory testing at the reference laboratory at the Folkehelseinstitut (serum and saliva) confirmed measles in all four children who had developed a rash, including the child who had been admitted to hospital in Beijing.

The children who went to the US and developed measles had an onset of illness between March 22 and April 6. The Norwegian cases had onsets between 24 March and 2 April. The Spanish case became ill during the flight to Spain on 1 May.

The four uninfected children were not tested for susceptibility. Two of the four children who stayed well during the outbreak were given immunoglobulin on 6 April. At least one of the measles patients admitted to hospital in Norway was malnourished, but all the children with measles are reported to have recovered fully. There have been no reports of secondary cases in Norway during this outbreak.

The vaccination programme in Norway includes one dose of measles, mumps, and rubella vaccine (MMR) at the age of 15 months and one at the age of 13 years. The coverage of MMR in children aged two years has been slightly below the coverage of the other programme vaccines, and has been approximately 90% in recent years (it has been slightly below this since 2001).

Over the last four years, 0-8 cases of measles have been notified per year in Norway, all either imported or linked to importation, and seldom resulted in any secondary cases in the country. Many of the measles cases in recent years have been in refugee children who have fallen sick shortly after arrival in Norway.

At present we regard Norway as free from endemic measles, but with MMR coverage somewhat below the desired level, we must be prepared for outbreaks in connection with imported cases. This outbreak is a reminder that children adopted abroad may bring diseases into their new home country. Adoption agencies should work with the authorities in the country of origin to make sure that adoptees receive the necessary vaccines and that vaccinations are properly documented. In situations of outbreaks, such as measles, particular care should be taken in the country of origin that children are not brought to their new country before possible risk of communicable disease is clarified and controlled.

The World Health Organization (WHO) has ambitious objectives of reducing measles in the world, and of eventual eradication. The WHO European Region has specifically targeted elimination of measles by 2010 [2]. For Norway, the challenges are to maintain and improve MMR coverage and to vigilantly maintain surveillance, adequate diagnosis and timely implementation of necessary actions when cases appear.

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Death of a child from rabies in Lithuania and update on the Lithuanian rabies situation

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Published online 15 April 2004
(http://www.eurosurveillance.org/ew/2004/040415.asp)

In March 2004, a five year old boy died from rabies in Lithuania. The boy originated from the district of Prienai (southern Lithuania) but had lived in the city of Alytus, also in the south of the country, since November 2003. On 21 February he fell ill with chills. The next day he had a fever (40°C). On 23 February the boy was admitted to Alytus city hospital, where he was diagnosed with an acute viral respiratory infection, acute nasopharyngitis and hyperthermia. On 24 February, he was admitted to the Respublikine Vilniaus universitetine vaiku ligonine (Vilnius University children's hospital) where he was diagnosed with acute viral respiratory infection, acute nasopharyngitis, acute encephalitis and neurotoxicosis. He became aggressive, anxious and was hypersalivating. All investigations (blood analysis, blood electrolytes and glucose, cerebrospinal fluid analysis, herpes virus test, blood culture, and a brain magnetic resonance scan) were negative or did not show any pathology. At a meeting of neurologists and infectious disease specialists, it was agreed that symptomatic treatment for the acute progressive encephalitis was having no effect, and so a diagnosis of rabies was not excluded. The boy died on 10 March. Final diagnosis was: rabies, not specified; complication: CNS activity deficiency. On 12 March, laboratory results were received: rabies had been detected by immunofluorescence. The case was reported beyond Lithuania [1].

Specialists from Vilnius and the regional public health centres undertook an epidemiological investigation to try to detect possible contacts of the patient with domestic and wild animals. The Alytus County department of the State Food and Veterinary Service (http://www.vet.lt) reported that between October and December 2003, there had been 11 animal rabies cases detected in the city of Alytus and surrounding county: one case in the city and 10 cases in the county (three foxes, five mongooses and three cows). In 2004 so far, there have been seven registered animal cases in Alytus county (two foxes, five mongooses, a dog and a cat).

Prienai district State Food and Veterinary Service reported that between October and December 2003, there were two detected animal rabies cases: in a dog and a mongoose and these cases were registered at 8-9 km distance from the place where the boy had been living. In 2004, no animal rabies cases have so far been detected in Prienai district. According to the patient's parents, in November 2003 in Prienai, a piglet died from unknown causes. It was not examined by a vet, and was buried.

TABLE 1

Rabies immunoprophylaxis distributed in 1996-2003, Lithuania.

YEAR	1996	1997	1998	1999	2000	2001	2002	2003
Number of people who sought medical advice after injuries caused by animals	9078	8866	8754	9794	12 800	10 966	10 944	11797
Number of people who underwent post-exposure immunoprophylaxis	4470	4461	4409	5310	8021	6306	6064	7016
%	42.2	50.3	50.4	54.2	62.6	57.5	55.4	59.5
Costs (in Litas)	602 195	507 235	476 520	570 359	867 679	747 312	899 771	781 874

The patient's parents reported no contact between the patient and domestic or wild animals, and no injury.

In recent years, the epidemiological and epizootiological rabies situation in Lithuania has worsened. Rabies cases in wild and domestic animals have been notified in all regions. Every year, a great number of people are injured by various wild and domestic animals, and the widespread rabies virus has increased the threat to humans [TABLE 1].

Many people are bitten by healthy and by infected dogs. Six per cent of people seeking medical advice following animal injuries in 2003 had been bitten by dogs infected with rabies (with a laboratory confirmed diagnosis) [TABLE 2]. Since 1994, the procedure for post-exposure vaccination in Lithuania has been rabies vaccine and human immunoglobulin.

TABLE 2

Data on animal injuries in 2003

Animals	Number of people injured by animals						
	Total	By healthy animals		By animals with unknown health status		By rabid animals	
	(100%)	Number	%	Number	%	Number	%
Dogs	8058	5257	65.2	2352	29.2	449	5.6
Cats	1493	758	50.8	505	33.9	230	15.4
Rats	98	17	17.3	72	73.5	9	9.2
Cattle	798	107	13.4	48	6	643	80.6
Other domestic animals	175	79	45.1	8	4.6	88	50.3
Wild animals	1175	46	3.9	280	23.8	849	72.3
Total	11797	6264	53.0	3265	27.7	2268	19.3

According to State Food and Veterinary Service data for 2003, 1108 animal cases of rabies were registered in all regions of Lithuania (an increase of 175 cases compared with 2002). There were 796 registered cases in wild animals (71.8%) and 312 cases in domestic animals (28.2%) [TABLE 3].

TABLE 3

Animal rabies cases 2000-2003

Year	Total	Domestic animals	Wild animals
2000	850	285	565
2001	677	192	485
2002	933	682	251
2003	1108	312	796

Note: there were many cases where a rabid animal bit more than one person, which accounts for the difference between total human injuries from rabid animals and the total number of rabid animals in 2003.

Regional branches of the State Food and Veterinary Service collect data on rabid or suspected animals and send samples to the National Veterinary Laboratory. The National State Food and Veterinary Service is informed by the regions through the monthly return of forms.

In wild animals, rabies was detected in foxes (378 cases) racoons (299 cases) martens (81 case) ferrets (18 cases) badgers (11 cases) roes (3 cases) lynxes (2 cases) mink, beavers, otters, bats, hamsters (1 case). Cases among domestic animals were registered in cows (152 cases) cats (81 case) dogs (65 cases) horses (12 cases) and goats (2 cases).

Cats and dogs are vaccinated regularly whereas cows are only vaccinated in areas where there is a concentration of rabies cases. In 2003, 201 638 dogs, 31 262 cats, 34 670 cows and 1694 other animals received prophylactic vaccination. Between 2000 and 2003, vaccination of foxes using baits was discontinued due to a lack of financial resources.

Cases of deaths from rabies in Lithuania are registered every 3 to 4 years. There were 11 human deaths between 1960 and 2004; seven of these patients had had contact with wild rabid animals and three with domestic rabid animals. The source of infection for the patient in 2004 patient remains unknown (TABLE 4).

TABLE 4

Human rabies in Lithuania in 1960-2004

Region	Year	Number of cases	Source of virus
Vilnius	1960	1	Dog
Kaisiadoriu distric	1962	1	Fox
Svencioniu district	1965	1	Racoon-dog
Kedainiu district	1972	1	Badger
Traku district	1979	1	Fox
Joniskio district	1992	1	Racoon-dog
Traku district	1992	1	Dog
Traku district	1993	1	Cat
Kedainiu district	1997	1	Fox
Pasvalio district	2000	1	Fox
Prienu district	2004	1	Unknown

If a human case of rabies is suspected, an immediate report is sent to the regional public health centre and the Centre for Communicable Diseases Prevention and Control. Epidemiologists from regional public health centres undertake the investigation.

In 2002, a Rabies Epidemiological and Epizootiological Surveillance and Control Programme was approved. According to this programme, wild fauna rabies vaccination will be funded across all regions of Lithuania. Financial support is also promised by Phare management committee (The Phare programme is one of the pre-accession projects financed by European Community. It assists applicant countries in preparing to join the European Union, http://europa.eu.int/comm/enlargement/pas/phare/), and this support will be used for oral wild animal vaccination. This programme will also be implemented in the neighbouring countries of Latvia, Poland and Belarus. A rabies surveillance programme will also be set up, and with these measures, the number of rabid wild animals should be reduced.

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SCOTTISH REPORT ON HEPATITIS C AND INJECTING PRACTICES HAS IMPLICATIONS FOR POLICY AND HARM REDUCTION STRATEGIES

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Published online 15 April
(http://www.eurosurveillance.org/ew/2004/040415.asp)

There is considerable evidence that needle/syringe exchange provision has helped to control HIV transmission among injecting drug users (IDUs) [1]. However, the indications are that current interventions may be reducing, but are not controlling, the spread of hepatitis C infection (HCV) [2]. It has been suggested that the sharing of other injecting paraphernalia may also be implicated in the spread of HCV infection [3,4] but there has been very little research that examines the precise ways in which injecting practices put IDUs at risk.

A recent study in Glasgow observed drug users as they injected in their own settings, at home and in outside locations [5]. The aim of the study was to examine the injecting practices of injecting drug users to a degree of detail not previously achieved in the United Kingdom (UK). The specific focus was practices that could potentially facilitate the transmission of HCV infection. Risk practices other than the direct sharing of needles and syringes were of special interest as these are not so well understood. Observations were recorded by video.

Thirty injectors were recruited to the study and were recorded injecting on 48 separate occasions. Within these 48 events, drugs were prepared for injecting a total of 65 times and a total of 103 injections were administered. Twenty two of the 48 recorded events and 47 of the 65 preparation episodes involved two or more IDUs injecting together.

The results showed that harm reduction messages about borrowing used needles and syringes are understood and largely adhered to by IDUs. Just over half of the injection episodes involved the use of new, sterile needles/syringes and only one episode of direct sharing was observed during the study. However the indirect sharing of potentially infected needles/syringes and the sharing of other potentially infected injecting paraphernalia, was more common and potentially put IDUs at risk of HCV infection.

The storage of used needles and syringes for further use was common. Indirect sharing could arise when, for example, cohabiting IDUs or IDU injecting partners stored their used needle/syringes next to each and then had difficulty in distinguishing one from another.

The utilisation of a pre-used needle/syringe in the preparation or drawing up of drug solute for more than one injector was another way in which needles/syringes were shared indirectly. It was common to prepare drugs in one batch for all participants. In more than three quarters of the preparation episodes involving two or more IDUs one batch of drug solute was prepared to be divided among the group. On just under half of these occasions a pre-used needle/syringe drew the solution up first. Although the needle/syringe did not come into direct contact with another IDU in such circumstances, it potentially contaminated any or all of the other injecting paraphernalia or drug solution [6].

The findings have important implications for public health policy and harm reduction strategies. Recommendations include increasing access times to needle and syringe exchanges, producing the fixed 1ml needle/syringe commonly used in the UK in different colours to allow IDUs to distinguish each other's equipment, and providing IDUs with more information about the ways in which injecting equipment can become contaminated in the injecting process. The full report is available at http://www.drugmisuse.isdscotland.org/eiu-/pubs/eiu_060.htm

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TUBERCULOSIS SCREENING OF AUSSIEDLER AT THE FRIEDLAND BORDER IMMIGRATION CENTRE, GERMANY

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Published online 29 April 2004
(http://www.eurosurveillance.org/ew/2004/040429.asp)

The Friedland immigration centre in Niedersachsen (Lower Saxony) is the central primary immigration centre for Aussiedler. The term Aussiedler refers to ethnic Germans who live as ethnic minorities in the former Soviet Union, and to a lesser extent in eastern Europe. According to German law, Aussiedler have a right of immigration into Germany, providing their German ethnicity can be proven. On arrival in Germany, they are firstly admitted for a short period (usually 3-5 days) to the Friedland immigration centre before they are referred to their final residence.

The German Infektionsschutzgesetz (the Protection against Infection Act, IfSG, see http://rki.de/INFEKT/IFSG/IFSG_E.PDF) states that these people must present a medical certificate, before or on entry to the centre, to show that they do not have infectious tuberculosis. For Aussiedler over the age of 15 years, this certification must be based on a chest x ray, while pregnant women and those under the age of 15 are medically examined. The reason for this measure is the assumption and experience that people from the former Soviet Union have lived in an area where there is a higher prevalence and incidence of tuberculosis than in the general population in Germany.

According to the IfSG, occurrence of tuberculosis requiring treatment and/or verification of the causative agent has to be notified to the local public health authorities. In the case of the Friedland centre, health authorities in Göttingen are responsible. This report analyses data from cases in Aussiedler reported to Göttingen health authorities.

Methods

The Göttingen health authorities collect the notified tuberculosis cases using a case-administration software (SurvNet@RKI) The Göttingen health authorities do not always receive supplementary details of cases, such as drug resistance status, which may become apparent only when treatment begins. In a few cases, the patients' permanent address is already known at the time of notification, and the tuberculosis case can be directly notified to the health authorities of that region. Such cases were not considered in the following analysis.

Tuberculosis screening in Friedland is done by chest x ray examination. If infectious tuberculosis is suspected, patients are usually admitted as inpatients to local hospitals for confirmation, where further radiological, microbiological and clinical diagnostic tests are done and if necessary, antituberculosis therapy is started.

Results

A total of 73 080 Aussiedler were registered at the Friedland immigration centre in 2003. Of these, 56 179 (76.9%) were screened by x ray, and 16 901 were medically examined. As a result of screening, 416 (0.6%) people were referred for further testing on suspicion of having tuberculosis. These tests revealed 221 tuberculosis cases, which were notified to Göttingen health authorities and fulfilled the German reporting system's tuberculosis case definition.

Prevalence

Based on these 73 080 Aussiedler, the 221 notified cases represent a rate of 302 cases per 100 000 Aussiedler. As the start date of the illness is not known, it is more appropriate to think of 'continued existence' of tuberculosis illnesses in a particular year, and thus of a prevalence. Since there may be more cases of tuberculosis that are reported directly to the health authorities where the Aussiedler subsequently settle in Germany, the true prevalence may be underestimated. A comparable prevalence in the general population cannot be accurately estimated at present, although between 1995-2000, the prevalence in Niedersachsen was 20 per 100 000 inhabitants, and showed a decreasing trend.

Age and sex

The distribution of age and sex of the tuberculosis cases in Aussiedler in connection with the screening programme is as follows: about three quarters (76%) of those affected were men. Of these, 60% were under 50 years of age. Of the women affected, 48% were under 50 years. Age or sex specific prevalences could not be calculated from this data, since the age and sex distribution of all the people examined was unknown.

Verification of causative agent

In all 221 cases, the respiratory tract (lung parenchyma, bronchio-trachea and larynx) was the main affected organ. The proportion of open pulmonary tuberculosis with confirmation from laboratory cultured *Mycobacterium tuberculosis* and/or a microscopic examination showing acid fast rods in the sputum smear, was 38.5% (85 out of 221).

TABLE 1

Results of tuberculosis testing in Aussiedler tuberculosis patients - Friedland immigration centre, 2003.

Verification method	Number of cases	%
Culture and microscopy positive	22	10.0
Culture verification only	50	22.6
Microscopic verification only	13	5.9
Culture and microscopic verification negative	131	59.2
Unknown result or no particulars	5	2.3
Total	221	100

Details of drug resistance to isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (SM) were available for 25% of patients (55) [TABLE 2]. Resistance was determined for 76% of the culture positive cases. Two of the EMB resistant isolates were intermediary.

Particularly notable was the high proportion (18.2%) of resistance against the two first-line drugs, INH and RMP. In comparison, the 2002 data for the whole of Germany show a drug resistance rate against INH and RMP of 2%, and patients born in Germany had a drug resistance rate of only 0.7%.

TABLE 2

Drug resistance rate to antituberculosis medication in Aussiedler tuberculosis patients - Friedland immigration centre, 2003 (n=55).

Medication	Resistant	%
Isoniazid (INH)	19	34.5
Rifampicin (RMP)	10	18.2
Pyrazinamide (PZA)	1	1.8
Ethambutol (EMB)	9	16.4
Streptomycin (SM)	17	30.9
INH + RMP	10	18.2
Any resistance	23	41.8

Previous illness of tuberculosis and previous antituberculosis treatment

In 90% of cases, details of tuberculosis pre-illness and previous antituberculosis treatment could be ascertained. About one third of the affected people reported a pre-illness, and most of these reported previous tuberculosis treatment. Details of the success of the previous treatment were only available for nine people, six of whom reported an interruption in their previous tuberculosis treatment.

Discussion

In 2003, amongst the admitted 73 080 Aussiedler, there was a prevalence of 302 cases per 100 000 Aussiedler. In 25% of cases, details were reported of drug resistance. These show, in comparison to Germany-wide figures, a substantially higher proportion of drug resistant tuberculosis. The figures presented here support the particular need for an effective screening of this population at immigration centres. This health protection measure is contributing to tuberculosis control within the centre and also reduces further transmission in the German population. Lower Saxony spent approximately 1.6 million Euros on this screening programme in 2003.

Since further examinations are left to the federal region where the Aussiedler takes up residence, it remains to be determined how far these initially diagnosed cases stay within the surveillance system, and whether their identification through this screening actually leads to successful therapy.

This article was adapted and summarised from reference 1 by the authors.

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Emergence of Panton-Valentine leukocidin positive community-acquired MRSA infections in Belgium

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Published online 10 June 2004
(http://www.eurosurveillance.org/ew/2004/040610.asp)

The worldwide emergence of community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) infections caused by hypervirulent strains producing Panton-Valentine leukocidin (PVL, coded by *lukS-lukF*) is a cause for considerable concern. First reported in the early 1990s among aboriginal populations in Western Australia, outbreaks of CA-MRSA infections in healthy children and adults with no hospital contact have been recently described in the United States and Europe in communities such as prison inmates, sport teams and schoolchildren [1-3]. PVL-positive MRSA infections have been reported in France, the Netherlands, Germany, Switzerland, Finland, Norway and Scotland [1-3]. Molecular studies suggest spread of a limited number of PVL-producing MRSA clones that are genetically distinct from hospital-acquired strains. In Europe, most strains are thought to be multi-locus sequence type 80, and to possess the *agr* type 3 and SCC*mec* type IV genes. This emergence of PVL+ CA-MRSA represents a public health threat, because these strains are associated with severe soft tissue infection and necrotising pneumonia, the latter having a reported case-fatality rate of 75% [4]. Treatment failure occurs with the beta-lactam therapy that is usually prescribed for these infections.

We report the first two identified cases of PVL+ CA-MRSA infections in Belgium. The first was in a 49 year old woman living in Brussels who attended a clinic in November 2003 with recurrent furunculosis of the legs. She had no recent history of hospitalisation. *S.aureus* resistant to oxacillin, kanamycin, tetracycline and fusidic acid was isolated from the lesions. The patient recovered after several weeks of therapy with oral doxycycline and topical application of mupirocin and povidone iodine cream. No case of staphylococcal infection was reported among her family or close social contacts.

The second case was in a 46 year old man living in Namur, south Belgium who was admitted in April 2004 to a general hospital in Namur with fever and abdominal pain. He had no history of hospitalisation. On admission, an abscess of the upper lip, with cellulitis around the mouth from shaving cuts, was drained. The histology of a lip biopsy indicated necrosis of salivary glands. Bilateral lung infiltrates and pleural effusion were noted. *S.aureus* resistant to oxacillin, kanamycin and fusidic acid was isolated from two blood cultures and an abscess swab. The patient's fever and pain resolved slowly with intravenous clindamycin therapy for four weeks. Contact investigations showed no case of staphylococcal infection in his family; his wife was negative for *S.aureus* oronasal carriage.

Both isolates were positive for *mecA* and *lukS-luk*F genes, had *agr* type3 and sequence type 80-SCC*mec* type IV. They shared the same pulsed field gel electrophoresis (PFGE) genotype, although no common exposure or other connection was identified for these two cases. Further comparison of this PFGE type with CA-MRSA strains from other countries may clarify the extent of geographical dissemination of this strain across Europe.

Clinicians should be aware of the possibility of skin and respiratory CA-MRSA infections and request cultures from skin lesions or respiratory infections in outpatients who do not respond to therapy with beta-lactam drugs or topical fusidic acid. Screening for additional cases or carriers among social contacts is advisable. Moreover, surveillance should be intensified to monitor the incidence of MRSA and detect and control outbreaks in the community. A clue for microbiological laboratories is the isolation of *S.aureus* with the unusual antibiotic resistance profile: oxacillin, kanamycin, fusidic acid and occasionally tetracycline resistance. Such isolates should be sent to a reference laboratory for determination of PVL production and typing.

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Azithromycin failures in the treatment of syphilis in the United States

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Published online 1 April 2004
(http://www.eurosurveillance.org/ew/2004/040401.asp)

Since the late 1990s there has been a dramatic change in the incidence of infectious syphilis in many western industrialised countries and outbreaks have been seen in major cities in Europe, North America and Australia [1-6]. Syphilis has been increasing in the United States since 2000 and San Francisco has one of the highest rates of primary and secondary syphilis in the US. The San Francisco Department of Public Health (SFDPH) investigated several clinical failures in syphilis patients treated with azithromycin [7]. Single oral dose azithromycin therapy is more convenient to administer than intramuscular benzathine penicillin (CDC's recommended treatment for syphilis) and facilitates the management of cases and their sexual contacts [8].

Between September 2002 and July 2003, 8 cases of treatment failure were seen involving single dose azithromycin therapy. All the patients were men who have sex with men, and had a median patient age of 34 years (range 23 to 39). Five of the men were HIV seropositive. Each symptomatic patient was treated with 2 g of azithromycin. Of the two patients with penile ulcers, one ulcer was positive by dark field microscopy after five days, and the other was positive by dark-field microscopy after five weeks. A patient with an oral ulcer was positive by dark field microscopy after 18 days. Five patients who were seronegative contacts of the cases received a dose of 1 g of azithromycin, but all either seroconverted or developed early syphilis after treatment. Subsequently, all patients were treated successfully with either penicillin or doxycycline. Resistance to erythromycin has been reported in *Treponema pallidum* [9] and investigators at the University of Washington are collaborating with SFDPH and others to investigate the molecular mechanism that confers azithromycin resistance.

It is disappointing that these azithromycin treatment failures of early syphilis have been reported. Azithromycin as a single oral dose has good efficacy against a number of sexually transmitted infections including *Chlamydia trachomatis* and chancroid [8]. The availability of an effective single dose oral therapy might improve syphilis control by allowing treatment to be given in non-clinic and outreach settings. Indeed, this therapy was recently used in an attempt to control an epidemic of syphilis in Vancouver by widespread availability of single dose azithromycin amongst people at high risk of having syphilis [6]. This intervention appeared to be unsuccessful and it is possible that treatment failure may have played a part in this lack of success. The evidence base for the use of azithromycin in the treatment of syphilis remains poor. Animal studies show good activity against *Treponema pallidum* [10] and uncontrolled open studies of longer courses of azithromycin appear to show efficacy in early disease [11]. But poor transplacental [12] and cerebrospinal fluid [13] penetration of azithromycin is likely to limit its usefulness in pregnancy and late syphilis respectively, and to date, only small randomised studies suggest it is efficacious in early syphilis [8]. Many clinicians will consider that until more evidence is available, macrolides (including azithromycin) remain fourth line agents for syphilis after penicillin, tetracyclines (such as doxycycline) and cephalosporins (such as ceftriaxone) [14].

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POLICY & GUIDELINES

DANISH PROGRAMME FOR CONTROL OF SALMONELLA IN POULTRY HAS RESULTED IN FEWER CASES IN BOTH POULTRY AND HUMANS

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Published online 3 June 2004
(http://www.eurosurveillance.org/ew/2004/040603.asp)

The Danish National *Salmonella* Control Programme, launched in December 1996, was reviewed in March 2003 [1,2]. The control programme was designed to be a 'top-down' effort based on an elimination strategy, whereby infected poultry flocks were eradicated by compulsory slaughter. Public funding for the programme expired in 2002, after which the poultry industry took over administrative and financial responsibility, while Salmonella control and prevention continues to be under public regulation and surveillance. The Fødevaredirektoratet (Danish Veterinary and Food Administration, http://www.fdir.dk) has overall control of the programme, and the public sector will continue to set the goals of the continued efforts.

The National *Salmonella* Control Programme covers all Salmonella serotypes (except for the host-specific serotypes S. Pullorum and S. Gallinarum), and both the layer and broiler production systems at all levels. Infected flocks are detected as early as possible by sampling and testing, including serological and bacteriological analyses.

Results for broiler production

As a result of this elimination strategy, the percentage of broiler flocks positive for *Salmonella* before slaughter has declined from 12.9% in 1997 to 1.5% in 2002.

Results for breeding flocks

Since the launch of the programme, the percentage of breeding flocks infected with Salmonella has hovered around 1.2%, since Denmark like most other member states, has had a control plan for S. Enteritidis and S. Typhimurium in breeding flocks since the early 1990s, as a result of Directive 92/117 [3]. None of these flocks have transmitted Salmonella down through the production pyramid, because the detection of infection results in flock eradication. This is very important, because Denmark has only a few breeding flocks supplying many production flocks.

Results for egg-producing ('layer') flocks

The percentage of infected flocks providing table eggs has declined from 13.4% in 1998 to 2.6% in 2002; the dominant serotype has been S. Enteritidis phage type 8.

Impact on human cases

This improvement in primary production is reflected in a striking 59% decline in the number of registered human *Salmonella* cases, from 5015 in 1997 to 2071 in 2002. In 2003, only 1712 cases were recorded. The estimated number of human cases attributable to eggs has been reduced by 80% from 1997 to 2002. While 60% of the infections (a total of 3009) in Denmark were egg-related in 1997, only 31% (a total of 636) in 2002 were attributable to eggs. The majority (some 75%) of chicken

and nearly all eggs consumed in Denmark are produced there, and it is therefore likely that the decrease in the number of human infections is a direct result of the control programme.

The full report: *The National Salmonella Programme for the Production of Table Eggs and Broilers*, 1996 - 2002 is available at http://www.foedevaredirektoratet.dk/FDir/Publications/2004006/Rapport.pdf

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Protecting the United Kingdom blood supply from variant CJD: donors who have received a blood transfusion can no longer donate blood

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Published online 18 March 2004
(http://www.eurosurveillance.org/ew/2004/040318.asp)

On 16 March 2004, the Department of Health in England announced that people who have received a blood transfusion in the United Kingdom (UK) since 1 January 1980 will no longer be able to donate blood [1,2]. This additional donor selection criterion will be implemented by all four of the UK Blood Services (UKBS), including the National Blood Service (http://www.blood.co.uk/), on 5 April 2004.

This additional precautionary measure to safeguard the blood supply is being taken in the light of the first possible transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion which was reported in December 2003 [3]. The transfusion occurred in 1996; the blood donor was well at the time but developed symptoms of vCJD in 1999 and died the following year. The recipient was diagnosed with vCJD in 2003.

Since 1997, in view of the uncertainty as to whether vCJD could be transmitted by blood or blood products, the UKBS have put in place a number of other measures to reduce the risk of a potential onward cycle of transmission:

- Withdrawal and recall of any blood components, plasma derivatives or tissues obtained from any individual who later develops vCJD (December 1997)
- Importation of plasma from the US for fractionation to manufacture plasma derivatives (announced May 1998, implemented October 1999)
- Leucodepletion (removal of white blood cells) of all blood components (announced July 1998, implemented Autumn 1999)
- Importation of fresh frozen plasma from the United States for patients born on or after 1 January 1996 (announced August 2002, to be implemented spring 2004)
- Promotion of appropriate use of blood and tissues and alternatives throughout the National Health Service (NHS)

This is a highly precautionary approach and the benefit of receiving a blood transfusion when needed far outweighs any possible risk of contracting vCJD. To date there has been only one possible case of vCJD being transmitted by blood, yet the UKBS issue over 2.5 million units of blood every year.

As of 1 March 2004 there have been 146 definite and probable cases of vCJD in the UK, 1 case each in the Republic of Ireland, Italy, United States, Canada and Hong Kong, and six cases in France. The eventual number of individuals within the UK population likely to develop vCJD remains uncertain; estimates range from the current numbers up to 540. It is not known how many current or past blood or tissue donors may develop vCJD in the future. Further information and advice to blood donors and members of the public who are concerned about the risk of contracting vCJD from a blood transfusion are being offered via a UKBS telephone hotline (+44 845 7711 711) and the NHS Direct service (http://www.nhsdirect.nhs.uk/).

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Modernisation of the International Health Regulations – WHO European Region consultation

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Published online 27 May 2004
(http://www.eurosurveillance.org/ew/2004/040527.asp)

The current International Health Regulations (IHR) [1], which were published by the World Health Organization (WHO) in 1969 [2], were originally intended to help monitor and control six serious infectious diseases. They require countries to report to WHO and apply control measures for just three infections: cholera, plague, and yellow fever. Since the 1980s, a series of developments and events have made it apparent that these Regulations are inadequate as a legal response to global outbreaks, emerging and re-emerging infections, and rising incidence of particular infectious diseases.

WHO and its member states have been responding to such events through the WHO Communicable Disease Surveillance and Response Division (WHO- CSR, http://www.who.int/csr/about/en/) and the Global Outbreak Alert and Response Network (GOARN, http://www.who.int/csr/outbreaknetwork/en/). However, there is no adequate legal underpinning for this work. For example, when concern was expressed that national authorities in China had been slow in reporting the outbreak of what became SARS in late 2002, it turned out that there was neither a legal reason for them to make such a report, nor any legal justification for WHO to insist on investigating when it became aware of rumours of severe outbreaks of pneumonia in Guangdong province. In contrast, the Chinese authorities are legally obliged to report even a single case of cholera.

WHO and its ruling body, the World Health Assembly, have been developing new regulations since 1995. Following a series of resolutions passed by the World Health Assembly between 2001 and 2003 [3,4], a draft set of radically improved Regulations was issued in January 2004 [5]. These regulations, which comprise 55 articles and ten annexes, are now being considered in WHO regional consultations with a view to a

final text being approved by the World Health Assembly in the spring of 2005. The regulations should come into force in January 2006.

Much of the regulations reflect what has become good practice by WHO and member states in the past years in response to threats such as SARS and viral haemorrhagic infections, and outbreaks of unknown diseases. More information can be found at http://www.who.int/csr/ihr/en/

There are six major proposals in the new Regulations:

- They would require member states to notify WHO of any event or disease that constitutes a potential public health event or emergency of international concern: a prescriptive list of diseases is not being used. Member states would also be obliged to respond to WHO's requests for verification of information regarding national risks when WHO becomes aware of other reports or rumours. This would enable WHO to ensure appropriate technical assistance for effective protection and management of such events.
- The scope of the Regulations will be extended beyond infections to include chemical and radiation threats as well as events where the cause is as yet unclear.
- Each WHO member state will be required to have one or more national IHR focal points and corresponding contact individuals. These will form the operational link between states and WHO, and communicate official information to and from WHO on a continual basis. This is so that recommendations for response actions and measures to protect each state can be communicated effectively.
- Each state will be required to have core public health capacities in order to detect, report, and respond to public health risks and potential or actual public health events of international concern. In addition to this, specific capacities will be required for the implementation of routine measures at points of entry (airports, seaports and land borders).
- WHO's response to an event may include temporary or standing recommendations for measures for application by the state affected by a public health risk or event of international concern, other states, and operators of international transport. Ad hoc, time-limited recommendations could be made by WHO on a risk-specific basis. Standing recommendations made by WHO under the revised IHR, would indicate the appropriate measures for routine application for specific on-going public health risks.
- Finally, the proposed Regulations include procedures for member states and WHO to obtain independent advice concerning implementation of the Regulations. First is the establishment of a committee to be used during public health emergencies to provide advice on temporary recommendations. The second is the establishment of an IHR review committee, which will consider disputes, the development of standing recommendations and evaluate how the Regulations are functioning.

The Regional Consultation for the WHO European Region (http://www.euro.who.int/) is taking place in Copenhagen from 9 to 11 June. The process of consultation will not finish with the Copenhagen meeting, as WHO regional views will subsequently be combined and a revised set of Regulations will probably be issued later in 2004.

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News

News update, full text available at:
www.eurosurveillance.org

First large outbreak of multidrug resistant tuberculosis in the Netherlands reported
18 March 2004
The first large outbreak of multidrug resistant tuberculosis (MDR TB) in the Netherlands has been reported...

European Commission adopts working paper on Community influenza pandemic preparedness and response planning
1st April 2004
The European Commission has adopted a working paper on Community influenza pandemic preparedness and response planning, addressing key issues of both national and European Union (EU) relevance...

Worldwide recall of Aventis Pasteur rabies vaccine
8 April 2004
Aventis Pasteur Marketing Services Division Limited has issued a worldwide recall of a rabies vaccine manufactured by the company in France...

Unusual type of scrapie detected in sheep in the United Kingdom
23 April 2004
Brain tissue samples from a sheep carcass in the United Kingdom (UK) have undergone tests which have detected a type of scrapie (a transmissible spongiform encephalopathy (TSE) found in sheep and goats).....

Communicable disease surveillance in Malta
29 april 2004
Malta's national communicable disease surveillance centre is the Disease Surveillance Unit of the Department of Public Health.....

Communicable disease surveillance, prevention and control in Lithuania
6 May 2004
The Lithuanian Centre for Communicable Diseases Prevention and Control in Vilnius was established in 1997...

Communicable disease surveillance, prevention and control in Slovakia
6 May 2004
The Public Health Authority of the Slovak Republic fulfils the role of the executive body of the Ministry of Health of the Slovak Republic. The Authority's operations cover the whole of the Slovak Republic...

Communicable disease surveillance, prevention and control in Cyprus
6 May 2004
The Medical and Public Health Services of the Ministry of Health of Cyprus have recently developed a new Network for the Surveillance and Control of Communicable Diseases...

Communicable disease surveillance, prevention and control in Poland
13 May 2004
In 1918, the Polish government established the Central Epidemiological Institute in Warsaw, which was renamed the National Institute of Hygiene in 1923...

Communicable disease surveillance, prevention and control in Slovakia
20 May 2004
The European Parliament and Council have published a regulation, which comes into force today, establishing the European Centre for Disease Prevention and Control (ECDC)...

Tetanus in an injecting drug user in the Netherlands: single case so far
6 May 2004
In March 2004, a 61 year old female intravenous drug user (IDU) was taken to hospital because she was found unwell at home. She was a long-term drug user who reportedly injected heroin intramuscularly...

Further evidence that vCJD incidence in the UK is currently in decline
13 May 2004-06-16
In the first quarter of 2004 there was only one death from variant CJD reported in the United Kingdom. This follows a total of 18 deaths reported in 2003...

Regulation establishing the European Centre comes into force
20 May 2004
The European Parliament and Council have published a regulation, which comes into force today, establishing the European Centre for Disease Prevention and Control...

Tonsil study provides estimate of the number of people in the UK who could be incubating vCJD
10 June 2004.
A study providing an estimate of the number of individuals in the United Kingdom (UK) who may be incubating variant Creutzfeldt-Jakob disease (vCJD), has recently been published...

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National Bulletins

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Mitteilungen der Sanitätsverwaltung

Bundesministerium für Gesundheit
und Frauen
Stabsstelle I/A/4
Radetzkystrasse 2
A-1031 Wien - Austria

Monthly, print only. In German.

Ministry Website: http://www.bmgf.gv.at

Belgium

Epidemiologisch Bulletin van de Vlaamse Gemeenschap

Gezondheidsinspectie Antwerpen
Copernicuslaan 1, bus 5
2018 Antwerpen

Quarterly, print and online versions available. In Dutch, summaries in English.

http://www.wvc.vlaanderen.be/epibul/

and

Infectious Diseases in the Spotlights

Institut Scientifique de la santé Publique
Louis Pasteur
14, rue Juliette Wytsman
B-1050 Bruxelles

Weekly, online only. In English.

http://www.iph.fgov.be/epidemio/epien/plaben/idnews/index_en.htm

Bulgaria

Epidemiological Surveillance
National Centre of Infectious and Parasitic Diseases
26 Yanko Sakazov blvd.
Sofia 1504

Print version available, online version available soon. In Bulgarian, titles translated into English.

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EPI-NEWS

Department of Epidemiology
Statens Serum Institut
Artillerivej 5
DK-2300 København S

Weekly, print and online versions available. In Danish and English.

http://www.ssi.dk

England and Wales

Communicable Disease Report Weekly

Health Protection Agency
61 Colindale Avenue
London NW9 5EQ

Weekly, online only. In English.

http://www.hpa.org.uk/cdr

Finland

Kansanterveys

Department of Infectious Disease Epidemiology
National Public Health Institute
Mannerheimintie 166
00300 Helsinki

Monthly, print and online versions available. In Finnish.

http://www.ktl.fi/kansanterveyslehti/

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Bulletin Epidémiologique Hebdomadaire

Institut de veille sanitaire
12, rue du Val d'Osne
94415 Saint-Maurice Cedex

Weekly, print and online versions available. In French.

http://www.invs.sante.fr/beh/default.htm

Germany

Epidemiologisches Bulletin

Robert Koch-Institut
Division of Infectious Disease Epidemiology
Nordufer 20
D-13353 Berlin

Weekly, print and online versions available. In German.

http://www.rki.de/INFEKT/EPIBULL/EPI.HTM

Hungary

Epinfo (Epidemiológiai Információs Hetilap)
National Center For Epidemiology
Gyali ut 2-6
1097 Budapest

Weekly, online version available. In Hungarian

http://www.antsz.hu/oek/epinfo/szoveg/Heti2004/hetiindit04.htm

Ireland

EPI-INSIGHT

National Disease Surveillance Centre
25-27 Middle Gardiner Street
Dublin 1

Monthly, print and online versions available. In English.

http://www.ndsc.ie/Publications/EPI-Insight/

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Notiziario dell'Istituto Superiore di Sanità

Istituto Superiore di Sanità
Reparto di Malattie Infettive
Viale Regina Elena 299
I-00161 Roma

Monthly, online only. In Italian.

http://www.iss.it/publ/noti/index.html

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Istituto Superiore di Sanità
Reparto di Malattie Infettive
Viale Regina Elena 299
I-00161 Roma

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In Italian and English.

http://www.ben.iss.it

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Epidemiologijas Bileteni

State Public Health Agency
7 Klijanu Street
1012 Riga

Online. In Latvian.

http://www.sva.lv/epidemiologija/bileteni/

Netherlands

Infectieziekten Bulletin

Rijksinstituut voor Volksgezondheid en Milieu
PO Box 1
NL-3720 Bilthoven

Monthly, print and online versions available. In Dutch, some summaries in English.

http://www.infectieziektenbulletin.nl

Northern Ireland

Communicable Disease Monthly Report

Communicable Disease Monthly Report
Communicable Disease Surveillance Centre (Northern Ireland)
McBrien Building, Belfast City Hospital,
Lisburn Road
Belfast BT9 7AB

Monthly, print and online versions available. In English.

http://www.cdscni.org.uk/publications/

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MSIS-rapport

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N-0403 Oslo

Weekly, print and online versions available. In Norwegian.

http://www.folkehelsa.no/nyhetsbrev/msis/

Poland

Reports on cases of infectious disease and poisonings in Poland
National Institute of Hygiene Department of Epidemiology
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00-791 Warsawa

Fortnightly. In Polish and English.

Portugal

Saúde em Números

Direcção Geral da Saúde
Alameda D. Afonso Henriques 45
1049-005 Lisboa

Sporadic, print only. In Portuguese.

Ministry website: http://www.dgsaude.pt/

Scotland

SCIEH Weekly Report

Scottish Centre for Infection and Environmental Health
Clifton House, Clifton Place
Glasgow G3 7LN

Weekly, print and online versions available. In English.

http://www.show.scot.nhs.uk/scieh/wrhome.html

Spain

Boletín Epidemiológico Semanal

Centro Nacional de Epidemiología - Instituto de Salud Carlos III
C/ Sinesio Delgado 6 - 28029 Madrid

Bi-weekly, print and online versions available. In Spanish.

http://cne.isciii.es/bes/bes.htm

Sweden

EPI-aktuellt
Smittskyddsinstitutet
171 82 Solna

Weekly, online only. In Swedish.

http://www.smittskyddsinstitutet.se

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ISSN 1025 - 496X
7000 copies
Graphic design © Françoise Parraud, Paris
Printing by CARACTERE SAS
Registered July 2004

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