Eurosurveillance
Europe's leading journal on infectious disease epidemiology, prevention and control

Vol. 16 | Weekly issue 26 | 30 June 2011

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Insights from Europe related to pandemic influenza A(H1N1)2009 have international relevance

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Citation style for this article:
Kelly HA, Cowling BJ. Insights from Europe related to pandemic influenza A(H1N1)2009 have international relevance.
Euro Surveill. 2011;16(26):pii=19899. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19899

Article published on 30 June 2011

In this issue of Eurosurveillance Amato Gauci and colleagues collate a summary of surveillance data related to pandemic influenza A(H1N1)2009 from the 27 European Union Member States plus Norway and Iceland [1]. While much has already been published on experiences of individual countries, this report is an important summary of the impact of the first influenza pandemic of the 21st century in Europe as a whole. The authors acknowledge the inherent difficulties in summarising data collected from countries with varying surveillance systems and where the pandemic had differential impact. For instance, it was only in England – and only there in London and the West Midlands – that there was a significant spring pandemic wave in 2009 [2]. Like many aspects of the pandemic, this observation remains unexplained.

From a summary of the epidemiological and virological data, the authors recapitulate features of the pandemic that are now generally accepted (Box). However many of these features were not recognised early when an informed understanding was critical to an appropriate pandemic response. For instance, the authors quote a report from the World Health Organization published in 2009 that suggested early estimates of the effective reproduction number (R), defined as the average number of secondary infections attributable to one infectious case, were in the range 1.1-1.4 for the United Kingdom (UK) at the start of the pandemic, although up to 2.6 elsewhere [3]. Only the lower estimates for R are supported by recent studies [4]. Early estimates of R may have been overestimated for a number of reasons [5]. Firstly, ignoring imported cases or counting imported cases as locally acquired could increase the estimated R. Secondly, early estimates of R based on outbreaks could be overestimated due to selection bias. Thirdly, many early estimates of R reflected a high proportion of cases among school-age children, amongst whom R was higher than in the general population [3]. Finally, R could have been overestimated if transmission occurring prior to testing was not recognised [6].

The consensus estimates for R are now similar to those accepted for seasonal influenza [1], suggesting similar transmissibility for both viruses. While early outbreak investigations in schools or households, such as the UK First Few Hundred initiative [7], have the potential to provide timely data on the transmissibility characteristics of a new virus, further work is needed to clarify the extrapolation of transmissibility from outbreak studies to implications for population epidemiology.

Box

Generally accepted understanding of the 2009 influenza pandemic

- The highest cumulative incidence of disease was in the 0-4 year old age group, although the highest cumulative incidence of infection (including asymptomatic infection) was in school-aged children, the age group which was instrumental in the spread of the pandemic.
- Deaths associated with virologically confirmed influenza were lower than the number of excess deaths thought to occur from seasonal influenza, but the majority of deaths from pandemic influenza A(H1N1)2009 occurred at a younger age than is typically seen with seasonal influenza. However excess mortality and laboratory-confirmed deaths are not directly comparable.
- Although older adults were affected less commonly, this was the age group with the highest case fatality ratio.
- Intensive care units were stressed by the increase in the number of young adults with severe disease due to pandemic influenza A(H1N1)2009, a phenomenon first recognised in the southern hemisphere (19) but not experienced in all countries.
- Pregnant and post-partum women and indigenous people, both recognised risk groups for infection with seasonal influenza, were at apparently increased risk for a severe outcome from pandemic influenza A(H1N1)2009 infection.
- Although pandemic influenza A(H1N1)2009 appears to have completely replaced previous seasonal influenza A(H1N1) subtypes, it has not replaced influenza A(H3N2) subtypes which have continued to co-circulate as a small proportion of all typed influenza A viruses. This contrasts with the observations from previous pandemics, when the pandemic virus replaced all influenza A viruses.
- Unlike the pattern for seasonal influenza A(H1N1) viruses, no significant neuraminidase resistance of pandemic influenza A(H1N1)2009 has been detected to date, although variants with reduced oseltamivir sensitivity may be emerging in the Asia-Pacific region [20].
- The pandemic virus was less virulent than had been anticipated in many pandemic plans.

In trying to further disentangle the comparison of pandemic influenza A(H1N1)2009 and seasonal influenza in the community, the authors have re-examined data from sentinel surveillance schemes that were operating in Europe during the pandemic and shown that influenza-like illness (ILI) rates were higher during the pandemic than during the previous influenza season (Figure 1 in reference 1). However it is generally acknowledged that the pandemic was associated with increased testing for influenza as well as potential changes in healthcare-seeking behaviour [8]. The proportion of ILI patients who test positive for influenza can be a useful method for comparing influenza seasons, as it can potentially adjust for differential testing between jurisdictions and across seasons [9]. When the metric of percentage positive tests was applied to the European surveillance data, the predominantly pandemic season of 2009/10 looked similar in magnitude to the preceding 2008/9 influenza season (Figure 2 in reference 1).

Comparing ILI rates for pandemic and seasonal influenza is a specific example of a more general problem with influenza epidemiology – the extent to which common things are unknown. Further evidence of this problem is provided in the European review when it is suggested that asymptomatic infection was more common for pandemic influenza A(H1N1)2009 than for seasonal influenza, an observation based on admittedly weak evidence [1]. While around one third of experimental infections with a range of influenza types and sub-types are asymptomatic [10], this proportion depends on the definition of asymptomatic infection. Prospective intensive follow-up of people in household studies has found that only around 10% of virologically-confirmed A(H1N1)2009 infections were completely asymptomatic, while around one half were associated with febrile illness [11-13]. The precise asymptomatic fraction of naturally acquired infections due to seasonal and pandemic influenza remains uncertain, as does the potential for variability in this fraction by age.

Trying to understand the pandemic in Europe and around the world has highlighted other uncertainties about influenza epidemiology.

- Except for infants and children aged 0-4 years, for whom routine laboratory testing is common in many places, the number of hospitalisations due to laboratory-confirmed influenza is poorly estimated for other age groups. This number will vary by year, and by influenza type and subtype. The proportion of those requiring admission to intensive care will also vary by these parameters.
- Similarly, the number of deaths that can be directly attributed to laboratory-confirmed influenza is not known for the same parameters. Although underestimated, the increased testing associated with the pandemic provided estimates of laboratory confirmed deaths, but generally only for A(H1N1)2009 infections.
- Controversy persists over estimates of excess deaths attributable to influenza. These estimates place a substantial burden of seasonal influenza on the elderly and are not directly comparable to estimates of virologically confirmed deaths. Although estimates of years of life lost have been made, these have not yet been adjusted for the presence of pre-existing conditions.
- The proportion of people with confirmed influenza who seek medical attention is poorly understood in most countries. This proportion is very likely to reflect differences in cultural attitudes to illness, the provision of medical services and the public health interventions implemented in different countries. Serologic studies in combination with outpatient and inpatient surveillance can improve these estimates [14,15].
- There are very limited published data on the proportion of people with naturally acquired laboratory-confirmed influenza whose infections are asymptomatic. The likelihood of transmission from people with asymptomatic infections to susceptible contacts is not known.
- Vaccine is known to be effective in healthy children and adults but vaccine effectiveness is poorly understood in the elderly and in individuals at higher risk of severe disease if infected. These are the groups targeted for vaccination [1,16].
- Influenza usually circulates in the winter in temperate settings, but was able to spread in the spring in some parts of Europe and North America, raising questions about the diverse causes of influenza seasonality.

Three of the highlighted recommendations made by Amato Gauci and colleagues reflect the importance of filling these gaps in our knowledge of influenza epidemiology [1]:

Firstly, they recommend making ‘severe end’ influenza surveillance routine. Routine community-based influenza surveillance was very useful during the pandemic and routine hospital-based surveillance (’severe end’ surveillance) would have been equally useful. A study from Australia suggested that the hospital course for adults was similar for those infected with pandemic influenza A(H1N1)2009 and those infected with seasonal influenza - but that the burden on the hospital system resulted from the increased number of adults admitted to hospital during the pandemic [17]. Uncertainties surround this issue because of the lack of quality surveillance data from hospitals over a number of influenza seasons [18].

Secondly, they recommend sharing data early in any future outbreak. Data sharing facilitated international attempts to gauge the severity of the pandemic in 2009. This undertaking was supported by the unique rapid peer-reviewed publication policy of Eurosurveillance. The accuracy of shared articles was less certain when rapid publication dispensed with peer-review.

Thirdly, they suggest that sero-epidemiological studies should be included in revised pandemic plans to provide information in real time. This may be the most optimistic of the recommendations [15]. Serological studies remain the best approach to estimate the cumulative incidence of infection following a wave of infection but technical issues remain unsolved. These include the correlation between antibody titres and immunity, the characteristics of antibody profiles over time, the potential effect of antiviral treatment on convalescent antibody [11], and the interpretation of serological data after the introduction of a vaccine. The use of serological data for real-time evaluation of severity also requires reliable surveillance of severe infections [14].

Many aspects of improved understanding require descriptive and analytical epidemiological studies in diverse countries over consecutive influenza seasons in order to capture the range of potential outcomes due to laboratory-confirmed influenza, the outcome of choice in attempting to understand influenza control measures [16]. This level of understanding appears to be long overdue and should not be deferred until the next pandemic.

Acknowledgments

We thank the following people for their comments on the manuscript: Dr Aeron Hurt from the WHO Collaborating Centre for Surveillance and Research on Influenza, Melbourne, Australia; and Dr Geoffry Mercer and Dr Kathryn Glass from the Australian National University, Canberra, Australia. BJC is supported by supported by the Harvard Center for Communicable Disease Dynamics from the US National Institutes of Health Models of Infectious Disease Agent Study program (grant number 1 U54 GM088558). BJC has received research funding from MedImmune Inc. HK has received funding from CSL Biotherapies. The authors report no other potential conflicts of interest. The views expressed are those of the authors.

References

1. Amato-Gauci A, Zucs P, Snacken R, Ciancio B, Lopez V, Broberg E, et al. Surveillance trends of the 2009 influenza A(H1N1) pandemic in Europe. Euro Surveill. 2011;16(26):pii=19903. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19903
2. Flasche S, Hens N, Boelle PY, Mossong J, van Ballegooijen WM, Nunes B, et al. Differential transmission patterns in the early stages of the influenza A (H1N1)v pandemic: a comparative analysis of 12 European countries. Epidemics. 2011;3(2):125-33.
3. World Health Organization (WHO). Transmission dynamics and impact of pandemic influenza A (H1N1) 2009 virus. Wkly Epidemiol Rec. 2009;84(46): 481-4.
4. Nishiura H, Chowell G, Castillo-Chavez C. Did modeling overestimate the transmission potential of pandemic (H1N1-2009)? Sample size estimation for post-epidemic seroepidemiological studies. PLoS One 2011;6(3):e17908.
5. Mercer G, Glass K, Beckers N. Effective reproduction numbers are commonly overestimated early in a diseases outbreak. Stat Med. 2011;30(9):984-94.
6. Kelly H, Mercer G, Fielding J, Dowse G, Glass K, Carcione D, et al. Community circulation of pandemic influenza H1N1 was established in one Australian state at the same time the virus was first recognised in North America. PloS One 2010;5(6):e11341.
7. Pebody RG, Harris R, Kafatos G, Chamberland M, Campbell C, Nguyen-Van-Tam JS, et al. Use of antiviral drugs to reduce household transmission of pandemic (H1N1) 2009, United Kingdom. Emerg Infect Dis. 2011;17(6).
8. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. Lancet. 2010;375(9720):1100-8.
9. Lambert SB, Faux CE, Grant KA, Williams SH, Bletchly C, Catton MG et al. Influenza surveillance in Australia: we need to do more than count. Med J Aust. 2010;193(1):43-5.
10. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol. 2008;167(7):775-85.
11. Cowling BJ, Chan KH, Fang VJ, Lau LL, So HC, Fung RO, et al. Comparative epidemiology of pandemic and seasonal influenza A in households. N Engl J Med. 2010;362(23):2175-84.
12. Suess T, Buchholz U, Dupke S, Grunow R, an der Heiden M, Biere B, et al. Shedding and transmission of novel influenza virus A/H1N1 infection in households--Germany, 2009. Am J Epidemiol. 2010;171(11):1157-64.
13. Papenburg J, Baz M, Hamelin MÈ, Rhèaume C, Carbonneau J, Ouakki M, et al. Household transmission of the 2009 pandemic A/H1N1 influenza virus: elevated laboratory-confirmed secondary attack rates and evidence of asymptomatic infections. Clin Infect Dis. 2010;51(9):1033-41.
14. Wu JT, Ho A, Ma ES, Lee CK, et al. Estimating infection attack rates and severity in real-time during an influenza pandemic. PLoS Med. 2011; forthcoming.
15. Kelly H, Peck H, Laurie K, Wu P, Nishiura H, Cowling BJ. The age specific cumulative incidence of infection with pandemic influenza H1N1 2009 was similar in various countries prior to vaccination: a review of serological surveys. PloS One. 2011; forthcoming.
16. Valenciano M, Kissling E, Cohen J M, Oroszi B, Barret AS, Rizzo C, et al. Estimates of pandemic influenza vaccine effectiveness in Europe, 2009–2010: Results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case-control study. PLoS Med. 2011;8(1):e1000388.
17. Chang YS, van Hal SJ, Spencer PM, Gosbell IB, Collett PW. Comparison of adult patients hospitalised with pandemic (H1N1) 2009 influenza and seasonal influenza during the "PROTECT" phase of the pandemic response. Med J Aust. 2010;192(2):90-3.
18. Kelly PM, Kotsimbos T, Reynolds A, Wood-Baker R, Hancox B, Brown SG, et al. FluCAN 2009: initial results from sentinel surveillance for adult influenza and pneumonia in eight Australian hospitals. Med J Aust. 2011;194(4):169-74.
19. ANZIC Influenza Investigators, Webb SA, Pettilä V, Seppelt I, Bellomo R, Bailey M, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009;361(20):1925-34.
20. Hurt AC, Lee RT, Leang SK, Cui L, Deng Y, Phuah S, et al. Increased detection in Australia and Singapore of a novel influenza A(H1N1) 2009 variant with reduced oseltamivir and zanamivir sensitivity due to a S47N neuraminidase mutation. Euro Surveill. 2011;16(23):pii=19884. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19884

Outbreak of haemolytic uraemic syndrome and bloody diarrhoea due to *Escherichia coli* O104:H4, south-west France, June 2011

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Citation style for this article:
Gault G, Weill FX, Mariani-Kurkdjian , Jourdan-da Silva N, King L, Aldabe B, Charron M, Ong N, Castor C, Macé M, Bingen E, Noël H, Vaillant V, Bone A, Vendrely B, Delmas Y, Combe C, Bercion R, d'Andigné E, Desjardin M, de Valk H, Rolland P. Outbreak of haemolytic uraemic syndrome and bloody diarrhoea due to Escherichia coli O104:H4, south-west France, June 2011.
Euro Surveill. 2011;16(26):pii=19905. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19905

Article published on 30 June 2011

As of 12:00 28 June 2011, 15 cases of haemolytic uraemic syndrome (HUS) or bloody diarrhoea have been identified in the Gironde, south-west France. Investigations suggest the vehicle of transmission was sprouts, served at an event in Bègles on 8 June 2011. A strain of shiga toxin- producing *Escherichia coli* O104:H4 has been isolated from five cases. This strain is genetically related to the strain identified in the recent *E. coli* O104:H4 outbreak in Germany, and shares the same virulence and antimicrobial resistance characteristics.

Outbreak description

On 22 June 2011, the Cellule interrégionale d'épidémiologie (CIRE) Aquitaine, the regional office of the French Institute for Public Health Surveillance, was notified by the Robert Picqué Hospital in Bordeaux, south-west France, of eight cases of haemolytic uraemic syndrome (HUS) or bloody diarrhoea. Six of the cases lived in close proximity to one another in the commune of Bègles, in Bordeaux. Of these six cases, four were women (aged 41–78 years) and two were men (aged 34–41 years). Dates of symptom onset were between 15 and 20 June.

A case of HUS was defined as a person with acute renal failure and either microangiopathic haemolytic anaemia and/or thrombocytopenia. A possible outbreak case was defined as a case of HUS or a case of bloody diarrhoea without an alternative diagnosis in the French department (administrative region) of Gironde with a date of symptom onset since 10 June 2011. Active case finding has been carried out through contact with emergency, nephrology and intensive care departments of local hospitals, and general practitioners and out-of-hours doctors, and through the existing paediatric HUS surveillance network. Enhanced surveillance for cases of HUS or bloody diarrhoea in the rest of France has been implemented.

As of 12:00 28 June 2011, a further seven cases have been identified and investigated, bringing the total number of cases investigated to date to 15 cases of bloody diarrhoea, eight of whom have developed HUS.

Epidemiological investigations

The initial eight cases were interviewed using a standardised semi-structured questionnaire exploring food consumption, travel history and contact with other people with diarrhoea in the seven days before symptom onset. Initially no common food, visits to markets, restaurants or events, animal contact or leisure activity was identified. None of the cases reported eating sprouts. Only three of the cases shared the same municipal tap-water network. One of the cases had travelled away from home in France during the seven days before symptom onset and none had travelled abroad.

Given that a common exposure had not been identified, the predominance of adult women among the cases and the recent experience of the German sprout-related *Escherichia coli* O104:H4 outbreak in Germany [1,2], a second questionnaire was developed that included an in-depth exploration of vegetable consumption in the two weeks before illness.

Further questioning of the initial eight cases and seven newly identified cases indicated that 11 of these 15 cases had attended an open day at a children's

community centre on 8 June, at which a cold buffet was served consisting of crudités (raw vegetables), three dips, industrially produced gazpacho, a choice of two cold soups (carrot and cumin, and courgette), pasteurised fruit juices and individual dishes composed of white grapes, tomatoes, sesame seeds, chives, industrially produced soft cheese and fresh fruit. The soups were served with fenugreek sprouts, a small amount of which were also placed on the crudité dishes. Mustard and rocket sprouts, still growing on cotton wool, were used to decorate the crudité dishes. One of the 11 cases has not yet been fully questioned because of a deteriorating clinical condition, but is known to collect their grandchildren from the centre and may have attended the event. The remaining four cases had no obvious links to the centre.

Among the 11 cases with links to the centre, nine reported consuming sprouts at the event on 8 June; two cannot yet be fully questioned. Of these 11 cases, eight have HUS and three bloody diarrhoea. Seven are women aged 31–64 years and four are men aged 34–41 years. Dates of symptom onset are between 15 and 20 June (Figure). For the eight cases with a well-defined date of symptom onset, the incubation period ranges from 7 to 12 days (median: 9 days).

Microbiological investigations

A strain of *E. coli* O104:H4 possessing the stx2 gene, encoding Shiga toxin, has been isolated from five HUS cases, all of whom consumed sprouts at the event at the children's community centre. The strain is negative for the genes coding for intimin (*eae*), haemolysin A (*hlyA*) and EAST1 toxin (*astA*) and positive for the *aggR* gene which regulates the expression of aggregative adherence fimbriae. The antimicrobial resistance pattern of the strain is similar to that seen in the outbreak strain in recent *E. coli* O104:H4 outbreak in Germany [3](ampicillin resistant (R), cefotaxime R, ceftazidime R, imipenem sensitive (S), streptomycin R, kanamycin S, gentamicin S, sulfamethoxazole R, trimethoprim R, cotrimoxazole R, tetracycline R, chloramphenicol S, nalidixic acid R and ciprofloxacin S). Our PCR analysis indicates the presence of the extended-spectrum beta-lactamase (ESBL) $bla_{\text{CTX-M-15}}$ (group 1) gene and the penicillinase bla_{TEM} gene.

Strains of *E. coli* O104:H4 isolated from two imported cases in France linked to the *E. coli* O104:H4 outbreak in Germany in May and June 2011 were compared by two molecular techniques (Rep-PCR [4,5] and pulsed-field gel electrophoresis (PFGE), using a standardised PFGE using either *Xba*I or *Not*I [6]) with strains of *E. coli* O104:H4 isolated from three patients in the Bordeaux outbreak. The results of these analyses show the genetic relatedness of the outbreak strains in France and Germany. The profile of the outbreak strains in the two countries differs from the profiles of two *E. coli* O104:H4 stx2 strains isolated in 2004 and 2009 and from two other strains of serotypes *E. coli* O104:H21 and O104:H12. Comparison by whole-genome sequencing and optical maps will be performed in the coming days.

Food trace-back investigations

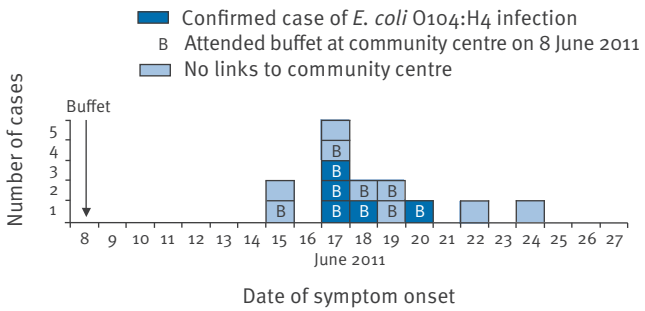
Food trace-back investigations were initiated on 24 June. The sprouts served at the event on 8 June had been grown from rocket, mustard and fenugreek seeds planted at the centre during 2 to 5 June. The fenugreek seeds were first soaked in tap water for 24 hours then placed in a jam jar topped with gauze and then rinsed with tap water two or three times a day. The mustard and rocket seeds were germinated on cotton wool moistened with tap water. They were harvested on 8 June to be served at the buffet. The seeds were purchased from a branch of a national chain of gardening retailers, having been supplied by a distributor in the United Kingdom. Leftover mustard and rocket seeds, gazpacho and tap water samples from the community centre have been sent for microbiological analysis, as have samples of rocket, mustard, fenugreek and other seeds from the French gardening retailer. Preliminary results are currently being analysed.

Control measures

Consumers have been advised by the French authorities not to eat raw sprouts, to thoroughly clean utensils used for germination and cooking, and to wash their hands thoroughly after contact with seeds and sprouts. Colleagues in other European countries were informed of this outbreak on 24 June via the Epidemic Intelligence Information System (EPIS) and Early Warning Response System (EWRS) of the European Centre of Disease Prevention and Control (ECDC). A European Food Standards Agency (EFSA) and ECDC joint rapid risk assessment has been carried out [7]. This assessment strongly recommends that consumers do not grow sprouts for their own consumption and do not eat sprouts or sprouted seeds unless thoroughly cooked.

Figure

Cases of HUS or bloody diarrhoea due to enterohaemorrhagic *Escherichia coli* O104:H4 with date of symptom onset since 10 June 2011, Gironde, France, June 2011 (n=14)



HUS: haemolytic uraemic syndrome.

Of the 15 cases of HUS or bloody diarrhoea, date of symptom onset was unavailable for one case, who attended the buffet on 8 June 2011.

Conclusions

Preliminary data indicate that this outbreak shares the same novel epidemiological, clinical and microbiological features identified in the *E. coli* O104:H4 outbreak in Germany [8], including a predominance of adult women among the cases, an unusually high proportion of HUS cases among identified possible outbreak cases, a longer median incubation period than expected for cases of Shiga toxin-producing *E. coli* infection, and a genetically related *E. coli* O104:H4 producing a CTX-M ESBL. The two outbreaks may share the same vehicle of transmission. A cohort study of those attending the event at the community centre and further epidemiological, microbiological and food trace-back investigations are underway. The possibility of similar outbreaks in France or elsewhere in Europe cannot be excluded.

Acknowledgments

Special thanks to the Agence Régional de la Santé Aquitaine, Bégles town council, Alexandra Mailles, Véronique Goulet, Gilles Delmas, Elisabeth Couturier, Christine Saura, Didier Gruson, Bruno Souillé, Isabelle Carles, Monique Lejay-Collin, Corinne Ruckly and Charlotte Balière for their assistance in the investigation of this outbreak.

References

1. Frank C, Faber MS, Askar M, Bernard H, Fruth A, Gilsdorf A, et al. Large and ongoing outbreak of haemolytic uraemic syndrome, Germany, May 2011. Euro Surveill. 2011;16(21):pii=19878. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19878
2. Frank C, Werber D, Cramer JP, Askar M, Faber M, an der Heiden M, et al. Epidemic profile of Shiga-toxin-producing Escherichia coli O104:H4 outbreak in Germany - preliminary report. N Engl J Med. 2011 Jun 22. [Epub ahead of print].
3. Bielaszewska M, Mellmann A, Zhang W, Köck R, Fruth A, Bauwens A, et al. Characterisation of the Escherichia coli strain associated with an outbreak of haemolytic uraemic syndrome in Germany, 2011: a microbiological study. Lancet Infect Dis. 2011 Jun 22. [Epub ahead of print].
4. Bonacorsi S, Bidet P, Mahjoub F, Mariani-Kurkdjian P, Ait-Ifrane S, Courroux C, et al. Semi-automated rep-PCR for rapid differentiation of major clonal groups of Escherichia coli meningitis strains. Int J Med Microbiol. 2009,299(6):402-9.
5. Boumghar-Bourtchai L, Mariani-Kurkdjian P, Bingen E, Filliol I, Dhalluin A, Ifrane SA, et al. Macrolide-resistant Shigella sonnei. Emerg Infect Dis. 2008;14(8):1297-9.
6. Ribot EM, Fair MA, Gautom R, Cameron DN, Hunter SB, Swaminathan B, et al. Standardization of pulsed-field gel electrophoresis protocols for the subtyping of Escherichia coli O157:H7, Salmonella, and Shigella for PulseNet. Foodborne Pathog Dis. 2006;3(1):59-67.
7. European Food Safety Authority (EFSA)/European Centre for Disease Prevention and Control (ECDC). EFSA/ECDC joint rapid risk assessment. Cluster of haemolytic uremic syndrome (HUS) in Bordeaux, France. 29 June 2011 (updated from 24 June). Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/2011June29_RA_JOINT_EFSA_STEC_France.pdf
8. Jansen A, Kielstein JT. The new face of enterohaemorrhagic Escherichia coli infections. Euro Surveill. 2011;16(25):pii=19898. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19898

Rapid emergence of carbapenemase-producing *Enterobacteriaceae* isolates in Belgium

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Citation style for this article:
Huang TD, Bogaerts P, Berhin C, Jans B, Deplano A, Denis O, Glupczynski Y. Rapid emergence of carbapenemase-producing Enterobacteriaceae isolates in Belgium. Euro Surveill. 2011;16(26):pii=19900. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19900

Article published on 30 June 2011

We report on the evolution and epidemiology of carbapenem non-susceptible *Enterobacteriaceae* (CNSE) including carbapenemase-producing *Enterobacteriaceae* (CPE) in Belgium between January 2007 and April 2011. Significantly higher numbers of CNSE and of CPE were detected in 2010 and 2011 compared to the years 2007 to 2009. The majority of patients carrying CPE did not have history of travel abroad. The rapid emergence of autochthonous CPE strains in Belgium since 2010 warrants strengthened epidemiological surveillance at national level.

Introduction

Dissemination of *Enterobacteriaceae* that have acquired carbapenemase genes is a growing public health problem worldwide [1]. The prevalence of particular types of carbapenemases differs significantly between countries: *Klebsiella pneumoniae* carbapenemase (KPC) variants are prevalent in the United States, Greece, and Israel; Verona integron-encoded metallo-beta-lactamases (VIM) are frequently found in Greece and Italy; oxacillinase (OXA)-48 was first recovered and becoming prevalent in Turkey, while imipenemase (IMP)-type enzymes were mostly reported in the Far East [2]. Recently, isolates with New Delhi metallo-beta-lactamases (NDM-1) have been identified, mostly in patients who had a history of travel to the Indian subcontinent [3].

In Belgium, sporadic cases of carbapenemase-producing *Enterobacteriaceae* (CPE) isolates have been reported, the majority of which occurred in patients returning from travel abroad [4-6].

This longitudinal survey aimed to summarise the microbiological characteristics and clinical data of carbapenem-non-susceptible *Enterobacteriaceae* (CNSE) isolates, with a special focus on CPE isolates referred to the National Reference Centre (NRC) for multidrug-resistant *Enterobacteriaceae*.

Methods

Enterobacteriaceae isolates were referred by local Belgian laboratories on a voluntary basis to the NRC (Centre Hospitalier Universitaire Mont-Godinne, Yvoir, Belgium). They were invited to send isolates that, according to antimicrobial susceptibility guidelines used in the respective laboratories, were resistant to third or fourth generation cephalosporins or carbapenem non-susceptible, for detection or confirmation of enzymes conferring antibiotic resistance. In September 2008, following the detection of the first VIM-1-producing *Klebsiella pneumoniae* isolates causing nosocomial outbreaks in two Belgian hospitals [7], a national alert was issued and local laboratories were asked to send carbapenem-non-susceptible isolates to the NRC for the detection or confirmation of carbapenemase production. All isolates referred between Janurary 2007 and April 2011 were re-tested at the NRC for antimicrobial susceptibility by the disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) and meropenem inhibition zones were recorded. Isolates displaying an inhibition zone of ‹23 mm to 10 µg meropenem disks, categorised retrospectively as intermediately resistant according to the CLSI interpretative criteria of January 2011 [8], were screened for the presence of carbapenemase-encoding genes by PCR using primers specific for ^{bla}VIM, ^{bla}IMP, ^{bla}KPC, ^{bla}NDM and ^{bla}OXA-48 [6]. Carbapenemase-encoding genes were identified by sequencing of the amplicons. Clinical and demographic data, including recent travel and/or hospitalisation abroad, were collected for all patients carrying CPE strains.

Results

A total of 155, 133, 125, 93 and 49 *Enterobacteriaceae* isolates were referred to the NRC during the years 2007, 2008, 2009, 2010 and the first four months of 2011, respectively. Numbers and the respective proportions of CNSE (including CPE) isolates referred during the study period are shown in Figure 1. The proportion of CNSE increased significantly from 8% (33 of 413 isolates) in the years 2007 to 2009 to 50% (71 of 142 isolates) in the years 2010 and 2011 ($p<0.0001$). The total number of CPE isolates we detected was also significantly higher in 2010 (n=17) and 2011 (n=13) than in the years 2007 to 2009 ($p<0.0001$).

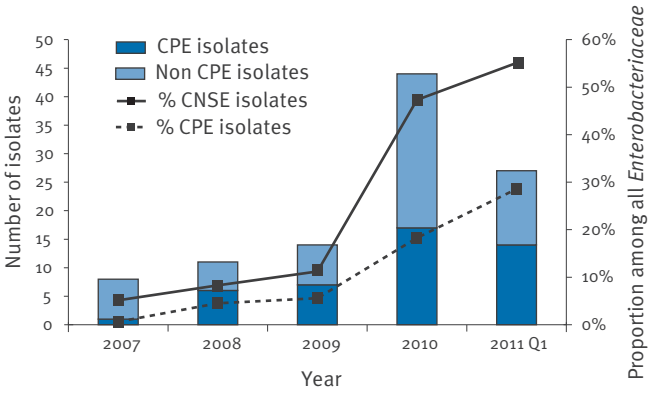
The evolution over time and the microbiological characteristics of the 44 CPE isolates detected during the study period are shown in Figures 2, 3 and 4. VIM-1 (n=18) and OXA-48 (n=16) were the most frequent carbapenemase enzymes found among CPE isolates.

Of the 44 different CPE isolates recovered from 39 different patients at 16 Belgian hospitals during the study period, 20 were isolated from urine, nine from rectal screening swabs (for the detection of asymptomatic carriers), seven from wound/drainage fluids, six from lower respiratory tract samples and three from blood culture specimens.

Of the 39 patients colonised or infected with a CPE isolate, only 16 had travelled abroad (13 of them in Mediterranean countries of Europe or North Africa) in the six months before the diagnosis (Table). Eleven of the 23 autochthonous CPE cases, probably resulting from local secondary acquisition, carried VIM-1-positive isolates (seven *Klebsiella pneumoniae*, two *Serratia marcescens* and two *K. oxytoca*) and were identified in eight hospitals. The 12 remaining patients harboured OXA-48-producing isolates (seven Enterobacter cloacae, four *K. pneumonia* and 1 *Escherichia coli*) and were detected in four hospitals. Four patients harboured more than one CPE isolates. Two patients were colonised by two NDM-1-positive isolates of two different species: one of them carried *K. pneumonia*e associated with E. coli and the other patient *Morganella morganii* with *E. cloacae*. One patient was colonised by two OXA-48-producing isolates (one *E. cloacae*

Figure 1

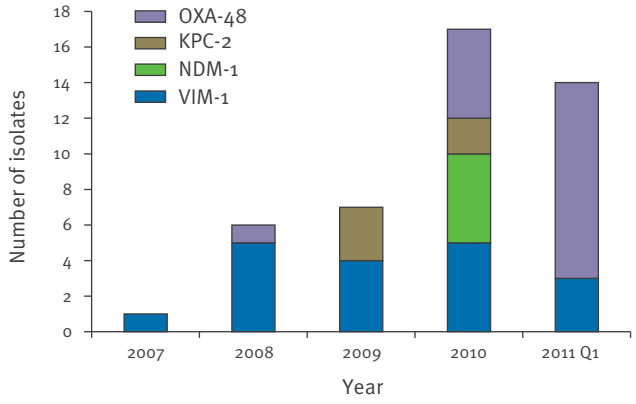
Evolution of number and proportion of carbapenem-non-susceptible *Enterobacteriaceae* isolates including carbapenemase producers, National Reference Centre, Belgium, January 2007–April 2011 (n=555)



CNSE: carbapenem-non-susceptible *Enterobacteriaceae*; CPE: carbapenemase-producing *Enterobacteriaceae*; Q1: first quarter.

Figure 2

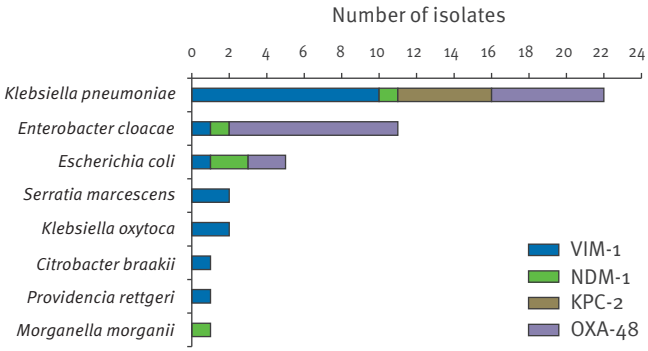
Evolution of the distribution of resistance mechanisms of carbapenemase-producing *Enterobacteriaceae* isolates, National Reference Centre, Belgium, January 2007–April 2011 (n=44)



KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Delhi metallo-beta-lactamase; OXA: oxacillinase; Q1: first quarter; VIM: Verona integron-encoded metallo-beta-lactamase.

Figure 3

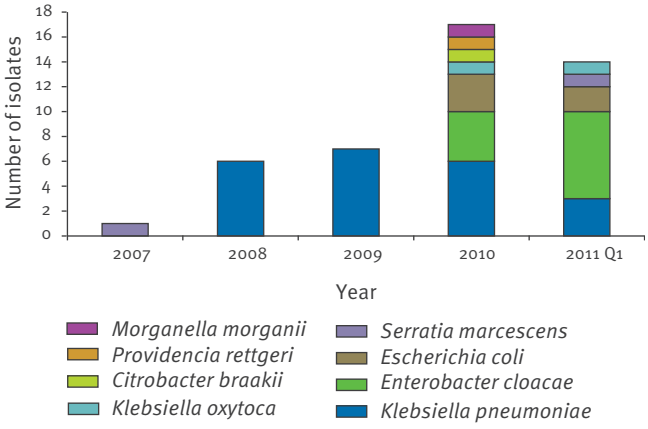
Species and resistance genes distribution of carbapenemase-producing *Enterobacteriaceae* isolates, National Reference Centre, Belgium, January 2007–April 2011 (n=44)



KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Delhi metallo-beta-lactamase; OXA: oxacillinase; VIM: Verona integron-encoded metallo-beta-lactamase.

Figure 4

Evolution of the species distribution of carbapenemase-producing *Enterobacteriaceae* isolates, National Reference Centre, Belgium, January 2007–April 2011 (n=44)



Q1: first quarter.

and one E. coli). In one patient one VIM-1-producing *Providencia rettgeri*, one VIM-1-positive *Citrobacter freundii* and one KPC-2-producing *K. pneumoniae* were detected simultaneously. Retrospective review of clinical data charts showed that 25 patients were considered colonised by CPE isolates while 14 patients were considered to be infected. The infections were urinary tract infections (n=7), lower respiratory tract infections (n=2), soft-tissue and skin infections (n=2) and blood stream infections (n=3).

Discussion

Our data clearly demonstrate a significant increase of CNSE isolates referred to the NRC and of CPE isolates detected in Belgian hospitals particularly since 2010. While for the period from 2007 to 2009 almost all carbapenemase-producing isolates were *K. pneumoniae*, eight different *Enterobacteriaceae* species were detected from 2010 onwards. Of note, OXA-48 CPE isolates emerged since 2010 and have now become the predominant carbapenemase in CPE isolates causing nosocomial outbreaks at two different hospitals in Belgium during the first quarter of 2011 (unpublished data). Vaux et al. reported similar trends of emergence of CPE isolates in France since 2010, and OXA-48 carbapenemase represented the majority of the resistance mechanism in CPE isolates in France as well [9].

In Belgium, no resistance survey of *Enterobacteriaceae* isolates with decreased susceptibility to carbapenems has been conducted to date and thus no data are available regarding the true prevalence of CNSE isolates. It is possible that a certain number of CNSE and CPE isolates were missed, especially those producing OXA-48 and lacking expanded-spectrum cephalosporin-hydrolysing beta-lactamase [10].

It is presently unclear whether the apparent increase in the isolation of CNSE and CPE is due to the spreading potential of these microorganisms or rather reflects the application of more effective detection methods by clinical laboratories. The decreasing number of total isolates referred to NRC from 2007 to 2010 cannot be explained, but together with the significantly increasing number of CNSE isolates referred, could result in the relative increase of CNSE or CPE. Since that the isolates were referred on a voluntary basis, a better knowledge or application of detection methods for ESBL-carrying or AmpC cephalosporinase-producing strains by local laboratories could result in a decreased need for confirmation and referral of these isolates to the NRC. It is possible as well that the adherence to the EUCAST breakpoints or to the revised CLSI interpretative criteria for carbapenems published in June 2010 [11] could have improved the detection of CNSE and of CPE isolates by clinical laboratories. The increased sensitivity of detection, together with a better awareness of clinical microbiologists, might in part explain the higher number of CNSE isolates referred to the NRC since 2010. Nevertheless, the diversification of both the species and the carbapenemase-encoding genes detected in CPE isolates is a matter of concern. Moreover, the significant proportion of non-travel associated CPE-positive patients suggests the local establishment and spread of carbapenemase-producing enterobacteria in Belgium. These data clearly underline the importance of a systematic and coordinated national surveillance programme for rapid detection and reporting of CPE isolates in order to prevent their further dissemination. Finally, our experiences suggest that at a European level, the implementation of harmonised and accurate detection methods should be encouraged and that specific guidelines of management including infection control measures are urgently needed in order to limit the spread of these multidrug-resistant organisms.

References

1. Cornaglia G, Rossolini GM. The emerging threat of acquired carbapenemases in Gram-negative bacteria. Clin Microbiol Infect. 2010;16(2):99-101.
2. Queenan AM, Bush K. Carbapenemases: the versatile -lactamases. Clin Microbiol Rev. 2007;20(3):440-58.
3. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010;10(9):597-602.
4. Cuzon G, Naas T, Bogaerts P, Glupczynski Y, Huang TD, Nordmann P. Plasmid-encoded carbapenem-hydrolyzing beta-lactamase OXA-48 in an imipenem-susceptible Klebsiella pneumoniae strain from Belgium. Antimicrob Agents Chemother. 2008;52(9):3463-4.
5. Bogaerts P, Montesinos I, Rodriguez-Villalobos H, Blairon L, Deplano A, Glupczynski Y. Emergence of clonally related Klebsiella pneumoniae isolates of sequence type 258 producing KPC-2 carbapenemase in Belgium. J Antimicrob Chemother. 2010;65(2):361-2.
6. Bogaerts P, Bouchahrouf W, de Castro RR, Deplano A, Berhin C, Piérard D, et al. Emergence of NDM-1-producing Enterobacteriaceae 1 in Belgium. Antimicrob Agents Chemother. 2011;55(6):3036-8.
7. Glupczynski Y, Rodriguez-Villalobos H, Bogaerts P, Blairon L, Gérard M, Aoun M, et al. Emergence of pan-resistant VIM-1 producing Klebsiella pneumoniae in Belgian hospitals. Abstract presented at the 19th European Congress of Clinical Microbiology and Infectious Diseases, Helsinki, Finland. 2009. Abstract no P1692.
8. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. Twentieth Informational Supplement M100-S21. Wayne, Pennsylvania: CLSI; 2011.
9. Vaux S, Carbonne A, Thiolet JM, Jarlier V, Coignard B, RAISIN and Expert Laboratories Groups. Emergence of carbapenemase-producing Enterobacteriaceae in France, 2004 to 2011. Euro Surveill. 2011;16(22):pii=19880. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19880
10. Carrer A, Fortineau N, Nordmann P. Use of ChromID extended-spectrum beta-lactamase medium for detecting carbapenemase-producing Enterobacteriaceae. J Clin Microbiol. 2010;48(5):1913-4.
11. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. Twentieth Informational Supplement M100-S20-June Update. Wayne, Pennsylvania: CLSI; 2010. Available from: http://www.clsi.org/source/orders/free/m100-s20-u.pdf

Surveillance trends of the 2009 influenza A(H1N1) pandemic in Europe

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Citation style for this article:
Amato-Gauci A, Zucs P, Snacken R, Ciancio B, Lopez V, Broberg E, Penttinen P, Nicoll A, on behalf of the European Influenza Surveillance Network (EISN). Surveillance trends of the 2009 influenza A(H1N1) pandemic in Europe.
Euro Surveill. 2011;16(26):pii=19903. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19903

Article published on 30 June 2011

We describe the epidemiology and virology of the official length of the 2009 pandemic (68 weeks from April 2009 to August 2010) in the 27 European Union Member States plus Norway and Iceland. The main trends are derived from published literature as well as the analysis and interpretation of data provided to the European Centre for Disease Prevention and Control (ECDC) through the European Influenza Surveillance Network (EISN) and data collected by the ECDC itself. The 2009 influenza A(H1N1) pandemic started in Europe around week 16 of 2009 (although the World Health Organization (WHO) declared only in week 18). It progressed into an initial spring/summer wave of transmission that occurred in most countries, but was striking only in a few, notably the United Kingdom. During the summer, transmission briefly subsided but then escalated again in early autumn, just after the re-opening of the schools. This wave affected all countries, and was brief but intense in most, lasting about 14 weeks. It was accompanied by a similar but slightly delayed wave of hospitalisations and deaths. By the time the WHO declared the pandemic officially over in August 2010 (week 32), Europe had experienced transmission at low level for about 34 weeks.

Objectives

This review article provides a broad epidemiological overview of the entire official period of 68 weeks of the 2009 pandemic, from week 18 (end April) 2009 to week 32 (mid-August) 2010, in the 27 European Union (EU) Member States plus Norway and Iceland (in the following called EU+2). It is linked to a more extensive document developed with the help of national surveillance experts that provides further background on influenza epidemics and pandemics, notably their variability and unpredictability [1]. The review also identifies some initial lessons learnt, especially relating to surveillance needs in a pandemic, as discussed and agreed at the annual expert meeting of the European Influenza Surveillance Network (EISN) held in Sofia, Bulgaria, in June 2010 [2].

Data collection

The main surveillance trends and information presented here are derived from epidemiological analyses of the primary care and virological data (Table 1) reported to the European Centre for Disease Prevention and Control (ECDC)'s European Surveillance System (TESSy) by the European Influenza Surveillance Network (EISN; for more information on this network see: http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/home.aspx). Building on the existing reporting systems, new surveillance mechanisms were developed to meet additional needs for the pandemic, especially of capturing data on severe and fatal cases of influenza (Table 1). These were collected and reported in one of the Weekly Influenza Surveillance Overviews (WISO) published by ECDC during the pandemic [3,4].

Concurrently, epidemic intelligence [5] and targeted science watch methods (experts scan scientific journals and grey literature and summarise significant publications with public health relevance, significant developments or upcoming meetings) were employed to determine, as early as possible, the important parameters needed for risk assessment, adjusting projections and informing counter-measures in areas where the routine EU surveillance systems are less informative.

Early pandemic

Following its emergence in Mexico in March 2009 [6], the pandemic influenza A(H1N1)2009 virus appears to have started circulating in Europe around week 16 of 2009, initially in travellers returning from Mexico, or their direct contacts (Figures 1 and 2). Early on it was clear that this virus met the previously agreed criteria for a pandemic strain (see summary at: http://www.ecdc.europa.eu/en/healthtopics/H1N1/Documents/100503_health_topics_pandemic_definition_of_a_pandemic.pdf). In response to the threat, EU/EEA countries started to submit detailed case-based reports to the ECDC in May 2009, using an ad hoc database hosted on the secure Early Warning and Response (EWRS) platform. The earliest validated date

of onset of a European case was 19 April 2009 (week 16). When country representatives agreed in week 39 that central collection of case-based data was no longer justified, the database contained 11,275 individual records (11,207 of which were laboratory-confirmed) submitted by 28 countries. A detailed analysis of these first cases is available elsewhere [7].

The surveillance data, supplemented by the ECDC epidemic intelligence and targeted science watch activities, helped to quantify the main pandemic parameters resulting in a 'dynamic scientific risk assessment that was updated 10 times in 2009 as more information became available [8]. For example, the reproductive number R_0 for the infection was estimated with 95% confidence intervals between 1.1 and 1.4 [9] (95% confidence interval) [9], a serial interval between 2.2 and 2.3 days [10], a mean generation time between 2.5 and 3 days [9] and a mean incubation period of 1.5 to 2 days. These figures are consistent with those found for previously circulating influenza strains [9].

There was a paucity of reliable data early on but even so, organisations such as the ECDC and WHO agreed that this was not a severe pandemic. For example, the ECDC interim risk assessment issued on 12 June 2009 [8] concluded:

"The current ECDC threat assessment for Europe is that the new influenza A(H1N1)v virus will continue to spread. Though it seems that most of those infected in the US and in Europe experience a mild and self-limiting infection, this picture is still unclear as there has not been enough transmission to judge the effects, especially in those more at risk."

The pandemic waves spring/summer and autumn/winter

Following the detection of the initial cases imported from North America into Europe, there was a spring and summer wave of transmission in Europe which affected most countries. Figure 1 shows the weekly percentage of influenza-like illness (ILI) notifications over the total number of reports throughout the whole reporting period, accumulated for all reporting countries. However, the wave and burden on the health services was only striking in very few European countries, especially the United Kingdom (UK) [11,12] and to a lesser extent Spain [13].Transmission subsided as the summer progressed, in temporal association with the closure of schools [12,14]. However, transmission accelerated again following the re-opening of the schools, this time affecting all countries, as an early autumn/winter wave started around week 43 of 2009 (Figures 1 and 3) and progressed from west to east across the EU. The modal peak week for the 24 countries consistently reporting their sentinel ILI consultations in the season 2009/10 was week 48, 2009 (six countries), as opposed to week 4, 2009 (seven countries) for the previous season 2008/09. In most countries, the autumn/winter wave of disease was short and intense, lasting about 14 weeks and resembling the epidemic curve seen in the 1957 pandemic in Europe [15].

A similar wave of hospitalisations and deaths followed soon after (Figure 4), although these data on deaths and especially hospitalisation are less readily available because surveillance of severe disease attributable to influenza is not routine in most countries. For the whole pandemic period of 68 weeks (week 18, 2009 to week 35, 2010), the EISN experts reported 925,861 cases of ILI (25 reporting countries) and 7,202,014 cases of acute respiratory infections (ARI) (16 reporting countries) attending their clinics. This is just a small proportion of the true number of cases in the

Table 1

Data collected for the EU+2 Weekly Influenza Surveillance Overview

Type of data	Includes
Sentinel syndromic surveillance of influenza-like illness (ILI)/acute respiratory infection (ARI)	Subjective assessment of intensity and degree of geographic spread as well as reporting of aggregated cases
Virological surveillance	Laboratory data of the results of tests requested by sentinel physicians, and of tests done on non-sentinel respiratory specimens collected, describing virus type and subtype, the predominant strains, their antigenic and genetic characteristics and antiviral susceptibility
Hospital sentinel surveillance of severe acute respiratory infection (SARI)	Case-based data of the more severe forms of acute respiratory infection including influenza and other causes
Influenza deaths	Both case-based deaths resulting from SARI and aggregated deaths reported by the countries[a]
Qualitative reporting[b]	Planned to become the principle routine data to be collected should surveillance systems become overwhelmed and unable to generate the other data: includes subjective assessment of geographic spread, intensity, trend (as for ILI and ARI above), and impact

EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.

[a] This was complemented by active monitoring of official national public health websites for announcements of deaths (see Figure 4).

[b] It was not necessary to activate this element.

Source: [3].

Figure 1

Percentage of weekly reported sentinel ILI caseload of the overall reports, cumulated for 25 EU+2 countries, week 40, 2008–week 34, 2010

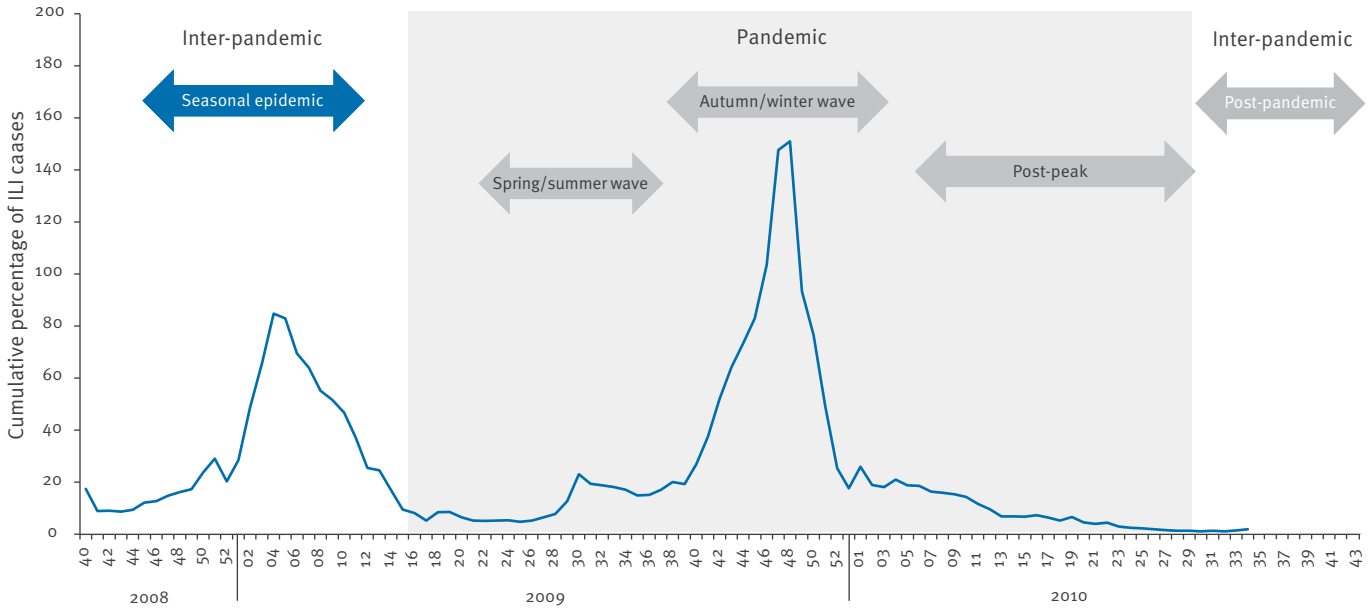
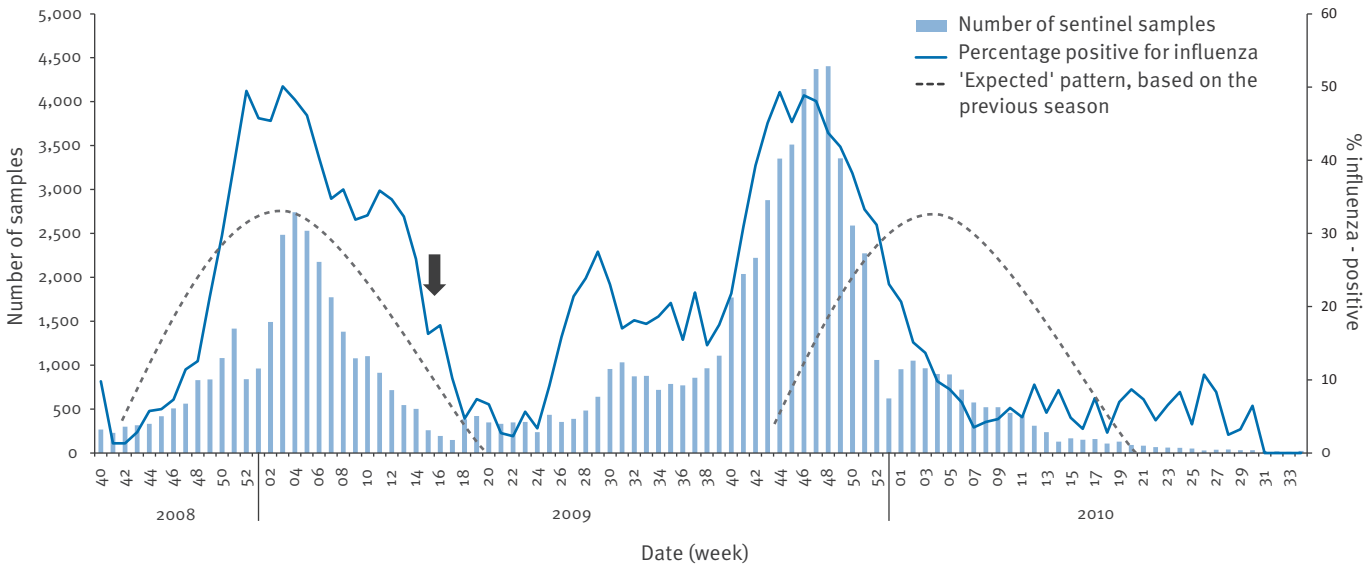


Figure 2

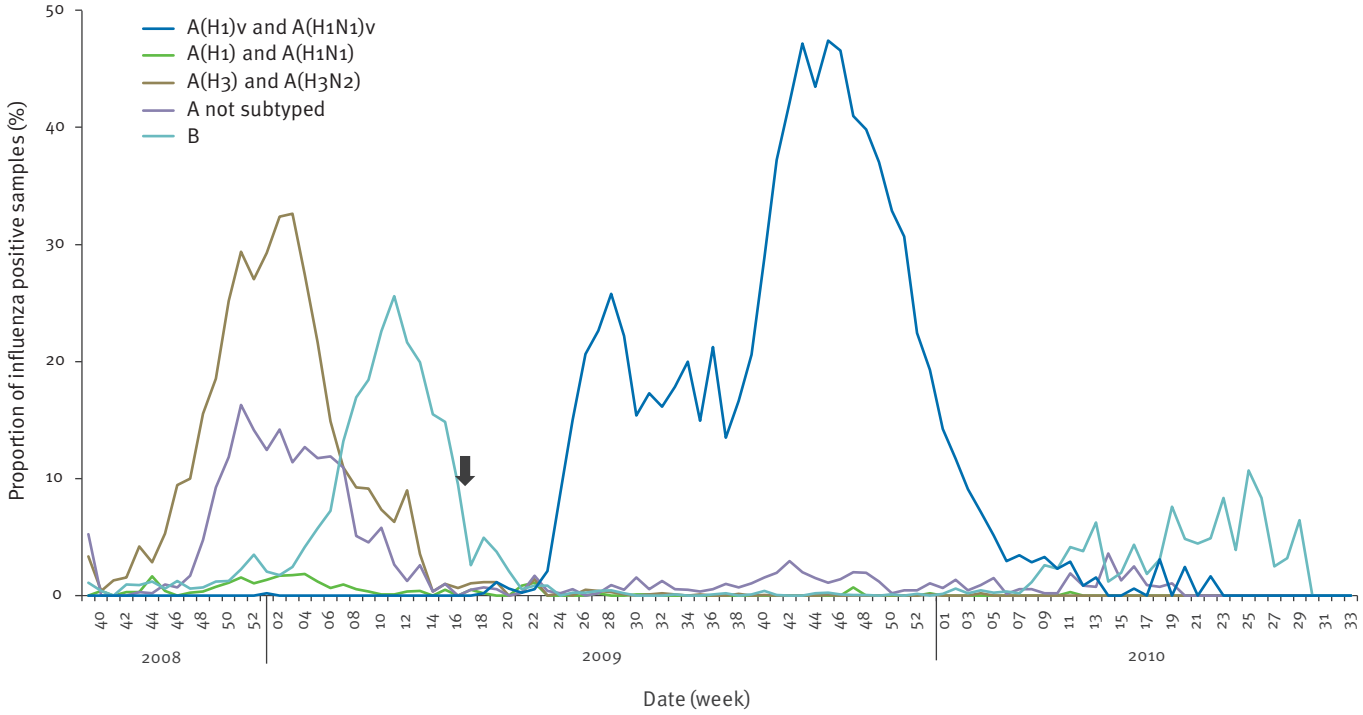
Distribution of the number of sentinel samples submitted and the percentage found positive for influenza, 28 EU+2 countries, seasons 2008/09–2009/10



EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.
The arrow denotes the probable start of the pandemic in Europe.
Source: European Influenza Surveillance Network (EISN) reports.
Data reported by 28 of 27 plus 2 countries.

Figure 3

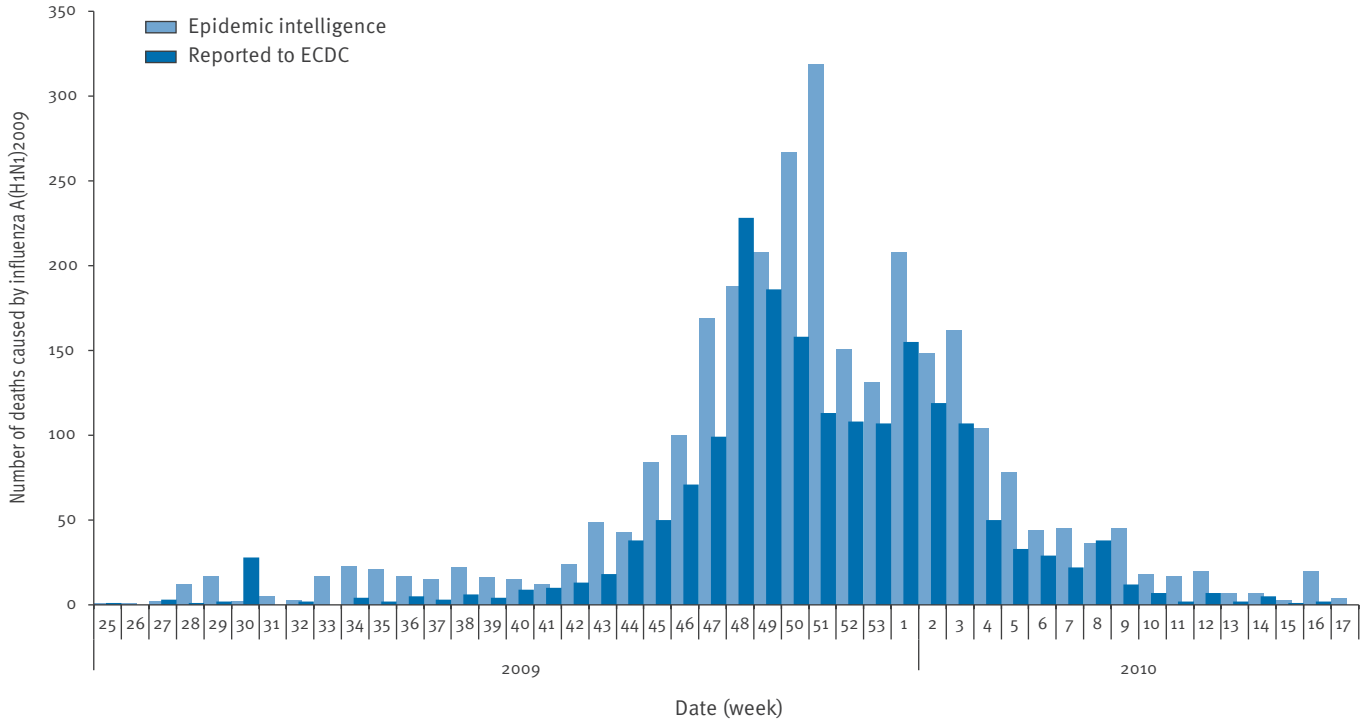
Distribution of virus types and subtypes detected from sentinel samples, seasons 2008/09 and 2009/10 in 28 EU+2 countries



EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.
The arrow denotes the probable start of the pandemic in Europe.
Source: European Influenza Surveillance Network (EISN) reports.

Figure 4

Officially announced and reported deaths due to pandemic influenza A(H1N1)2009 in the EU+2, by week of report, season 2009/10



ECDC: European Centre for Disease Prevention and Control; EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.
Source: European Influenza Surveillance Network (EISN) reports and ECDC epidemic intelligence data collected from official national websites.

general population as the network data are collected from sentinel sites and not representative of the general population. Overall rates for the EU/EEA cannot be estimated due to the different denominators used in the different countries.

The sentinel ILI and ARI networks also provide data on a limited number of age groups, but not on sex. All countries showed a consistent age distribution with children under the age of 14 years affected most. The ratio of the four age groups (under 4 years, 5–14 years, 15–64 years and over 65 years) was: 8:5:2:1.

These figures represent only a small proportion of the true attack rate, i.e. those who felt unwell enough to attend a primary care practice that happened to be part of the sentinel reporting system for that country [16], and should only be used to compare with the figures and proportions of similar data collected in a normal influenza season. The proportion of those experiencing illness or infection differed considerably from what was seen outside the pandemic [17] and this is described in more detail elsewhere [1].

There was considerable geographic heterogeneity in the amount of transmission, within Europe and even within countries, especially in the spring/summer wave. While there was transmission in most countries, only Spain and the UK recorded a prevalence of infection high enough to produce substantial numbers of severely affected people [11-13]. Overall attack rates estimated by serology were higher than for seasonal influenza, although the pandemic virus affected fewer older persons (65 years and older), who had been exposed to a similar virus circulating in the 1950s and before [16,18]. There is clear evidence that there were many mild or asymptomatic cases in this pandemic, but whether they were more common than in the previously recorded pandemics is impossible to determine because it is only in this pandemic that there has been enough accurate seroepidemiology which combined with case reporting allowed such estimates to be made [7,12,17]. Attack rates were highest in young people, with country reports revealing that the highest rates of infection occurred in school-age children [16,18] and some hospital paediatric services and intensive care services were especially stressed [19]. There was also pressure on primary care services in some areas because attack rates exceeded what was normally seen with seasonal influenza. No countries reported any pressure on critical services outside the healthcare sector, which is consistent with the WHO description of the pandemic: *this pandemic, at least in its early days, will be of moderate severity* (statement to the press by WHO Director-General Dr Margaret Chan, 11 June 2009)

Virological surveillance

The pandemic influenza A(H1N1)2009 virus displaced the previously dominant seasonal influenza A virus strains in Europe, although late in both seasons 2008/09 and 2009/10, influenza B viruses were still prevalent enough to cause significant disease (Figures 2 and 3). From week 21, 2009 to week 16, 2010, 60,827 clinical samples were submitted by the sentinel practices reporting to the EISN, of which 25,304 (41.6%) tested positive for influenza virus, almost all for the 2009 pandemic virus.

All pandemic influenza A(H1N1)2009 viruses isolated from samples submitted by the EISN sentinel practices for testing, were found to be resistant to antiviral drugs in the adamantane class, but very few of these samples (2.5%) were found to be resistant to oseltamivir (Table 2). All oseltamivir-resistant strains were accounted for by the presence of the H275Y mutation. Most of these mutations were observed following treatment of immunocompromised patients, and in Europe, resistant virus was only rarely transmitted

Table 2

Antiviral resistance by influenza virus type and subtype in samples collected by primary care sentinel networks in the EU+2, week 40, 2008–week 18, 2010 (n=1,454)

Influenza virus type and subtype	Resistance to neuraminidase inhibitors								Resistance to M2 inhibitors			
	Oseltamivir				Zanamivir							
	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)
	Week 40, 2008–week 39, 2009		Week 40, 2009–week 18, 2010		Week 40, 2008–week 39, 2009		Week 40, 2009–week 18, 2010		Week 40, 2008–week 39, 2009		Week 40, 2009–week 18, 2010	
A(H3N2)	653	0	0	0	612	0	0	0	644	644 (100)	0	0
A(H1N1)	260	256 (98)	0	0	260	0	0	0	124	1 (1)	0	0
A(H1N1)v	424	0	1,453	37 (2.5%)	415	0	1,447	0	56	56 (100)	205	205(100%)
B	117	0	0	0	113	0	0	0	NA	NA	NA	NA

EU+2: the 27 European Union (EU) Member States plus Norway and Iceland; NA: not applicable, as M2 inhibitors do not act against influenza B viruses.

Source: European Influenza Surveillance Network (EISN) and Influenza Community Network of Reference Laboratories (CNRL) data in the European Centre for Disease Prevention and Control (ECDC)/European Surveillance System (TESSy).

from one human to another unlike the seasonal influenza A(H1N1) virus with the same mutation, which is readily transmitted [20]. Although the viruses circulating during the pandemic were not identical, there is little evidence of significant drift or the emergence of dominant new variants to date [21]. A previously observed influenza A(H1N1)2009 variant with a D222G mutation has been associated with more severe disease, but it is still unclear whether this is due to a higher pathogenicity or a tropism for cells in the lower respiratory tract [21].

Mortality, severe disease and risk groups

In total, 2,900 pandemic deaths were announced by Member States in the first 12 months (Figure 4). This is probably only a proportion of the true burden of deaths due to the pandemic, but it remains unclear what that proportion is for Europe overall or for individual countries [22,23]. Pooling data from eight pilot countries, the EU-funded project European Monitoring of Excess Mortality for Public Health Action (EuroMOMO) detected excess all-cause mortality only in the 5-14 year-olds in the period between weeks 27 and 51 of 2009, compared with mortality in the previous three years. This estimate is probably conservative due to delays in reporting [24].

Before the autumn/winter wave of the pandemic, the EISN attempted to establish hospital-based sentinel surveillance of severe acute respiratory infection (SARI) cases, although this met with limited success [25]. During the autumn/winter wave, i.e. from week 36, 2009 to week 20, 2010, 11,904 SARI cases and 586 SARI-related fatalities were reported to ECDC by eleven EU countries (Austria, Belgium, Cyprus, Finland, France, Ireland, Malta, the Netherlands, Romania, Slovakia and the United Kingdom, France only reported pandemic influenza A(H1N1)2009 cases admitted to intensive care units) [1]. Information on those with severe disease can be ascertained partially from this data and also from focused studies in EU Member States [13,26].

Building on these findings, the EU Health Security Committee defined pregnant women, those over six months of age with chronic ill health and healthcare workers as the primary risk groups that should be offered immunisation against pandemic influenza [27,28]

Differences between the pandemic and seasonal influenza

The pandemic differed from the preceding influenza season in a number of ways (Table 3). Most notable was the difference in the age of those most severely affected. Previously, were concentrated persons aged 65 years and older accounted for 90% of deaths from seasonal influenza [29,30]. In the 2009 pandemic, nearly 80% of the deaths reported to ECDC occurred in persons under 65 years [25], probably because a sizable proportion of older adults were protected by prior exposure to a similar influenza virus that had been circulating before the mid-1950s [16,18]. However, not all those older than 64 years were immune, and those without immunity who were infected had the highest case fatality rate of all age groups [25,31]. While the majority of deaths occurred in persons with chronic medical conditions, especially respiratory and neurological conditions, between 20% and 30% of the deaths reported in studies occurred in previously healthy individuals [31]. A considerable proportion of deaths were caused by acute respiratory distress syndrome (ARDS, mortality rate in 612 ARDS patients: 24.5% [25]), an extremely rare condition that is difficult to treat and that requires high dependency support for several weeks [32,33] One of the reasons may have been that the new virus has shown a tropism for receptors found in the alveolar epithelium of the lungs [33].

Serological data

To date, there has been only limited data from serological surveys. These support the surveillance data indicating high infection rates, but they also suggest higher than expected levels of asymptomatic infection [16,39]. While the serological findings do not allow reliable predictions for the influenza season 2010/11, the experience of the temperate countries in the southern hemisphere during the European summer period of 2010 would probably provide some valuable clues.

Conclusions

The pandemic influenza A(H1N1) 2009 virus started circulating in Europe around week 16 of 2009 (although the declared phase 5 only in week 18). It progressed into an initial spring/summer wave of transmission which occurred in most countries, but was striking only in a few, notably the UK. As the summer advanced, transmission briefly subsided, but then escalated again in the early autumn, just after the re-opening of the schools, this time affecting all countries. This autumn/winter wave was seen to progress from west to east across the continent. In most countries, this second wave of infection was brief but intense, lasting about 14 weeks, and was accompanied by a similar but slightly delayed wave of hospitalisations and deaths. By the time the WHO declared the pandemic officially over in August 2010 (week 32, 2010), the EU+2 had experienced transmission at a very low level for about 34 weeks.

An excess of all-cause deaths in school-age children was observed. Even though this was an influenza virus never seen previously, prior exposure to an antigenically similar influenza virus circulating before the mid 1950s meant that many older people in Europe exhibited some immunity. Although many older people appeared to be protected, persons over the age of 65 years still had the highest case fatality rate of any age group.

The pandemic virus displaced the previously dominant seasonal influenza A viruses in Europe, although influenza B viruses continued to appear at a low level late in the seasons. Few pandemic viruses were resistant

to oseltamivir, and of these, very few seemed capable of human-to-human transmission. Although the pandemic viruses are not identical, there is little evidence of significant drift or the emergence of dominant new variants to date. One variant, influenza A(H1N1)2009-D222G has been associated with more severe disease, but a causative relationship has yet to be established.

Serological data suggest that there were a higher proportion of mild and asymptomatic infections than in the preceding influenza seasons. Nevertheless, transmission rates were higher than for seasonal infection and there were sufficient amounts of severe disease and notably cases of ARDS, which put a strain on intensive care services in many places. Young children (under five years of age) experienced the highest rates of disease, while country reports and serology indicate that the highest rates of infection (including asymptomatic) were in children at school age. These high rates of illness presented a particular burden for primary services, hospital paediatric services and especially intensive care in some areas.

Pandemic planning will now need to be revisited as the occurrence of this pandemic does not exclude the possibility of an influenza A(H5) or (H7) pandemic emerging in the future. The next generation of plans need to include more flexibility for reacting to different severity of disease and different combinations of epidemiological parameters. In this context it would be useful to reach

Table 3

Comparing influenza seasons 2000/01–2008/09 with 2009 pandemic influenza

	Seasonal influenza 2000/01– 2008/09	2009 pandemic influenza
Circulating influenza viruses	Two influenza A viruses: A(H1N1) and A(H3N2), and some influenza B viruses; the mix varies with the season	Almost exclusively the pandemic influenza A(H1N1)2009, a few influenza A(H3N2) viruses and increasing numbers of influenza B viruses towards the end of the season
When waves occurred	In season, in recent years most often starting after Christmas	Started out of season with a spring/summer wave, then an early autumn/winter wave in Europe
Levels of transmission	Variable from year to year, with local heterogeneity, but estimated to be 5–15% annually	Hard to estimate, local heterogeneity, estimated to be over 15% through serological studies in New Zealand [34] and in the United Kingdom [16]
Setting for transmission	Probably any setting where people come together	Schools considered especially important, along with household transmission
Experiencing severe disease	Those in clinical risk groups and older people	Young children, pregnant women and those in clinical risk groups; about 30% with severe disease were outside risk groups; many born before the mid-1950s were immune, but people in this age group who were not immune experienced severe disease outcomes [31]
Premature deaths	Around 90% considered to have occurred in people 65 years or older	In confirmed reported deaths, around 80% were under 65 years of age Increase in all-cause deaths in children detected across eight EU countries by EuroMOMO system[24]
Mortality and years of potential life lost	Few confirmed deaths reported each year in official statistics; estimates of up to 40,000 in a bad year using statistical methods	Substantial numbers of confirmed deaths announced by EU+2 Member States (n=2,900, Figure 4) but recognised to be an underestimate Only estimated in one EU Member State (the Netherlands, 35 disability-adjusted life years per 100,000 population) [35], but estimated in the United States with considerably higher levels [36]
Acute respiratory distress syndrome	Extremely rare	Uncommon, but recorded in many countries, even in young fit adults; partially explained by the tropism of the pandemic virus for epithelial receptors that predominate in the alveoli of the lung, while the previous seasonal viruses bind best to receptors found predominately in the upper airways [33]
Pathological findings	Viral pneumonia rare, but secondary bacterial infections more common in fatal cases	Fatal viral pneumonias relatively common with alveolar lining cells, including type I and type II pneumocytes the primarily infected cells; more than 25% of fatalities also involved bacterial infections [33,37]
Antiviral resistance	Common and transmissible oseltamivir resistance in influenza A(H1N1) emerged in season 2007/08 [38]	Observed most often following antiviral treatment of susceptible individuals; however, as of July 2010, only transmitted very rarely under certain circumstances [33]; resistant seasonal influenza A(H1N1) seemingly displaced by the new influenza, at least for now

ECDC: European Centre for Disease Prevention and Control; EU: European Union; EU+2: the 27 European Union (EU) Member States plus Norway and Iceland; EuroMOMO: project European Monitoring of Excess Mortality for Public Health Action; WHO: World Health Organization.

This table lists ten characteristics in which the new pandemic influenza differs from the 'old' seasonal influenza, especially as they appeared in more recent years (seasons 2000/01–2008/09).

Source: http://ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f%2D77d4%2D4ad8%2Db6d6%2Dbf0f23083f30&ID=911&RootFolder=%2Fen%2Factivities%2Fsciadvice%2FLists%2FECDC%20Reviews

a European consensus on describing and assessing the severity of a pandemic, and matching the response with the different scales and characteristics. These plans must also provide for the consolidation and sustainability of the influenza surveillance systems that were introduced to meet the demands of the 2009 pandemic, in particular SARI, attributable mortality, and seroepidemiological surveillance. This surveillance work needs to be prioritised, given the right level of resources and allowed to develop and be tested during the interpandemic period so that the systems will be more resilient and effective in a future public health crisis.

At an early stage, it was appreciated that this pandemic was much less severe than what many European countries had feared and prepared for. This was highlighted in the first ECDC Risk Assessments (available at: http://ecdc.europa.eu/en/healthtopics/H1N1/risk_threat_assessment/Pages/risk_threat_assessment.aspx), WHO reports and briefings given by ECDC to national and European authorities. With low rates of absenteeism, there was also little impact on services outside the health sector. In conclusion this pandemic was a mild one for Europe [40], testing the flexibility of existing preparedness plans in many countries. The greatest challenge during this pandemic was in the area of risk communication, as both the professionals and the general population expected something more severe [41].

The pandemic occurred at a time when diagnostic tests could be made available quickly, as well as preventive pharmaceutical countermeasures (antiviral drugs for a virus with little resistance to the neuraminidase inhibitors but almost complete resistance to the older adamantanes) and when appropriate vaccines were developed and made available faster than ever before. The occurrence of cases of ARDS when many intensive care units were already busy put particular pressure on the system without the ability to redeploy hospital staff internally, even though the rest of the hospitals were not that stressed [33]. The rapidly produced pandemic vaccines showed such a good immunological response that several formulations only required a single dose in adults [42]. They have also proved to be effective and relatively safe [42], although post-marketing surveillance still needs to be maintained to determine exactly how safe they are and to investigate initial signals of adverse events following immunisation (AEFIs) [43]. There were still delays in the production of vaccines, so that even countries with advance purchase agreements received too little vaccine too late to have any real impact at the population level. However, the high vaccine efficacy and targeting of risk groups may have saved lives of European citizens. Where vaccines were made available, they were greeted with varying degrees of enthusiasm among health professionals. That these vaccines were not widely accepted was partly due to the difficulty in transmitting the complex risk communication message. On the one hand the chance of severe disease following infection was very low unless the individual belonged to a risk group (young children, people with chronic ill health and pregnant women [33]). On the other hand, there was a small but real risk of severe disease and death from the pandemic in all healthy persons. The challenge of communicating this risk was considerable.

Limitations of the EU+2 data

The data used here were subject to limitations and the results should be interpreted with a degree of caution. The reported ILI or ARI surveillance data were not comparable between countries as there was variability in the data sources, size and representativeness of the networks. The ILI/ARI epidemic curves were also distorted because several countries, at different points in time, actively recommended that anyone with influenza-like symptoms should stay at home and not approach their primary care provider, (contrary to what the patients would do in a normal influenza season), thus excluding them being reported. In addition, there are indications from specialist studies that the usual patterns of seeking care were distorted during the pandemic and that this varied over time as the perception of risk changed [17].

The virological data are derived from samples sent for laboratory testing and confirmation. They represent only a selected subset of the cases, usually the more severely affected seeking medical help. The sentinel samples were representative of patients attending general practices, while the non-sentinel samples derive from a varying mix of general practitioners' diagnoses not included in the sentinel system and more seriously affected cases that were admitted to hospital. Therefore the non-sentinel data were a mixture of mild and severe cases, which can differ by country. One important aspect of laboratory- based surveillance that was missing at the European level was routine seroprevalence monitoring. Although a few countries carried out local studies that provided valuable information [16,18,44,45], this work was not carried out in a standardised and comparable manner early on in the pandemic. Also, the results were made available too late to be of use and it was not clear if the information they provided could be extrapolated to other countries.

The systems for collecting data on the more severe cases (SARI) or deaths were introduced in response to the pandemic, after the pandemic had already reached Europe. This is not the optimal time to introduce a new system, as the countries' surveillance systems had to adapt or introduce new processes at a time when their resources were already stretched. There seem to be difficulties in capturing data on SARI cases in many European hospitals because it is not a diagnosis recognised by clinicians as it encompasses young children with bronchiolitis, older people with pneumonia and ARDS. Some countries found it easier to collect data on people hospitalised with an influenza diagnosis. Also, there was variability in what different sites reported as SARI as well as in providing reliable estimates of the denominators and the representativeness of the data, shedding doubt on the estimated rates.

Not only reported cases were underestimated, but also deaths due to the 2009 pandemic influenza, especially in the elderly where influenza is known to be frequently masked by other conditions as the underlying cause of death [46]. Presently, only ad hoc studies can attempt to estimate influenza-related mortality more accurately, and while such studies have been done in the United States [47], there have not been any in Europe

New characteristics of the 2009 influenza pandemic

Nevertheless, the EU/EEA surveillance data permit us to conclude on a number of new characteristics of this pandemic (Box), notably the reliance on clinicians to deliver the most powerful countermeasures. Much prominence was given to the doubts expressed by the professionals in some countries on the value of the countermeasures. Moreover, the role of the media in this pandemic was unprecedented and this was not always positive, for example when vaccine opponents and pandemic skeptics were given the same platform as expert opinions.

Lessons learnt for surveillance

The fact that the 2009 influenza A(H1N1) pandemic was less of a threat than what many countries had prepared for, tested the flexibility of existing plans. Nevertheless no country appears to have over-responded, while the systems developed by the European Commission, WHO and ECDC for discussing and sharing information and analyses proved resilient and useful. On balance, the EU+2 managed the response to the pandemic well [49], although this can be further improved. The EISN virological and primary care-based surveillance in particular worked well, and served to augment the data emerging from the ECDC epidemic intelligence and targeted science watch sources. Establishing surveillance in hospitals and sharing analyses from the first affected countries were less successful. It was fortunate that data and analyses were quickly available from North America and the southern hemisphere. Lessons to be learnt include:

- Routine 'severe end' surveillance of hospitalised cases and deaths due to severe respiratory infection should be established in Europe.
- In the future, the process for sharing early analyses from the first affected countries can work better, possibly by increasing the faith of expert colleagues in the confidentiality and security of certain communication systems and the discretion of other experts in the country not to pass on provisional data.
- Much work, including research and development, needs to take place to make seroepidemiology available in real time.

Box

New characteristics about the 2009 pandemic in Europe

- The first pandemic with instant communication so that early impressions (such as the experience in Mexico and the Ukraine) were transmitted ahead of any reasonable or thoughtful analysis;
- The first pandemic that took place within the context of a set of International Health Regulations [48] and global governance, although essentially untried;
- The first pandemic with early diagnostic tests which led to rapid diagnosis but also an early overly strong focus by the media and policymakers on the numbers of infected people;
- The first pandemic with antiviral drugs available which led to an expectation that the pandemic might be containable and the invention of a containment phase by some countries
- The first pandemic in which effective countermeasures (antiviral drugs and vaccines) could be provided by clinicians, which meant the confidence of those doctors and nurses had to be earned and retained;
- The first pandemic in a setting with effective intensive care and thus with a (false) expectation that everyone could be treated and cured;
- The first pandemic which received uncontrolled coverage in blogs that policy makers needed to monitor closely.

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References

1. European Centre for Disease Prevention and Control (ECDC). The 2009 A(H1N1) pandemic in Europe. Stockholm: ECDC; 2010. Available from: http://ecdc.europa.eu/en/publications/Publications/101108_SPR_pandemic_experience.pdf
2. European Centre for Disease Prevention and Control (ECDC). Meeting report. Annual meeting of the European Influenza Surveillance Network. Sofia, 1–3 June 2010. Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/1101_MER_EISN_2010.pdf
3. European Centre for Disease Prevention and Control (ECDC). Technical document. Overview of surveillance of influenza 2009/2010 in the EU/EEA. Stockholm: ECDC; 2009. Available from: http://ecdc.europa.eu/en/publications/Publications/0909_TED_Overview_of_Surveillance_of_Influenza_2009-2010_in_EU-EEA.pdf
4. European Centre for Disease Prevention and Control (ECDC). Meeting report. Surveillance and studies in a pandemic: Fourth meeting of the SSiaP working group. Stockholm, July 2009. Stockholm: ECDC; 2009. Available from: http://ecdc.europa.eu/en/publications/Publications/0908_MER_Surveillance_and_Studies_in_a_Pandemic_Meeting_Report.pdf
5. Kaiser R, Coulombier D. Different approaches to gathering epidemic intelligence in Europe. Euro Surveill. 2006;11(17):pii=2948. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?PublicationType=W&Volume=11&Issue=17&OrderNumber=1
6. Centers for Disease Control and Prevention (CDC).Outbreak of swine-origin influenza A (H1N1) virus infection - Mexico, March-April 2009. MMWR Morb Mortal Wkly Rep. 2009;58(17):467-70.
7. Devaux I, Kreidl P, Penttinen P, Salminen M, Zucs P, Ammon A; et al. Initial surveillance of 2009 influenza A(H1N1) pandemic in the European Union and European Economic Area, April-September 2009. Euro Surveill. 2010;15(49):pii=19740. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19740.
8. European Centre for Disease Prevention and Control (ECDC). ECDC interim risk assessment. Human cases of influenza A(H1N1)v. 12 June 2009. Stockholm: ECDC; 2009. Available from: http://www.ecdc.europa.eu/en/healthtopics/H1N1/Documents/1001_RA_090612.pdf
9. Transmission dynamics and impact of pandemic influenza A (H1N1) 2009 virus. Wkly Epidemiol Rec. 2009;84(46):481-4.
10. White LF, Wallinga J, Finelli L, Reed C, Riley S, Lipsitch M, et al. Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. Influenza Other Respi Viruses. 2009;3(6):267-76.
11. Health Protection Agency (HPA). The role of the Health Protection Agency in the 'containment' phase during the first wave of pandemic influenza in England in 2009. London: HPA; March 2010. Available from: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1274088320581
12. Health Protection Agency (HPA). Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave. v4. 2 December 2009. London: HPA. Available from: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1258560552857
13. Santa-Olalla Peralta P, Cortes-García M, Vicente-Herrero M, Castrillo-Villamandos C, Arias-Bohigas P, Pachon-del Amo I, et al. Risk factors for disease severity among hospitalised patients with 2009 pandemic influenza A (H1N1) in Spain, April – December 2009. Euro Surveill. 2010;15(38):pii=19667. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19667. 2010.
14. Health Protection Agency West Midlands H1N1v Investigation Team. Preliminary descriptive epidemiology of a large school outbreak of influenza A(H1N1)v in the West Midlands, United Kingdom, May 2009. Euro Surveill. 2009;14(27):pii=19264. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19264
15. European Centre for Disease Prevention and Control (ECDC), ECDC forward look risk assessment. Likely scenarios for influenza in 2010 and the 2010/2011 influenza season in Europe and the consequent work priorities. Stockholm: ECDC; March 2010. Available from: http://www.bepast.org/docs/global%20biodefense/2010-3-9_RA_forward_look_influenza_ECDC.pdf
16. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. Lancet. 2010;375(9720):1100-8.
17. Lim MSC, Bermingham A, Edmunds J, Fragaszy E, Harvey G, Johnson A, et al. Flu watch – community burden of influenza during three inter-pandemic influenza seasons and the summer wave of the 2009 H1N1 pandemic in England – implications for interpretation of surveillance data. Presented at the Options for the Control of Influenza VII. Hong Kong SAR, China, 3-7 September 2010.
18. Hardelid P, Andrews NJ, Hoschler K, Stanford E, Baguelin M, Waight PA, et al. Assessment of baseline age-specific antibody prevalence and incidence of infection to novel influenza A/H1N1 2009. Health Technol Assess. 2010;14(55):115-92.
19. Kilander A, Rykkvin R, Dudman SG, Hungnes O. Observed association between the HA1 mutation D222G in the 2009 pandemic influenza A(H1N1) virus and severe clinical outcome, Norway 2009-2010. Euro Surveill. 2010;15(9):pii=19498. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19498
20. Meijer A, Lackenby A, Hay A, Zambon M. Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season. Euro Surveill. 2007;12(4):pii=698. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=698
21. Preliminary review of D222G amino acid substitution in the haemagglutinin of pandemic influenza A(H1N1) 2009 viruses. Wkly epidemiol rec. 2010;85(4):21-2.
22. Gran JM, Iversen B, Hungnes O, Aalen OO. Estimating influenza-related excess mortality and reproduction numbers for seasonal influenza in Norway, 1975-2004. Epidemiol Infect. 2010;138(11):1559-68.
23. Pebody RG, McLean E, Zhao H, Cleary P, Bracebridge S, Foster K, et al. Pandemic Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Euro Surveill. 2010;15(20):pii=19571. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19571
24. Mazick A, Gergonne B, Wuillaume F, Danis K, Vantarakis A, Uphoff H, et al. Higher all-cause mortality in children during autumn 2009 compared with the three previous years: pooled results from eight European countries. Euro Surveill. 2010;15(5):pii=19480. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19480
25. Snacken R. Surveillance of severe ARI, experiences from the first season. Presentation at the annual meeting of the European Influenza Surveillance Network (EISN). Sofia, Bulgaria, 2 June 2010.
26. Nguyen-Van-Tam JS, Openshaw PJ, Hashim A, Gadd EM, Lim WS, Semple MG, et al. Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May-September 2009). Thorax. 2010;65(7):645-51.
27. Nokleby H, Nicoll A. Risk groups and other target groups – preliminary ECDC guidance for developing influenza vaccination recommendations for the season 2010-11. Euro Surveill. 2010;15(12):pii=19525. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19525
28. European Centre for Disease Prevention and Control (ECDC), ECDC interim guidance. Use of specific pandemic influenza vaccines during the H1N1 2009 pandemic. August 2009. Stockholm: ECDC; 2009. Available from: http://ecdc.europa.eu/en/publications/Publications/0908_GUI_Pandemic_Influenza_Vaccines_during_the_H1N1_2009_Pandemic.pdf
29. Nicoll A, Ciancio BC, Tsolova S, Blank PR, Yilmaz C. The scientific basis for offering seasonal influenza immunisation to risk groups in Europe. Euro Surveill. 2008;13(43):pii=19018. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19018
30. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292(11):1333-40.
31. Donaldson LJ, Rutter PD, Ellis BM, Greaves FE, Mytton OT, Pebody RG, et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ. 2009;339:b5213.
32. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1334-49.
33. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw Met al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus Infection. N Engl J Med. 2010;362(18):1708-19.
34. Environmental Science and Research Limited (ESR). Seroprevalence of the 2009 influenza A (H1N1) pandemic in New Zealand. ESR; May 2010. Available from: http://www.moh.govt.nz/moh.nsf/pagesmh/10124/$File/seroprevalence-flu-2009.pdf

35. Wielders CC, van Lier EA, van 't Klooster TM, van Gageldonk-Lafeber AB, van den Wijngaard CC, Haagsma JA, et al. The burden of 2009 pandemic influenza A(H1N1) in the Netherlands. Eur J Public Health. 2010 Dec 22. [Epub ahead of print].

36. Centers for Disease Control and Prevention (CDC). Updated CDC estimates of 2009 H1N1 influenza cases, hospitalizations and deaths in the United States, April 2009 - April 10, 2010. Atlanta: CDC. [Accessed 20 Jun 2010]. Available from: http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm

37. Shieh WJ, Blau DM, Denison AM, Deleon-Carnes M, Adem P, Bhatnagar J, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol. 2010;177(1):166-75.

38. Meijer A, Lackenby A, Hungnes O, Lina B, van-der-Werf S, Schweiger B, et al. Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007-08 season. Emerg Infect Dis. 2009;15(4):552-60.

39. Waalen K, Kilander A, Dudman SG, Krogh GH, Aune T, Hungnes O. High prevalence of antibodies to the 2009 pandemic influenza A(H1N1) virus in the Norwegian population following a major epidemic and a large vaccination campaign in autumn 2009. Euro Surveill. 2010;15(31):pii=19633. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19633

40. Nicoll A, McKee M. Moderate pandemic, not many dead--learning the right lessons in Europe from the 2009 pandemic. Eur J Public Health. 2010;20(5):486-8.

41. Abraham T. The price of poor pandemic communication. BMJ. 2010;340:c2952.

42. European Medicines Agency (EMA). European Medicines Agency reaffirms efficacy and safety of H1N1 pandemic vaccines. London: EMA; 20 November 2009. EMEA/748707/2009. Press Release. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015558.pdf

43. Merecekiene_J. Overview of pandemic A(H1N1) 2009 influenza vaccination in Europe. Preliminary results of survey conducted by VENICE, 2010. Presentation at ESCAIDE 2010, Lisbon, Portugal, 13 November 2010. Available from: http://ecdc.europa.eu/en/ESCAIDE/ESCAIDE%20Presentations%20library/ESCAIDE2010_Late_Breakers_Mereckiene.pdf

44. Ikonen N, Strengell M, Kinnunen L, Österlund P, Pirhonen J, Broman M, et al. High frequency of cross-reacting antibodies against 2009 pandemic influenza A(H1N1) virus among the elderly in Finland. Euro Surveill. 2010;15(5):pii=19478. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19478

45. Seroepidemiological studies of pandemic influenza A(H1N1) 2009 virus. Wkly Epidemiol Rec. 2010;85(24):229-35.

46. World Health Organization (WHO). Comparing deaths from pandemic and seasonal influenza. Pandemic (H1N1) 2009 briefing note 20. 22 December 2009. Available from: http://www.who.int/csr/disease/swineflu/notes/briefing_20091222/en/index.html

47. Reed C, Angulo FJ, Swerdlow DL, Lipsitch M, Meltzer MI, Jernigan D, et al. Estimates of the prevalence of pandemic (H1N1) 2009, United States, April-July 2009. Emerg Infect Dis. 2009;15(12):2004-7.

48. World Health Organization (WHO). International health regulations (2005). 2nd ed. Geneva: WHO; 2008. Available from: http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf

49. Council of the European Union. Council conclusions on Lessons learned from the A/H1N1 pandemic – Health security in the European Union. 3032nd General Affairs Council meeting. Brussels, 13 September 2010. Available from: http://ec.europa.eu/health/preparedness_response/docs/council_lessonsh1n1_en.pdf

Swedish Medical Products Agency publishes report from a case inventory study on Pandemrix vaccination and development of narcolepsy with cataplexy

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Citation style for this article:
Swedish Medical Products Agency publishes report from a case inventory study on Pandemrix vaccination and development of narcolepsy with cataplexy. Euro Surveill. 2011;16(26):pii=19904. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19904

Article published on 30 June 2011

On 30 June 2011 the Medical Products Agency (MPA) in Sweden published the results of a case inventory carried out by the MPA in Sweden during 2009-2010 [1]. The study presents evidence to support a link between having been vaccinated with Pandemrix and narcolepsy in children and adolescents 19 years and younger.

The case inventory study was initiated by the MPA following a large number of reports of narcolepsy among children and teenagers. The study has gathered information on severe narcolepsy cases with cataplexy (sudden and transient episode of loss of muscle tone, often triggered by emotions) from all relevant clinical departments and sleep laboratories on all suspected and established narcolepsy cases during 2009-2010. The study did not differentiate between vaccinated and un-vaccinated cases. Experts studied medical records of the cases for the purpose of verifying the narcolepsy with cataplexy diagnosis according to the American Academy of Sleep Medicine criteria for narcolepsy with cataplexy [2]. The study specifically focuses on cases in children and adolescents 19 years old and younger. Results showed that 87 cases were verified, of whom 81 were included in the study as they had onset of symptom within t he defined study period, 1 January 2009 to 31 December 2010. In total 69 patients (85%) had been vaccinated with Pandemrix before onset of symptoms.
The incidence rates of narcolepsy varied by age, being around 2 per 100,000 in the 0 to 9 year age group, 3.5 in the 10 to 14 year age group and 1.7 in the 15 to 19 year age group.

Overall the incidence rate in those vaccinated was 4.2 versus 0.64 in unvaccinated per 100,000 person-years, respectively suggesting a relative risk of 6.6 (95% CI 3.1 -14.5) and an absolute risk of 3.6 (95% confidence interval 2.5 – 4.7) additional cases per 100,000 vaccinated cases or 1 case per 27,800 vaccinations (from 1 per 40,000 to 21,300 vaccination).

References

1. Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations - Results of a case inventory study by the MPA in Sweden during 2009-2010. Available from: http://www.lakemedelsverket.se/upload/nyheter/2011/Fallinventeringsrapport_pandermrix_110630.pdf
2. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed: Diagnostic and coding manual, American Academy of Sleep Medicine, Westchester, IL 2005. Available from: http://www.esst.org/adds/ICSD.pdf