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

Vol. 16 | Weekly issue 50 | 15 December 2011

Rapid communications

Surveillance and outbreak reports

News

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

S-OtrH3N2 viruses: use of sequence data for description of the molecular characteristics of the viruses and their relatedness to previously circulating H3N2 human viruses

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Citation style for this article:
Lina B, Bouscambert M, Enouf V, Rousset D, Valette M, van der Werf S. S-OtrH3N2 viruses: use of sequence data for description of the molecular characteristics of the viruses and their relatedness to previously circulating H3N2 human viruses.
Euro Surveill. 2011;16(50):pii=20039. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20039

Article published on 15 December 2011

Emergence of influenza viruses from the animal reservoir is a permanent challenge. The rapid description and immediate sharing of information on these viruses is invaluable for influenza surveillance networks and for pandemic preparedness. With the help of data generated from the World Health Organization Collaborating Centre for Reference and Research on Influenza at the United States Centers for Disease Control and Prevention*, we provide here information on the swine–origin triple reassortant influenza A(H3N2) viruses detected in human cases in the northeast of the United States.

On 23 November 2011, the World Health Organization Collaborative Centre (WHOCC) for Reference and Research on Influenza at the United States (US) Centers for Disease Control and Prevention (CDC)* reported three cases of documented infections with a triple reassortant influenza A(H3N2) virus of swine origin (S-OtrH3N2) that may have been acquired through human-to-human transmission [1]. In the last 10 years, at least 27 human cases of swine influenza virus infections had been observed in the US [2-4], all of which occurred after exposure to infected animals, and no human-to-human transmission had been reported so far. Noticeably, the 11 most recent cases recorded since August 2011 were due to viruses that had acquired the matrix (M) gene segment of the influenza A(H1N1) pdm09 virus through reassortment [1,5]. This may have resulted in enhanced transmission potential of the S-Otr H3N2 virus. Indeed, it has been reported that the acquisition by an S-Otr H1N1 virus of both the M and neuraminidase (NA) gene segments from the Eurasian swine lineage virus facilitated the emergence and the spread of the influenza A(H1N1)pdm09 virus [3]. In addition, epidemiological studies suggest that the four last cases reported between the 23 November and 9 December were observed in patients with no direct or indirect contact with swine, implying that limited human-to-human transmission has occurred.

This event raises concerns about the potential of such swine-origin viruses to establish a sustained human-to-human transmission and about our ability to fight against this virus, should it become pandemic. Sharing molecular data at a very early stage of emergence facilitates in silico analysis and risk assessment. Thanks to the WHOCC at the CDC*, the sequences of these viruses are available in the GISAID database (Table).

Phylogenetic relationship

Based on the data available, it was possible to draw a phylogenetic tree comprising haemagglutinin (HA) sequences from both human and S-Otr influenza A(H3N2) isolates, to determine if there were common characteristics between these two groups of viruses. We performed this analysis for a 966 nt sequence (nt 72 to 1,038) of the HA1 regions of the HA genes of all human reference strains used in the influenza vaccines between 1972 and 2011, of six S-Otr H3N2 viruses isolated from human cases in 2011, and of two S-Otr H3N2 viruses detected in the swine population in 2010 and 2011 (Figure 1).

This analysis shows that the human HA1 phylogenetically most closely related to the S-OtrH3N2 viruses was the A/Wuhan/359/95(H3N2) virus. This is consistent with the timing of introduction of the human H3N2 viruses into the swine population in North America [4]. This closest homology was confirmed when the evolutionary distances were computed using the Tamura-Nei method [6]. In our analysis, the 966 nt HA fragment of

the S-Otr A/Iowa/08/2011(H3N2) virus showed 5.5% divergence from the A/Wuhan/359/95(H3N2), compared with 9.3% from the more recent A/Perth/16/2009(H3N2) virus. The evolutionary distances suggest a division of the human H3N2 viruses into two groups: one group of strains isolated between 1986 and 1999, which had the highest homology to S-Otr A/Iowa/08/2011(H3N2), and a second group comprising strains isolated before 1983 or after 1999, for which the divergence is larger than 8% and can reach as much as 11% (Figure 1).

In order to speculate on possible cross-protection, it is important to analyse differences in the antigenic sites. An alignment of the amino acid sequences of the HA1 subunit spanning the five antigenic sites of the HA protein [7] shows differences between the S-OtrH3N2 viruses and the human influenza A(H3N2) strains (Figure 2). Although we observed only few differences in the antigenic sites C, D and E, the differences in antigenic sites A and B were more significant. Antigenic site B, closest to the receptor-binding site has been proposed to contribute most to the antigenic characteristics of the HA protein [8].

Implications for diagnostics

The sequence analysis of the other gene segments like M, NP or NA also provided information on the capability of molecular diagnostic procedures to detect the S-Otr H3N2 virus. These viruses acquired the M gene segment from the human influenza A(H1N1)pdm09 virus. This implies that the generic detection through RT-PCR targeting the M gene will have very good sensitivity also for the S-Otr viruses. However, depending on possible mismatches in the primers and/or probes, the RT-PCR targeting the HA or NA gene segments may either be lacking sensitivity or possibly fail to detect the S-Otr H3N2 virus. Conversely, in terms of alertness and surveillance, the use of H3 and/or N2 subtyping

Table

S-Otr influenza A(H3N2) viruses isolated from swine and humans in 2010 and 2011 used for the phylogenetic analysis

Segment ID	Segment	Country	Collection date	Isolate name	Originating Laboratory	Submitting Laboratory	Authors
PI_ISL_83701	HA	United States	10 Jun 2011	A/Minnesota/11/2010	Minnesota Department of Health	WHO Collaborating Centre for Reference and Research on Influenza, Centers for Disease Control and Prevention, Atlanta	Shu B, Emery S, Garten R, Lindstrom S
EPI_ISL_99213	HA	United States	23 Nov 2011	A/Iowa/07/2011	Iowa State Hygienic Laboratory	WHO Collaborating Centre for Reference and Research on Influenza, Centers for Disease Control and Prevention, Atlanta	Emery S, Shu B, Garten R, Lindstrom S
EPI_ISL_99214	HA	United States	23 Nov 2011	A/Iowa/08/2011	Iowa State Hygienic Laboratory	WHO Collaborating Centre for Reference and Research on Influenza, Centers for Disease Control and Prevention, Atlanta	Emery S, Shu B, Garten R, Lindstrom S
EPI_ISL_99215	HA	United States	23 Nov 2011	A/Iowa/09/2011	Iowa State Hygienic Laboratory	WHO Collaborating Centre for Reference and Research on Influenza, Centers for Disease Control and Prevention, Atlanta	Emery S, Shu B, Garten R. Lindstrom S
EPI_ISL_99419	HA	United States	23 Nov 2011	A/Indiana/08/2011	Indiana State Department of Health Laboratories	WHO Collaborating Centre for Reference and Research on Influenza, Centers for Disease Control and Prevention, Atlanta	Shu B, Emery S, Garten R, Lindstrom S
EPI_ISL_99418	HA	United States	23 Nov 2011	A/Indiana/10/2011	Indiana State Department of Health Laboratories	WHO Collaborating Centre for Reference and Research on Influenza, Centers for Disease Control andPrevention, Atlanta	Shu B, Emery S, Garten R, Lindstrom S
EPI_ISL_97080	HA	United States	07 Sep 2011	Sw/Indiana/ A01049653/2011	NA	NA	Nezami SG, Sun D, Zhang J, Stensland WR, Strait EL, Yoon K-J
EPI_ISL_93357	HA	United States	20 Jun 2011	Sw/Pensylvania/ A01049256/2010	NA	NA	Sun D, Nezami SG, Zhang J, Stensland WR, Strait EL, Yoon K-J

NA: not available.

We gratefully acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's EpiFlu Database, on which this analysis is based.

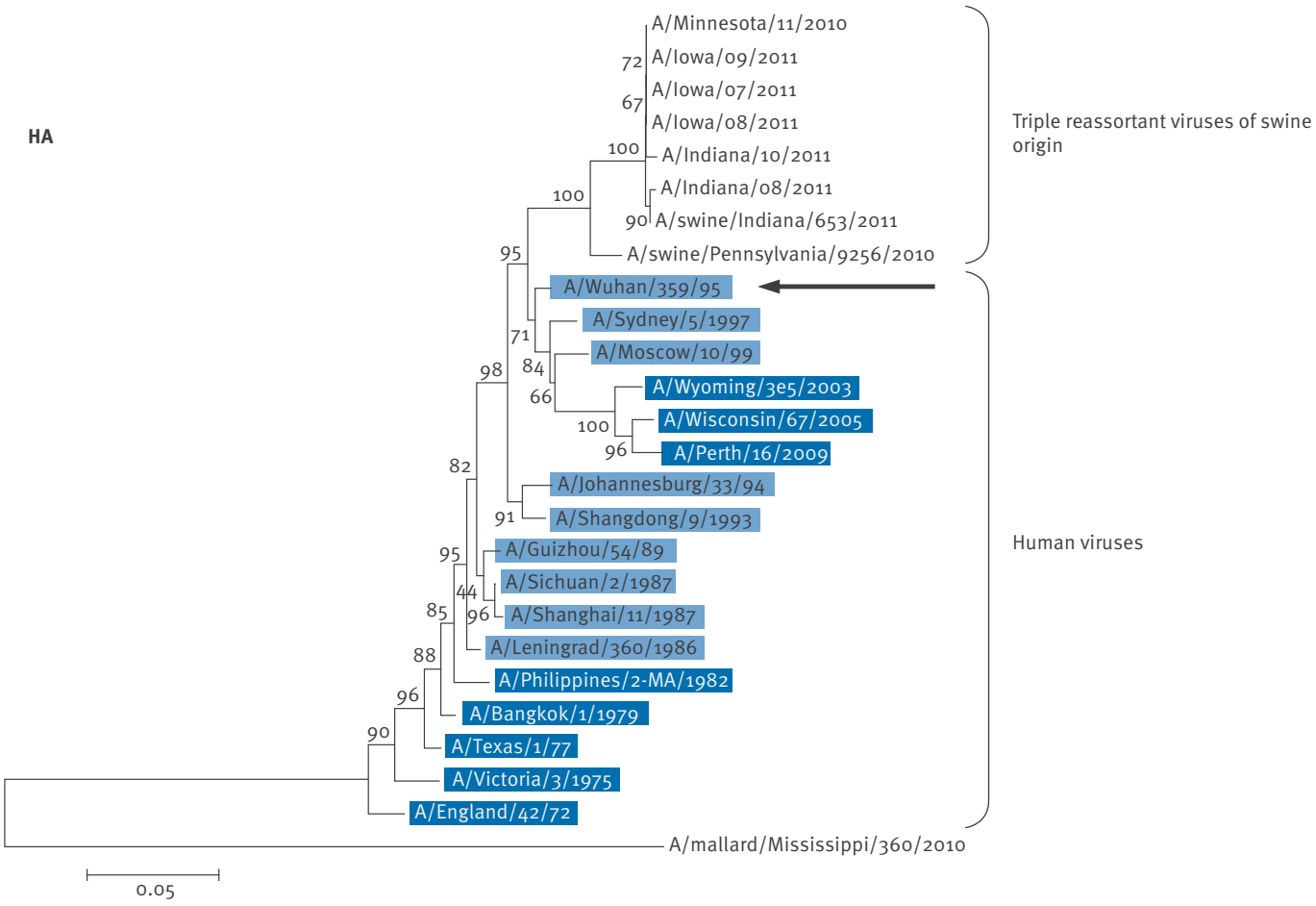
RT-PCRs that would have equal sensitivity for seasonal human and swine-origin H3N2 viruses, should not be promoted at this stage because these procedures may fail to recognise cases of S-Otr H3N2 virus infection. Hence, for accurate detection and surveillance, specific RT-PCR methods should be developed, or alternatively, predefined algorithms with already existing discriminating molecular tools need to be implemented [9]. Lastly, the NA and M2 sequences available from the recent isolates suggest that, as for the influenza A(H1N1)pdm09 virus, antiviral drugs that block the M2 ion channel will not be effective because the M2 sequence carries the S31N mutation associated with resistance. No known genetic markers for resistance to NA inhibitors have been detected in these new strains so far. This should be confirmed by phenotypic assays.

Implications for immunological cross-protection

In case of the emergence of a zoonotic virus with an HA derived from previously circulating human viruses, it needs to be established whether or not infections with human influenza viruses in the past seasons or vaccinations confer cross-protection against the new viruses. Indeed, during the recent pandemic in 2009, it was observed that upon infection or vaccination of elderly people previously exposed to influenza A(H1N1) viruses that shared common epitopes with the emerging pandemic virus, efficient cross-protection was induced through memory immune cells [10]. The comparison of the five antigenic domains of past influenza A(H3N2) human viruses with those of the S-Otr viruses showed similarities and differences. Hence, it is impossible to predict if pre-existing immunity will be efficient against this virus, even if it seems likely that some cross-protection will exist; seroepidemiological surveys should be carried out to support or disprove this

Figure 1

Phylogenetic analysis of the haemagglutinin genes (nt 72-1,038) of 26 influenza A(H3N2) viruses (vaccine strains and S-Otr viruses)



The evolutionary history and divergence were inferred using the neighbour-joining method. They were computed in MEGA5 (version 5.0), using the Tamura-Nei method and are in the units of the number of base substitutions per site. The percentages of replicate trees in which the associated taxa clustered together in the bootstrap test (1,000 replicates) are shown next to the branches. The analysis involved 26 nucleotide sequences and a total of 966 positions in the final dataset. The molecular data set was collected from GISAID.

The arrow shows the human strain with the closest homology (5.5% of divergence). The strains in light blue have less than 8% divergence with the S-Otr viruses, those in dark blue have more than 8% divergence.

hypothesis. One must also keep in mind that if there is pre-existing immunity to this virus, it may occur in different age groups than observed with the influenza A(H1N1)pdm09 virus.

Conclusion

Overall, even if neither the evolution of these S-Otr H3N2 viruses nor their putative impact in the general population can be predicted enhanced surveillance with adapted diagnostic procedures will become necessary if these sporadic cases turn into sustained dissemination. According to the similarities observed between the sequences of the S-Otr and human H3 influenza viruses (especially those circulating before 1995), the likelihood of cross-protection is high, but should be confirmed with seroepidemiological studies.

Acknowledgments

The authors acknowledge that this analysis has been possible only with the viruses and the molecular data provided in GISAID by the Indiana State Department of Health Laboratories, the Iowa State Hygienic Laboratory, the Minnesota Department of Health and the WHO Collaborative Centre for Reference and Research on Influenza at the Centers for Disease Control and Prevention.*

This work was supported in part by the European Union Seventh Framework Programme [FP7/2007-2013] under the project PREDEMICS, EC [grant agreement number 278433].

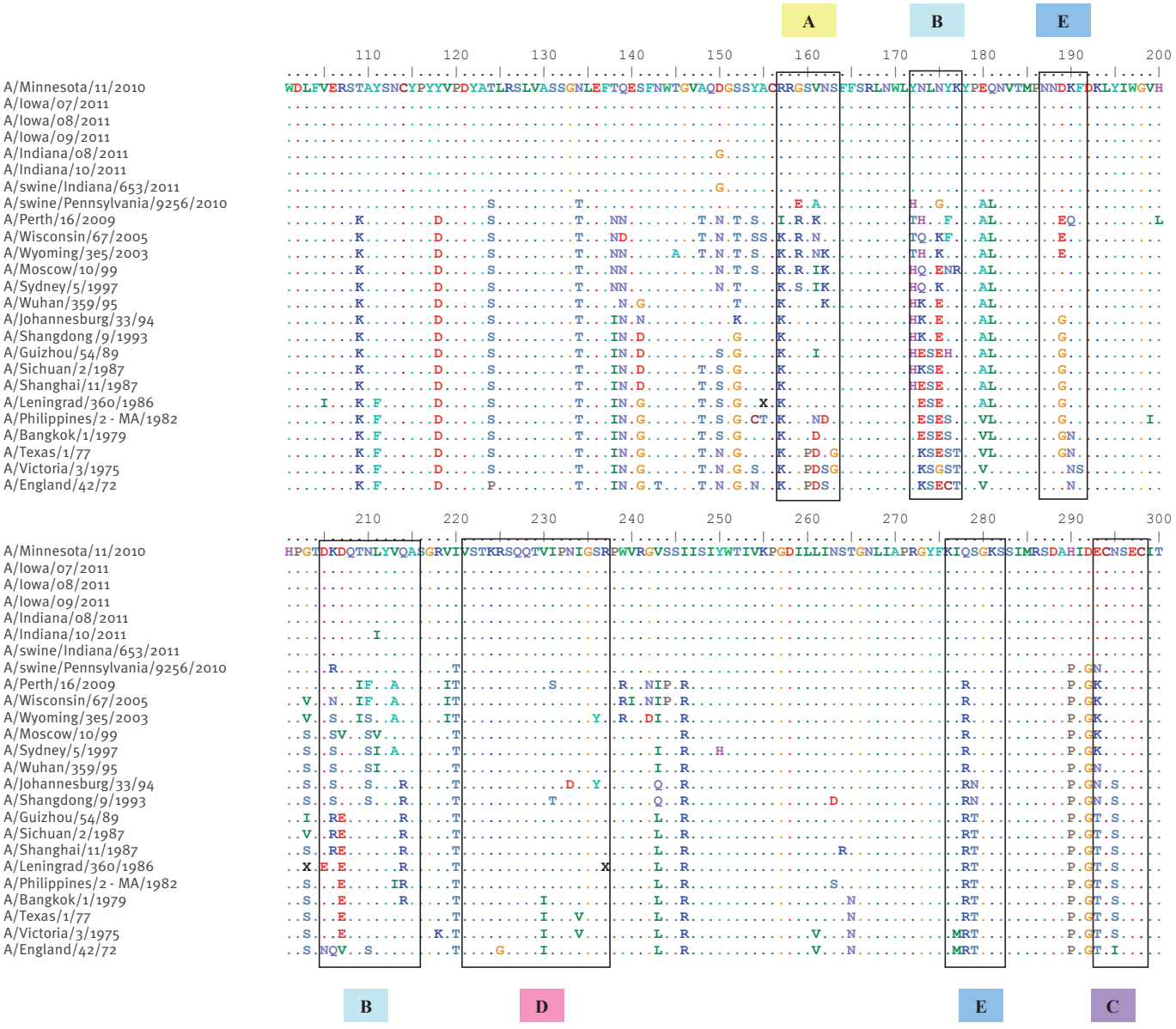
*Correction

On request of the authors, the following changes were made in this article on 23 December 2011:

The Table was replaced. The text “the United States Centers for Disease Control and Prevention” was replaced with “the

Figure 2

Amino acid sequence alignment of the haemagglutinin protein of 25 influenza A(H3N2) viruses (vaccine strains and S-Otr viruses) with antigenic sites A–E



WHO Collaborating Centre for Reference and Research on Influenza at the United States Centers for Disease Control and Prevention" in the Abstract, the Introduction and the paragraph before the Table. An acknowledgement was added.

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Preliminary implications for Europe of the 2011 influenza season in five temperate southern hemisphere countries

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Citation style for this article:
Lopez Chavarrias V, Broberg E, Nicoll A. Preliminary implications for Europe of the 2011 influenza season in five temperate southern hemisphere countries. Euro Surveill. 2011;16(50):pii=20044. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20044

Article published on 15 December 2011

The 2011 influenza season (May to October) in the southern hemisphere was dominated by the A(H1N1) viruses that emerged during the 2009 influenza A(H1N1) pandemic and influenza B viruses, although the proportion of these two varied between and within countries. Some influenza A(H3N2) viruses were also seen. We discuss here the preliminary implications for Europe of the 2011 influenza season in five temperate southern hemisphere countries.

Since 2009, the European Centre for Disease Prevention and Control (ECDC) has been monitoring the patterns of human influenza infection in five temperate southern hemisphere countries in their winters (May to October) as this gives some indication of what can be expected in the following northern hemisphere winter [1-8].

The pattern of influenza in the southern hemisphere is one of the many factors that the Centre takes into consideration in formulating its risk assessment in relation to severity and impact for epidemics of influenza [8].

From May to October 2011, ECDC monitored what was occurring in the five southern hemisphere countries in terms of virology, epidemiology and impact on healthcare of influenza and other respiratory viruses. One important source was the reports that the countries place regularly on the websites of their ministries of health and public health institutes [1-5]. In addition, more specific analyses and reports – especially related to the impact (in the sense of pressures on primary and secondary healthcare services) – as well as information on unusual features were sought from influenza experts in the countries by a simple questionnaire to get information that was not otherwise available. The aim of the questionnaires was to gather details on the impact on the healthcare service, risk factors associated with severe cases, observed complicating conditions, vaccine coverage among the general population and anything unusual that could have been observed. Three reference time-points were indicated for comparisons: before the 2009 influenza A(H1N1) pandemic, during the pandemic, and the first post-pandemic winter season (2010).

Findings and their implications for Europe

The findings for the five countries are shown in the Table, combining information from the questionnaire, the national websites and an earlier summary of the epidemiology and virology from the World Health Organization [9].

The observed respiratory virus pattern was mixed although no pre-pandemic seasonal influenza A(H1N1) viruses were seen in the southern hemisphere in the 2011 season. In 2011, in Argentina and Chile, respiratory syncytial virus (RSV) was the most frequent isolate, followed by influenza A(H1N1)pdm09 virus. South Africa also reported a predominance of RSV during 2011. In Australia, the most frequently isolated strains were influenza A(H1N1)pdm09 and influenza B viruses. New Zealand observed a pattern of influenza B viruses (Victoria lineage) dominating in 2011. This has been seen at intervals, approximately once every three seasons. All countries reported some influenza A(H3N2) circulation, although it was not the predominant influenza A subtype in any country.

The match with seasonal vaccines was found to be good overall [10]. Australia reported a regional cluster of oseltamivir-resistant influenza A(H1N1) viruses which were collected from patients without oseltamivir exposure (only one of the 29 cases infected with the resistant virus had received oseltamivir treatment). The individuals were not known to be immunosuppressed [11-13]. The viruses remained sensitive to zanamivir but were resistant to adamantanes. All the resistant influenza A(H1N1) viruses were found to carry a point mutation in their neuraminidase genes which encoded a histidine to tyrosine substitution at residue 275 (H275Y) of the neuraminidase active site.

Argentina reported higher burden on the healthcare system in 2011 than during the 2010 season and Chile noted higher pressure than usual on child healthcare

Table

Characteristics of the influenza season in five temperate southern hemisphere countries and their implications for Europe, 2011

Information requested in the questionnaire	Argentina	Australia	Chile	New Zealand	South Africa
What was the observed influenza viral mix circulating in your country during the 2011 influenza season?[a]	A(H3N2), A(H1N1) pdm09, peak of RSV in children under one year of age (from May to July which has been observed before)	A(H1N1)2009, B, occasionally A(H3N2), some emerging A(H1N1)pdm09 oseltamivir-resistant strains	RSV was more prominent than usually during the 2011 season. Its detections surpassed influenza A isolations, among which the A(H1N1) subtype was more frequently isolated than the A(H3N2).	The predominant strains have been of the B/Victoria subtype/lineage, with some A(H3N2) and A(H1N1).	A(H1N1) predominant subtype until August, associated with the first peak of influenza-like illness/severe acute respiratory infections; secondary peak associated with A(H3N2) and B viruses.
Are the primary care services in your country subject to unusual pressures of any kind?[b]	More than during the 2010 season but less than during the 2009 pandemic	No special burden during the 2011 season	High pressure during 2011 due to the early presence of RSV viruses, mostly in children	Less pressures observed than during the 2010 season and much less than during the 2009 pandemic	Not systematically measured in South Africa
Are there any reports of secondary health centres of your country being particularly subject to pressures of any kind, compared to previous seasons?[b]	More than during the 2010 season but less than during the 2009 pandemic	Less than during the 2010 season and the 2009 pandemic	More than during the 2010 season but less than during the 2009 pandemic; hospital admissions began earlier than usual	Less pressures observed than during both the 2010 season and the 2009 pandemic	Same pressure as during the 2010 season but less pressure than during the 2009 pandemic
Has there been marked heterogeneity (more pressures in some part(s) of the country) in primary and/or secondary care?	There were higher pressures in both primary and secondary care in the region of Mendoza	No differences observed	Higher pressures observed in the metropolitan regions	A slight geographic variation but this is the norm every winter	No big differences observed
Are the risk groups (people experiencing severe disease) the same this year?[c]	Healthy people with severe disease only observed in during the pandemic	People with co-morbidities, as in previous years	The same groups as in the 2009 pandemic and 2010 season	The same groups as in 2009 and 2010	The same groups as in the 2009 pandemic and 2010 season
Are the age groups (people experiencing severe disease) the same this year?[c]	The same as in 2010 and 2009 when the influenza A(H1N1) pdm09 virus was involved; the same episodes observed than in pre-pandemic times with regards to the A(H3N2) virus	Slight increase in the median age of infection, more like the expected seasonal pattern	The same as in the 2009 pandemic but different compared to the 2010 season	Children (0-19 years) and young adults (20-34 years) had a higher disease burden compared to other age groups, as in the 2009 and 2010 seasons	Greater proportion of patients in the age group of one to four year-olds and a lower proportion in the age group of 25-44 year-olds in 2011 as compared with 2010 season; no information indicated with regards to pre-pandemic times
Observed complicating conditions and other infections in severe cases[c]	Similar to the 2009 pandemic	None observed	Most of the severe acute respiratory infections cases were affected by influenza A(H1N1)pdm09 virus; some also attributed to influenza A(H3N2)	No relevant features observed	Not specific issues noted in relation to acute respiratory distress syndrome or secondary bacterial infections/ co-infections
Observed seasonal immunisation coverage and/ or acceptance of vaccination[d]	Higher than during the 2010 season and pre-pandemic times	Not reported	Lower than in the 2010 season and pre-pandemic times	Slightly lower than during the 2010 season and higher than in pre-pandemic times	About the same as during the 2010 season but higher than in pre-pandemic times

RSV: respiratory syncytial virus.

[a] None of the preceding seasonal influenza A(H1N1) viruses was observed in any of the five countries [9].

[b] As compared with the 2010 season and the 2009 influenza A(H1N1) pandemic.

[c] As compared with the 2010 season, the 2009 influenza A(H1N1) pandemic, and prior to the pandemic.

[d] As compared with the 2010 season and prior to the 2009 influenza A(H1N1) pandemic.

services from illness among children, but mostly due to RSV (Chile is one of the few countries in the world outside the European Union that routinely reports on RSV detections). Australia and New Zealand reported less burden on the healthcare system in 2011 than in 2010, and much less than during the 2009 influenza A(H1N1) pandemic. In hospitals, the only unusual impact was high burden on the secondary healthcare system in Argentina and the burden through childhood RSV in Chile. Some geographical differences were reported in the burden of respiratory illness on the primary healthcare system in Chile and on the secondary healthcare system in Argentina.

Australia reported that surveillance data on severe disease remained consistent with people with co-morbidities being at higher risk of severe disease but that the age groups with severe disease had reverted to the pattern seen in the period before the 2009 pandemic. However, during 2011, three other countries noted a similarity with the pandemic pattern of severe disease in younger people (Table). There were fewer reports of acute respiratory distress syndrome than during the 2009 influenza A(H1N1) pandemic.

Three of the four countries that reported information on vaccine coverage, Argentina, New Zealand, and South Africa, indicated that vaccine coverage for seasonal influenza among the recommended groups was higher than before the 2009 influenza A(H1N1) pandemic, whereas Chile reported that coverage was lower than during the 2009 influenza A(H1N1) pandemic and in 2010 (Table).

Discussion and limitations

The influenza virological pattern seen in the southern hemisphere in 2011 was not consistent enough to make a clear prediction for the season 2011/12 in Europe. However, it was different from what was seen in 2010/11 in the northern hemisphere for Europe (predominance of influenza A(H1N1)pdm09 and, to a lesser extent, influenza B viruses), North America and North Asia (predominance of influenza A(H3N2) virus).

In relation to the seasons before 2011, the overall impact of influenza in the southern hemisphere was lower in 2010 than in 2009, with some exceptions, e.g. locally in New Zealand [14,15].The reports of circulation of oseltamivir-resistant influenza A(H1N1) viruses are concerning, although these were also observed during the 2009 influenza A(H1N1) pandemic and in Europe in 2010/11 [16,17]. This indicates a particular need to monitor these viruses in Europe in the 2011/12 season to detect any rise in prevalence as was observed for the pre-2009 influenza A(H1N1) seasonal viruses in the 2007/08 season [18].

The main limitation of this survey lies in its descriptive character. In addition, the selection of the contributors did not follow a systematic procedure. Data derived from more thorough quantitative and statistical analysis would render the information more meaningful but cannot be generated while there are such differences in the surveillance systems in the countries concerned.

The findings on the impact of influenza in the southern hemisphere in 2011 are reassuring for Europe before the influenza season reaches its peak, usually around January. The differences in the impact of influenza observed within the 2011 season between Australasia, South Africa and the southern cone of South America may become more apparent in future seasons. This was the case in the last inter-pandemic period, when large differences existed between continents for both the southern and the northern hemisphere [19]. This may reduce, but not eliminate, the utility of this kind of surveillance for Europe in the future.

Acknowledgements

The authors would like to thank a number of colleagues for their assistance in preparing this report: Brett Archer, Jorge Camara, Cheryl Cohen, Rodrigo Fasce Pineda, Sue Huang, Darren Hunt, Heath Kelly, Anne Kelso, Andrea Olea Normandin, Viviana Sotomayor and Osvaldo Cesar Uez. However, the comments in the report are the responsibility of the authors alone.

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A case of diphtheria in Sweden, October 2011

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Citation style for this article:
Fredlund H, Norén T, Lepp T, Morfeldt E, Henriques Normark B. A case of diphtheria in Sweden, October 2011.
Euro Surveill. 2011;16(50):pii=20038. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20038

Article published on 15 December 2011

In October 2011, a child who had arrived in Sweden from Somalia presented with atypical tonsillitis, was treated with penicillin and the symptoms resolved. A throat swab was positive for toxigenic *Corynebacterium diphtheriae*. The child's family were then vaccinated with diphtheria, tetanus and pertussis vaccine and screened for *C. diphtheriae*. No secondary cases were found. A high level of adherence to childhood vaccination programmes is an effective way to protect populations against diphtheria.

Case report

In October 2011, a child who had recently migrated with their family from Somalia presented at a local general practitioner's (GP's) practice in Sweden with a sore throat and fever (40 °C). An atypical picture of unilateral tonsillitis led to the child being admitted to hospital, where penicillin was administered intravenously. The child was discharged the following day and was then treated at home with oral penicillin for one week, after which time the symptoms resolved. The other family members were healthy.

A throat swab taken on admission to hospital was cultured. The culture was positive for group A beta-haemolytic streptococci. Due to the referral information of tonsillitis in a person who had recently arrived in the country and given the atypical clinical presentation, the local laboratory also cultured for *Corynebacterium diphtheriae*, which was positive. The isolate was fully sensitive to penicillin and erythromycin. Further analysis using PCR to detect the diphtheria toxin gene and the Elek test at the Swedish Institute for Communicable Disease Control (SMI, Solna) verified that the isolate was a toxin-producing strain of *C. diphtheriae*.

Control measures

Once the laboratory results had been obtained, the child's family (parent and seven children), were immediately vaccinated with diphtheria, tetanus and pertussis (DTP) vaccine and screened for *C. diphtheriae*. Only one sibling was found to carry *C. diphtheriae* and was treated with oral penicillin. This *C. diphtheriae* strain was later shown to be non-toxigenic.

The family had arrived in Sweden four weeks before the case's illness from a refugee camp in Africa. They had lived at one address since their arrival and had no other relatives in Sweden. There was no history of the case having attended daycare or school during the incubation period. As the family had had limited contact with others, contact tracing was not needed. The hospital staff had very limited contact (one overnight stay) with the patient who received immediate antibiotic treatment. Checking of vaccination history confirmed that all staff were fully vaccinated against diphtheria. All were healthy when the disease was diagnosed several days later, and to date still are. Follow-up of the family has been carried out by the local nurse, responsible for migrant health, and GP and to date, no secondary case has been detected.

Background

Diphtheria is caused by toxin-producing *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis*. The best known and most widely studied species is *C. diphtheriae*, the most common causal agent of the disease.

The disease can result in an acute upper respiratory tract infection characterised by sore throat, fever (often <38 °C) and an adherent membrane on the tonsils, pharynx and/or nasal cavity. The severity of diphtheria is related to the degree of obstruction of the upper respiratory tract, caused by an acute bacterial toxic infection, and dissemination of the toxin which can cause myocarditis, polyneuritis and other systemic toxic effects. Overall, the case fatality rate may be as high as 20–30% in toxic forms [1]. A milder form of diphtheria may be restricted to cutaneous lesions even when caused by toxin-producing strains. The causative bacteria are spread by direct physical contact or breathing aerosolised secretions.

Due to the high degree of susceptibility of children to diphtheria, vaccination at an early age is universally advocated, for example, with DTP vaccine. Once quite common, diphtheria is rarely seen in developed nations due to the widespread use of DTP vaccine. Two minor outbreaks of diphtheria were notified in Sweden during the 1980s [2,3] and only two cases of the disease

due to *C. diphtheriae* have been diagnosed since 2001 (data not shown). Both cases were imported. The relative absence of diphtheria in Sweden is primarily due to the high vaccination coverage obtained through the childhood immunisation programme initiated in the 1950s. According to the programme, all children born in Sweden should receive four doses of diphtheria toxoid-containing vaccine. The first three doses should be administered within three months of age and the fourth dose should be given at the age of 10 years. All children of migrants are offered DTP immunisation as soon as they are in the Swedish health care system, often within weeks but at the latest within a few months after their arrival in Sweden. In 2010, a nationwide vaccination survey showed that 96% of all children aged 13 years living in Sweden were fully vaccinated with DTP vaccine and 2% were partly vaccinated (data not shown).

Discussion

Bacteriological analysis of a throat swab of the case reported here showed the presence of beta-haemolytic streptococci and toxigenic *C. diphtheriae*. Both pathogens may well have contributed to the clinical picture and the patient was successfully treated with penicillin.

In a country where the occurrence of diphtheria is low, such as Sweden, specific culturing for *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* is rarely performed. Usually throat swabs are cultured without searching for these pathogens. As special media are required, a specific request for this culture has to be included on the referral note to the diagnostic laboratory, along with an indication of the unusual features of the disease and/or the origin of the patient. The local laboratory has to take that information into account for appropriate culturing. Otherwise diphtheria could be overlooked at an early stage of the disease or when presenting with atypical features and may cause secondary cases among susceptible people.

Diphtheria is a rarely diagnosed disease in western Europe and the small number are most commonly associated with travel to endemic countries. A few case reports from the United Kingdom and France have been published in recent years [4-6].

A high level of adherence to childhood vaccination programmes in every country is an effective way to protect populations against diphtheria. Adequate diagnostic tools and appropriate treatment of cases with atypical tonsillitis are also paramount to prevent further cases and potential outbreaks.

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A case of OXA-48 carbapenemase-producing *Klebsiella pneumoniae* in a patient transferred to Slovenia from Libya, November 2011

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Citation style for this article:
Pirš M, Andlovic A, Cerar T, Žohar-Čretnik T, Kobola L, Kolman J, Frelih T, Prešern-Štrukelj M, Ružić-Sabljić E, Seme K. A case of OXA-48 carbapenemase-producing Klebsiella pneumoniae in a patient transferred to Slovenia from Libya, November 2011.
Euro Surveill. 2011;16(50):pii=20042. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20042

Article published on 15 December 2011

We report the first documented case of OXA-48-producing *Klebsiella pneumoniae* in Slovenia isolated from rectal surveillance cultures from a patient transferred from Libya. The patient was colonised with both ESBL-producing *Escherichia coli* and ESBL- and OXA-48-producing *K. pneumoniae*. Three further patients were colonised with ESBL-producing *E. coli*. This underscores the importance of an early warning system on European level and screening upon admission of patients transferred across borders and between healthcare systems.

In the beginning of November 2011, 25 patients from Libya were admitted to two rehabilitation facilities in Slovenia, 22 of whom were otherwise healthy amputees. None were transferred directly from a hospital; more detailed information regarding previous hospitalisation was not available. A rapid risk assessment circulated by the European Centre for Disease Prevention and Control (ECDC) on 31 October 2011 states that provision of healthcare to patients transferred from Libya to the European Union is likely to present a high risk of introduction of multidrug-resistant bacteria [1]. Therefore, the Slovenian National Institute of Public Health (NIPH) issued a warning and recommended rectal screening of all transferred Libyan patients for the presence of multidrug-resistant Gram-negative bacteria. The rapid risk assessment as well as another ECDC risk assessment on carbapenemase-producing *Enterobacteriaceae* [2] was distributed to the relevant institutions accepting Libyan patients and to relevant microbiological laboratories. Screening of all hospitalised patients from foreign countries, and patients transferred from hospitals and nursing homes is also part of the Slovenian national guidelines for screening for extended-spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing *Enterobacteriaceae* [3].

Microbiological screening

Methods

Rectal swabs were collected upon admission from all 25 patients and screened for the presence of ESBL- and/or carbapenemase-producing *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Samples from 14 patients were processed at the Institute of Microbiology and Immunology, Faculty of Medicine Ljubljana and the remaining 11 at the Institute of Public Health Celje.

Samples were vortexed in tryptic soy broth (TSB), aliquots were inoculated onto ChromID ESBL agar (bioMerieux, France), MacConkey (MAC) agar onto which 10 µg carbapenem discs were placed, and TSB. Following 24-hour incubation, TSB was subcultured onto MAC agar onto which 10 µg carbapenem discs were placed [4-7]. Reduced susceptibility to carbapenems was suspected in any colony growing within the 23 mm inhibition zone for *Enterobacteriaceae* or the 16 mm inhibition zone for non-fermentative Gram-negative bacilli. Antimicrobial susceptibility testing was performed according to guidelines of the Clinical Laboratory Standards Institute (CLSI) [8]. Phenotypic tests for the detection of carbapenemases, inhibition tests using boronic or dipicolinic acid and ethylenediaminetetraacetic acid (EDTA) as well as a modified Hodge test (MHT) were performed as per the CLSI and Giske et al. [8,9]. Molecular detection of *bla*OXA-48 was done by polymerase chain reaction (PCR) [10].

Results

Four of the 25 patients were colonised with ESBL-producing *Escherichia coli*, detected on solid media. In one of these colonised patients an ESBL-producing and carbapenem-resistant *K. pneumoniae* isolate was also isolated, however only after the enrichment step. Phenotypic tests for detection of carbapenemases were

performed on this strain and there was no inhibition by boronic, dipicolinic acid or EDTA. PCR for *bla*OXA-48 was positive. Laboratory contamination was ruled out as this is the first OXA-48 carbapenemase isolate in the laboratory and the resistance profile of this and the reference strain are completely different.

The OXA-48-producing *K. pneumoniae* isolate was susceptible to amikacin (minimal inhibitory concentration (MIC): 4 µg/mL), trimethoprim/sulfamethoxazole (MIC: 1 µg/mL) and colistin (MIC: 0.25 µg/mL) but resistant to all beta-lactams including carbapenems (MIC for cefotaxime, imipenem, meropenem and ertapenem were ≥32 µg/mL, MIC for piperacillin/tazobactam was ≥256 µg/mL), ciprofloxacin (MIC: 32 µg/mL) and tigecycline (MIC: 2 µg/mL; tigecycline MIC was interpreted according to criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [11]).

No carbapenem-resistant *A. baumannii* or *P. aeruginosa* were isolated.

Control measures

On admission, the patients were placed in a dedicated ward. Separate scheduling of treatment (last on the daily schedule) and disinfection of shared equipment were implemented during rehabilitation therapy. Following the warning from the NIPH the patients were additionally placed in contact isolation.

After isolation of multidrug-resistant Gram-negative bacteria, the colonised patients were cohorted, and the patient colonised with both ESBL-producing *E. coli* and ESBL- and OXA-48-producing *K. pneumoniae* was placed in a single room. The patients and staff were further educated and encouraged to perform increased hand hygiene and frequent hand disinfections. Special precautions such as separate scheduling of treatment (last on the schedule) and disinfection of shared equipment were continued for all patients until their discharge after approximately one month.

Discussion and conclusion

This is the first documented case of OXA-48-producing *K. pneumoniae* in Slovenia. The patient was colonised with both ESBL-producing *E. coli* and ESBL- and OXA-48-producing *K. pneumoniae*. Three further patients were colonised with ESBL-producing *E. coli*. The four cases clearly demonstrate the usefulness of alert systems on the European level where countries can share their experiences and translate them into public health action. Had the warning not been issued, the patients would not have been screened for the presence of carbapenemase-producing Gram-negative bacteria.

In addition, the carbapenemase-producing *K. pneumoniae* was only detected following the enrichment step, which may indicate a low-level colonisation with carbapenemase-producing *K. pneumoniae* and predominance of ESBL-producing *E. coli* which probably overgrew *K. pneumoniae* on ESBL agar. These results demonstrate the usefulness of an enrichment step as part of screening for carbapenemase-producing *Enterobacteriaceae*.

We hope that by the early warning from NIPH, the isolation of the patients that were transferred to Slovenia from Libya and the early detection of OXA-48-producing *K. pneumoniae*, the introduction of a novel carbapenemase into Slovenia was successfully contained.

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Outbreak of *Salmonella* Montevideo associated with a dietary food supplement flagged in the Rapid Alert System for Food and Feed (RASFF) in Germany, 2010

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Citation style for this article:
Stöcker P, Rosner B, Werber D, Kirchner M, Reinecke A, Wichmann-Schauer H, Prager R, Rabsch W, Frank C. Outbreak of Salmonella Montevideo associated with a dietary food supplement flagged in the Rapid Alert System for Food and Feed (RASFF) in Germany, 2010.
Euro Surveill. 2011;16(50):pii=20040. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20040

Article published on 15 December 2011

In March 2010 the Rapid Alert System for Food and Feed (RASFF) was used to inform about *Salmonella* Montevideo in a herbal food supplement, formulated in capsules, distributed under a Dutch label in Germany. Simultaneous to the first RASFF notice, in the last two weeks of March 2010 an unusual number of 15 infections with *S.* Montevideo was notified within the electronic reporting system for infectious diseases at the Robert Koch Institute. Adult women (median age: 43, range: 1–90 years) were mainly affected. An outbreak was suspected and the food supplement hypothesised to be its vehicle. Cases were notified from six federal states throughout Germany, which required efficient coordination of information and activities. A case–control study (n=55) among adult women showed an association between consumption of the specific food supplement and the disease (odds ratio (OR): 27.5, 95% confidence interval (CI): 3.1–infinity, p-value=0.002). Restricting the case–control study to the period when the outbreak peaked (between 29 March and 11 April 2010) resulted in an OR of 43.5 (95% CI: 4.8–infinity, p-value=0.001). Trace-back of the supplement's main ingredient, hemp seed flour, and subsequent microbiological testing by pulsed-field gel electrophoresis supported its likely role in transmission. This outbreak investigation illustrates that information from RASFF may aid in hypothesis generation in outbreak investigations, though likely late in the outbreak.

Introduction

Launched in 1979, the Rapid Alert System for Food and Feed (RASFF) was put in place to provide food and feed control authorities within the European Union (EU) with an effective tool to exchange information about measures taken in response to serious risks detected in relation to food or feed [1]. Information exchange via RASFF is required, if the suspected food or feed product has been traded or distributed across internal EU borders. The system is well established [2] and a rapid exchange is supposed to allow all Member States to verify immediately whether they are commonly affected by a problem. Whenever the product is on sale to consumers, it is the responsibility of the Member States´ authorities to take all necessary measures such as withdrawing or recalling food or feed products from the market in order to protect consumers' health, as well as informing the public.

In February 2010, a German federal state laboratory conducted a chemical-toxicological as well as microbiological investigation of the remainder of a food supplement after a female consumer of this supplement had developed a rash. In the course of the investigation, *Salmonella* Montevideo was unexpectedly found. The food supplement formulated in capsules, was produced by a German company but distributed under a Dutch label. It had been marketed online and via teleshopping to menopausal and postmenopausal women. On 27 March 2010, a nationwide recall and withdrawal of the product, limited to specific batches, was conducted by company A via individual post and telephone-calls to consumers in Germany registered through points of sale of the product. Additionally, recall and public warning were communicated via the teleshopping channel and various print media. On 29 March 2010, an RASFF alert notification informed about *S.* Montevideo in the withdrawn food supplement distributed under a Dutch label in Germany, followed by several additional notifications in RASFF throughout subsequent weeks with supplemental information on

laboratory test results and trade routes of the product and its ingredients, as well as measures taken in the affected federal states in Germany.

Simultaneous to the first RASFF notice, the electronic reporting system for infectious diseases at the Robert Koch Institute (RKI) showed an unusual increase in the number of salmonellosis notifications due to *S.* Montevideo. In March and April 2010 (date of disease onset - where available - between 28 March and 12 April), an unusual number of 15 infections were notified from six federal states throughout Germany. Most of this excess appeared to affect adult women.

Infections with *Salmonella* are a major cause of bacterial food-borne diarrhoea in humans. However, throughout the past years, only a few reports were published on food-borne outbreaks of *Salmonella* infections due to the serovar Montevideo [3-9]. The endemic level of *S.* Montevideo in Germany is low: In 2008 and 2009, 65 and 38 respective *S.* Montevideo infections were notified throughout the entire year, corresponding to 0.1% of all human salmonellosis notified within the German electronic reporting system in these years [10].

Given the RASFF notice, and the increase in case numbers, an investigation was initiated at RKI to identify the role of the food supplement in this outbreak, and to assess the usefulness of RASFF for retrospective outbreak explanation.

Methods

Descriptive epidemiology

In Germany, infections with *S.* Montevideo infections are legally notifiable within the category of non-typhoidal salmonelloses [11]. Case-definition is based on characteristic symptoms and laboratory confirmation, or epidemiological linkage to another laboratory-confirmed case [12].

A detailed exploratory questionnaire specifically designed by RKI experts was administered by telephone from 7 to 13 May 2010 to females with *S.* Montevideo infections notified within the national reporting system between 1 January and 28 March 2010. Data collection encompassed onset and nature of clinical symptoms and their duration, hospitalisation and regular intake of any medication including antacids and prescription of antimicrobial medication for salmonellosis, environmental and food exposures focusing on foods previously associated with outbreaks of *S.* Montevideo in other countries [5,7,13]. This included salami, alluding to a salami and pepper mediated *S.* Montevideo outbreak in the United States, published concurrently to this outbreak [6]. Furthermore, we inquired about animal contact, travel history, other underlying medical conditions and additional cases of diarrhoea or vomiting in the household in the seven days before symptom onset. In addition, cases were asked about consumption of food supplements in general, and about consumption of the specific, RASFF-flagged food supplement of company A. As hemp seed flour was one of the main ingredients of the food supplement, we also asked about exposure to places of sale of hemp seed flour or products containing it. Furthermore local health departments were asked to refer any remaining specific food supplement from company A, which was mentioned in the RASFF, from new cases´ households, to a food safety laboratory for microbiological testing.

Case–control study

A case–control study was initiated and coordinated by RKI to test the hypothesis that the specific food supplement from company A was associated with *S.* Montevideo-infections with disease onset in March or April 2010.

For this study a case was defined as a female resident in Germany, aged 20 years or more, notified between 1 and 25 April 2010 to the national electronic reporting system for communicable diseases, and for whom *S.* Montevideo was cultured from stool. Cases were excluded if they reported having had contact with a person with diarrhoea in the seven days prior to symptom onset because they could have arisen by secondary person-to-person transmission. Controls were identified by a two-stage sampling design: first, in federal states where cases occurred, counties were randomly selected with a probability of inclusion proportional to their population size. Second, the so chosen counties were asked to provide randomly 60 to 80 addresses of women aged between 20 and 80 years from population registries, for whom telephone numbers were looked up in public directories. Controls were frequency-matched to cases by state and age with a ratio of cases to controls of 1:4. A hypothesis-testing questionnaire was designed focussing mainly on the consumption of the food supplement from company A for the year 2010 up to the date of interview. We asked for underlying chronic diseases and regular intake of medicines. In addition, cases were asked about clinical symptoms around the Easter holidays (29 March–10 April) and duration of illness. Study participants were interviewed by telephone by RKI staff.

Data analysis

For descriptive analysis we calculated absolute numbers and proportions. All exposures were tested for association with the outcome variable (*S.* Montevideo infection) using univariable and multivariable exact logistic regression. We report odds ratios (OR) and 95% confidence intervals (CI). All reported p-values are two sided and $p<0.05$ was considered significant. Data were analysed with Stata, Version 11.0, StataCorp LP, Texas, USA.

Product tracing

Following the RASFF notification in March 2010, the investigation by food and veterinary authorities was tailored to trace the contaminated consignment. Detailed investigations according to the legal requirements regarding production and supply of the suspected

food supplement were carried out by affected federal states. Outcome of investigations and measures taken in Germany were communicated via RASFF.

Microbiological investigation and molecular subtyping

Cases' stool samples, as well as samples of the food supplement, its raw ingredients and environmental samples from production facilities were investigated by various laboratories for the presence of *S*. Montevideo. For comparison of *S*. Montevideo patterns, pulsed-field gel electrophoresis (PFGE) was used according to Ribot et al. [14]. The PFGE analysis included *S*. Montevideo isolates that were sent by laboratories in Germany to the National Reference Centre (NRC) for *Salmonella* and other Enterics between March and May 2010. The *S*. Montevideo isolates for the PFGE analysis consisted of: (i) isolates from stool specimens of two outbreak cases, (ii) isolates from respective stool samples of two cases who were unrelated to the outbreak, (iii) one isolate from the food supplement from an outbreak case's household, (iv) one isolate from an environmental sample from the facility where the food supplement was produced and (v) one isolate arising from biosolids retrieved during an official process control of a biogas plant.

Results

Descriptive epidemiology

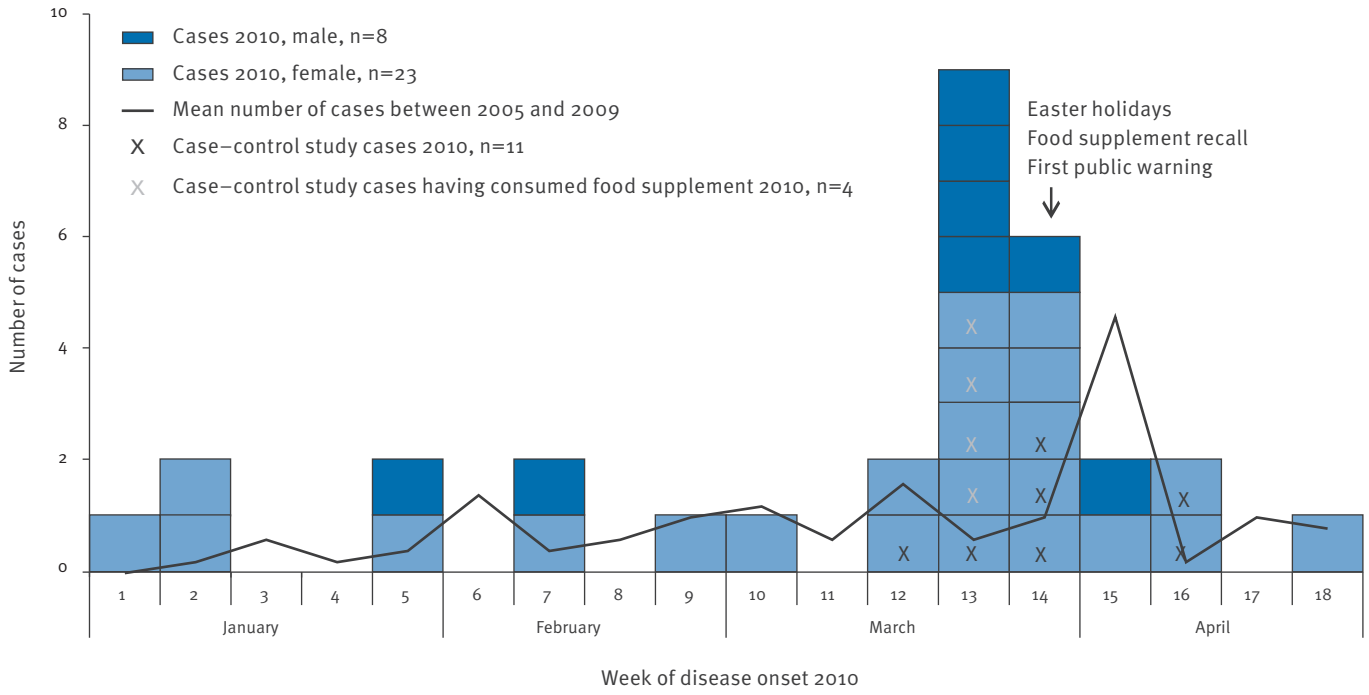
In 2010, the RKI received 37 reports of *S*. Montevideo until 9 May with a peak between 29 March and 11 April, 31 with known date of symptom onset (Figure 1).

Six of 16 German federal states reported *S*. Montevideo cases with onset of disease from week one through 18 (4 January–9 May). In the preceding five years, the mean case number per week of *S*. Montevideo infections for the same period had been one to two per week (background rate). In the two weeks between 29 March and 11 April 2010, however, 15 cases were registered. This peak was mainly due to an increase of reported *S*. Montevideo in adult women (› 18 years of age), with 10 infections in women versus five infections in men. In this period, the median age of women was 43 (range: 1–90 years) and the median age of men was 75 (range: 6–82).

Thirteen exploratory questionnaires were completed. An additional complete questionnaire was obtained by a proxy of the local health department who had already interviewed a patient unfit for further questioning. Onset of symptoms ranged from 21 March through 22 April 2010. Of the 14 persons from whom complete information was available, four were excluded as possible secondary cases. Four of the 10 remaining women indicated consumption of the food supplement from one of the implicated batches as of the end of March 2010, when they had received a notice from the distributor. One of the interviewed women was of advanced age (90 years) and could not exclude that she may have consumed the product even after receiving the notice. All four women had symptom onset between 29 March and 4 April 2010 (week 13) and had bought the product via teleshopping in January or February 2010. All of them consumed the product for at least four weeks with a daily dose of two capsules.

Figure 1

Reported cases of *Salmonella* Montevideo with known date of disease onset, Germany, 4 January–9 May 2010 (n=31)



Other potentially relevant exposures included consumption of peppered salami products (n=2) as well as fried or boiled eggs (n=8). Peppered salami was not investigated further due to low exposure proportion. Even though high egg consumption was likely due to the Easter holidays (29 March–10 April), this was included in the case–control study. Of all investigated cases, none remembered buying hemp seed flour or other products made from it.

Case–control study

Eleven cases (10 previously explored plus one additional case) and 44 controls were enrolled in the frequency-matched case–control study. The median age of cases was 56 years (range 20–90) and that of controls was 54.5 years (range 20–80). Reported symptoms ranged from diarrhoea (nine cases - none reported bloody diarrhoea), fever › 38.5°C (three cases) and vomiting (three cases). Three cases were hospitalised for five, seven and 10 days, respectively.

In univariable analysis only consumption of the specific food supplement and taking of medicines were significantly associated with *S.* Montevideo infection (Table). In a multivariable model including both risk factors, the specific food supplement was significantly associated with infection (OR: 19.2, 95% CI: 5.61–infinity, p-value=0.014) but not taking of medicines (OR: 3.79, 95% CI: 0.26–18.55, p-value=0.267). In a subanalysis restricted to cases with a date of disease onset between 29 March and 11 April, 2010 ("excess period") the association of disease and the food supplement was even stronger (OR: 43.5, 95% CI: 4.81–infinity, p-value=0.001). Four cases (one hospitalised) consumed the supplement but none of the controls. While the median age of all cases in the case–control study was 56 years (range 20–90), the median age of cases having consumed the specific food supplement was 65.5 years (range 47–90, difference not statistically significant in Kruskal-Wallis-test).There was no statistical significance on egg consumption (data not shown).

Product tracing

Product trace investigation revealed the trade route of ingredients and manufactured product. The main ingredient of the food supplement, hemp seed flour, was produced from hemp seed imported from China via the Netherlands by a German company (German State A). Later the seeds were milled in an oil mill (German State B) and the flour delivered to a wholesaler (German State A) who sold it to the food supplement producer (German State C), two bakeries in the south of Germany and a health food store in a city in the north of Germany. In addition, a fraction of the same batch of flour was exported to Slovenia.

Environmental investigation

Between February and May 2010 a total of 11 samples were taken for microbiological testing, with *S.* Montevideo found in six (54%) of the samples: in opened packages of food supplement from two cases' households (implicated lots), in two samples of food supplement (implicated lots) that had not been sold, in samples of hemp flour from opened and closed flour sacks at the production facility, as well as in a dust sample from the oil mill. Negative were a retain sample at the production facility (implicated lot), various hemp flour based products at the wholesale level, and other product and environmental samples from the oil mill.

Microbiological investigation and molecular subtyping

Two respective *S.* Montevideo isolates from stool specimens from two female outbreak cases who were included in the case–control study, one *S.* Montevideo isolate from the food supplement from a case's household, as well as an isolate from the oil mill in German State B were analysed by PFGE, together with *S.* Montevideo isolates from sources apparently unrelated to the outbreak, including two other human stool samples and a sample derived from bio-solids from a biogas plant.

The PFGE profiles of *S.* Montevideo isolates from the leftover of the food supplement of the case's household, the two female human case isolates and the isolate from the oil mill were indistinguishable (Figure 2).

Discussion

We describe an investigation of a disseminated outbreak of *S.* Montevideo infections where cases

Table

Risk factors for cases (n=11) and controls (n=44) of *Salmonella* Montevideo-associated illness in Germany, 29 March–11 April 2010

Exposure or underlying condition	Cases n/N[a]	Controls n/N[a]	Odds ratio[b]	95% Confidence interval[b]	p-value
Specific food supplement	4/11	0/43	27.5	3.15–∞	0.001
Other food supplements	5/10	20/44	3.3	0.63–17.82	0.092
Taking of medicines	8/9	21/44	8.7	0.99–405.20	0.030
Any chronic disease	5/9	15/44	2.4	0.56–10.35	0.273

[a] Total number of cases for whom information was available.

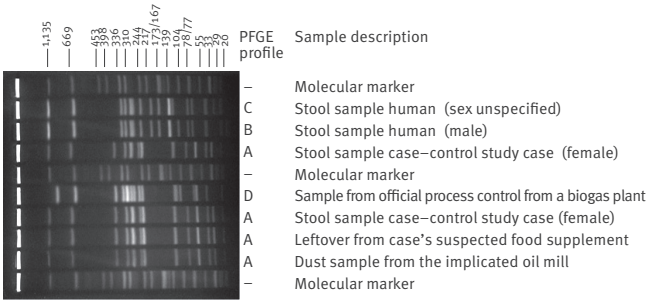
[b] Univariable exact logistic regression.

were ascertained in six German federal states. Epidemiological and microbiological evidence indicates that a herbal food supplement was a vehicle of infection and that hemp seed flour was most likely the contaminated ingredient, as a sample of hemp flour at the production facility tested positive for *S*. Montevideo. This is the first time that a RASFF notification could be connected to a human disease outbreak in Germany, albeit a small outbreak. A literature search provided only one other instance, where this had been achieved in another country [15]. Thus, food safety information of contaminated products can be a valuable source to public health authorities for hypothesis generation in outbreaks, provided that they are communicated in a timely manner.

Salmonella infections after consumption of food supplements are rarely noticed. They were first reported in 1966 in Tennessee, United States [16]. The food supplement in this outbreak tested positive both at the production site and in cases' households. Yet, a retain sample of an implicated lot had tested negative, demonstrating that tests on retain samples, which are often not representative of the entire lot, may convey a false sense of security. Hemp seed flour at the producer of the food supplement was confirmed as contaminated. In addition, the outbreak strain was also detected in dust samples of the oil mill. The source of the contamination before or at the oil mill remains elusive. There were no other links between hemp seed flour distributed to other customers (e.g. the bakeries) and additional cases. The distributor of the contaminated batches of hemp seed and hemp flour impounded all warehouse stocks of hemp seed and their derivates on 26 March. Some deliveries of hemp flour within Germany as well as to Slovenia took place beforehand. No resulting cases of infection were apparently noted in Slovenia.

Figure 2

Pulsed-field gel electrophoresis analysis (XbaI) of *Salmonella* Montevideo isolates obtained by the National Reference Centre during the outbreak-period, Germany, March–May 2010 (n=7)



PFGE: Pulsed-field gel electrophoresis.

The molecular marker fragments' sizes in kilobase pairs are shown on top of the picture.

Source of data: National Reference Centre for *Salmonella* and other Enterics, Robert Koch Institute, Wernigerode Branch, Germany.

Supplement consumption in this outbreak does not explain the increase in the number of cases entirely, leaving the possibility of more vehicles. Due to the low numbers of cases in exploration and the case–control study, we could not identify further risk factors. As the food supplement hypothesis could not have affected men, we cannot explain their infections directly, though we did not investigate if some of them were secondary cases to women infected by the food supplement. Interestingly, their greatest case excess was between 29 March and 4 April, when the four female cases explained by the supplement fell ill. Differential exposure recall of cases and controls is an inherent source of bias in case–control studies. However, taking such a supplement should be a well-remembered exposure, as the purchase would have required determined action and the consumption would have been regular over a longer period of time. The bias introduced in control selection by the requirement of a listed telephone number is recognised, but not thought to have made a significant difference in this study in view of the mainly affected age group.

The first evidence towards RASFF notification and subsequent product recall consisted of a first positive test result obtained from an official food control laboratory in one federal state due to a consumer's complaint. As this sample originated from an opened food supplement package the positive finding triggered further microbiological investigations of the product and its ingredients to render the evidence undisputable

In Europe, public warnings and product recalls are based on statutory instruments regarding the food legislation [17]. Producer and retailer of the food supplement and the ingredients were ascertained by product trace-back. The warning and product recall were issued at the time state laboratories found *S*. Montevideo in unopened packages and in the raw ingredients at the producer.

While investigations of the food safety authorities were thorough, without delay, and strictly following regulations, it is worth noting that the process from the beginning of the analysis of the first positive sample from an opened package to the recall took more than five weeks. In potential outbreak situations, strength of evidence for a suspected food product ought to be weighed against the potential harm to the consumers posed by the suspected food.

Interestingly, in the end there was no international aspect to this outbreak (as the Dutch label on the product did not correspond to sales in the Netherlands). Nevertheless it was only the RASFF directing the attention of German public health authorities to this contaminated product. Information from RASFF may aid in hypothesis generation investigations in addition to it being useful for early identification of emerging food safety hazards [18]. In Germany, unfortunately, currently there is no general requirement to communicate

non-international food contamination events to the public health authorities.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

We thank Dr. Manuel Dehnert for statistical support. We wish to sincerely acknowledge all women interviewed in the course of our investigation. Furthermore we are grateful to the local health departments involved for their support in contacting case patients as well as the local food authorities for their information on public health action in counties in response to this outbreak. We also thank the National Reference Laboratory (NRL) for the Analysis and Testing of Zoonoses (Salmonella) at the Federal Institute for Risk Assessment for their provision of data and specimens in this investigation. Finally we thank all registration offices providing contact data for the selection of controls.

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The European Commission proposes new measures against cross-border health threats

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Citation style for this article:
Eurosurveillance editorial team. The European Commission proposes new measures against cross-border health threats.
Euro Surveill. 2011;16(50):pii=20043. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20043

Article published on 15 December 2011

On 8 December 2011, the European Commission adopted a proposal that seeks to strengthen the existing means of the European Union (EU) to address cross-border health threats other than communicable diseases and to strengthen the preparedness for crises in the EU [1,2].

The draft proposal will now be transmitted to the Council and the European Parliament for amendment and would replace Decision No 2119/98/EC [3], which is one of the legal bases of the founding Regulation of the European Centre for Disease Prevention and Control (ECDC) [4]. ECDC currently identifies, assesses and communicates current and emerging threats to human health from communicable diseases in the EU and will continue to do so. The ECDC shall also act on its own initiative in the case of other outbreaks of illness of unknown origin which may spread within or to the Community, until the source of the outbreak is known. Other cross-border threats to health emerging from biological, chemical and environmental events are so far not being addressed in the same way.

The proposal would enable Member States and the Commission to set up additional ad hoc monitoring networks. This involves:

- coordinating actions between national planning and important economic sectors such as transport, energy and civil protection and supporting Member States in setting up a joint procurement mechanism for medical countermeasures;
- setting up an ad hoc network in situations where a Member State has raised an alert on a serious threat other than a communicable disease;
- expanding the remit of the Early Warning and Response System (EWRS) – which currently covers only communicable diseases – to cover all serious threats to health;
- coordinating development of national or European public health risk assessments for threats of biological, chemical or environmental origin in a crisis situation.

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