Impact factor 4.659

Eurosurveillance

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

Vol. 20 | Weekly issue 16 | 23 April 2015

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Human case of *Onchocerca lupi* infection, Germany, August 2014

A Bergua[1,2,3], B Hohberger[1,2,3], J Held[2,4], B Muntau[5], E Tannich[5], D Tappe (tappe@bnitm.de)[5]
1. Department of Ophthalmology and Eye Clinic, Friedrich Alexander Universität Erlangen-Nürnberg (FAU), Erlangen, Germany
2. Universitätsklinikum Erlangen, Erlangen, Germany
3. Both authors contributed equally to this study
4. Mikrobiologisches Institut, Friedrich Alexander Universität Erlangen-Nürnberg (FAU), Erlangen, Germany
5. Bernhard Nocht Institute, Hamburg, Germany

Citation style for this article:
Bergua A, Hohberger B, Held J, Muntau B, Tannich E, Tappe D. Human case of Onchocerca lupi infection, Germany, August 2014. Euro Surveill. 2015;20(16):pii=21099. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21099

Article submitted on 07 April 2015 / published on 23 April 2015

***Onchocerca lupi*, a nematode parasite infecting dogs and cats with a hitherto unknown arthropod vector, is also being recognised as a parasite also responsible for human eye infections. Here we describe a case of human eye infection diagnosed molecularly by nematode 12S rDNA PCR in a German patient who had travelled to Tunisia and Turkey. The patient recovered after treatment with antibiotic and anti-inflammatory therapy.**

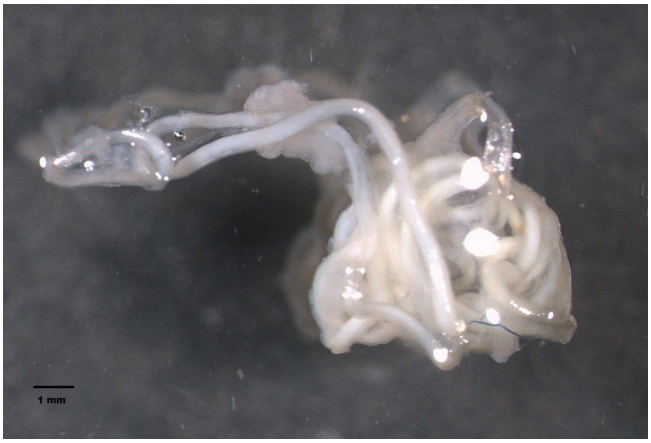
In this report we describe an eye infestation with *Onchocerca lupi* diagnosed in August 2014 by PCR in a German patient who had previously travelled to Tunisia and Turkey; the patient did not report a history of trauma or insect bite in the ocular or periocular region. *O. lupi* is an emerging nematode parasite found in dogs and cats in southern Europe (Portugal and Greece), central Europe (Germany and Hungary), and the United States (US) [1].

Case description

In August 2014, a 28-year-old German patient presented at the Department of Ophthalmology and Eye Clinic, University Hospital Erlangen-Nürnberg with a painful localised swelling of the bulbar conjunctiva supratemporally of the right eye, accompanied by severe episcleral and conjunctival hyperaemia. The swelling, mimicking a nodular scleritis, had developed two months before. It subsequently increased in size, became painful, and did not change under local and systemic steroids. The symptoms were not accompanied by fever or local lymphadenopathy. The patient did not report any history of trauma or insect bite in the ocular or periocular region, nor was animal contact reported. The patient had travelled to Tunisia (in June 2013, in the city of Sousse and its surroundings along the Mediterranean Sea) and Turkey (in July 2012, in the city of Alanya and its surroundings along the Mediterranean Sea). Visual acuity, intraocular pressure, anterior chamber, vitreous body, and the fundus of both eyes were normal. Inflammatory parameters and differential blood count were normal, but IgE was elevated (167 U/mL; norm: < 100). Slit lamp examination revealed a subconjunctival mass that after careful excision appeared to be an inactive nematode (Figure 1).

Figure 1

Macroscopic image of the *Onchocerca lupi* nematode removed from the eye of a German patient, August 2014



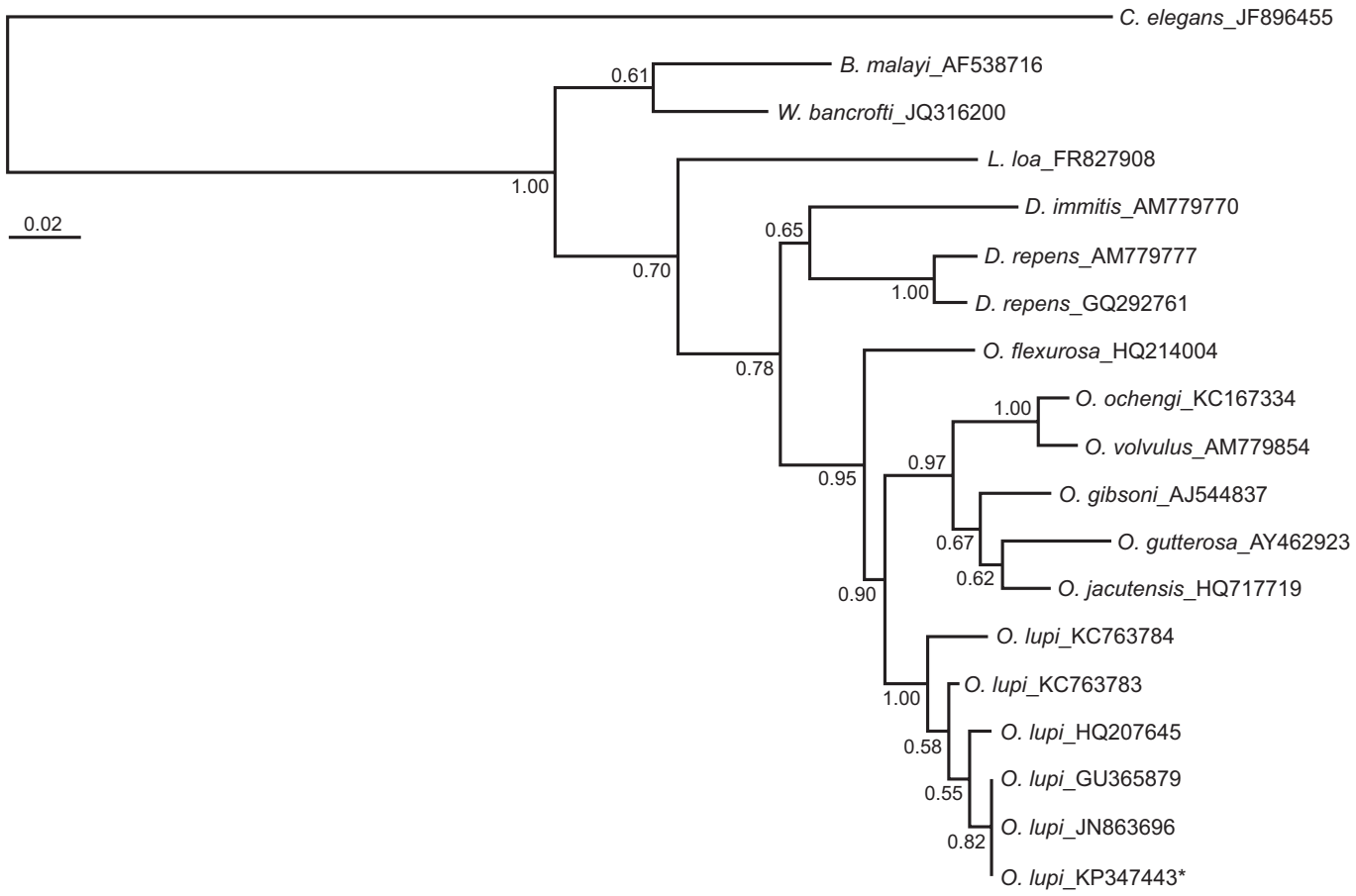
Recovered full subconjunctival specimen.
Magnification x 15.

Investigation of the cause of infection

The cuticle of the parasite showed external ridges resembling the cuticular serration of *Dirofilaria repens*, and ocular dirofilariosis was suspected. A nematode-specific PCR targeting the 12S rDNA [2] was conducted after DNA extraction from the removed parasite. The 393 bp amplicon was sequenced. BLAST analysis (www.ncbi.nlm.hih.gov/blast) showed 100% nt identity with *O. lupi* (GenBank accession number GU365879, canine infection in Portugal) and a 99% sequence identity with *O. lupi* from human infections in Iran and Turkey (JN863696 and HQ207645, respectively). The sequence

Figure 2

Molecular phylogeny of various *Onchocerca* species and other filaria species pathogenic for humans based on partial sequences of parasite 12S rRNA genes



The phylogenetic sequence tree was inferred using a Bayesian approach with 1,000,000 generations assuming the HKY model, and samples were taken every 100th generation. Bayesian posterior probabilities are given at the nodes and the scale bar is equal to 0.2 expected substitutions per site. GenBank accession numbers of the sequences used are provided and *Caenorhabditis elegans* was chosen as outgroup. The sequence of the specimen recovered from the patient's eye (KP347443) is marked with asterisk. It clusters in particular with *Onchocerca lupi* sequences from Portugal (canine infection, GU365879 (100% nt identity, 393 of 393 nt)) and Iran (human infection, JN863696 (99% nt identity, 393 of 395 nt)), followed by those from Turkey (human infection, HQ207645 (99% nt identity, 373 of 375 nt)) and California (canine infections, KC763783 (100% nt identity, 326 of 326 nt) and KC763784 (97% nt identity, 383 of 396 nt)).

from the patient's isolate was deposited in GenBank (KP347443) and clustered with European, Middle East, and Californian *O. lupi* sequences from humans and animals (Figure 2).

Follow-up of the patient

One month after this episode, a second, but smaller subconjunctival swelling developed supranasally on the same side. The mass impressed the retina, as observed by funduscopy and echography. Again, there was no lymphadenopathy and differential blood count was normal. Surgical exploration and subsequent histological examination revealed no obvious nematode structures; however, PCR was again positive for *O. lupi*. This discrepancy might be explained by the fact that the PCR was performed from a different, not microscopically examined part of the excised tissue than the part which underwent histopathological examination. Both lesions healed well under antibiotic therapy with topic tobramycin and cefuroxime in order to prevent bacterial superinfection, and anti-inflammatory therapy. Ivermectin or albendazole were not administered as complete resection was assumed.

Discussion

O. lupi is a nematode parasite infecting dogs and cats with a hitherto unknown arthropod vector, usually found in southern and central Europe and in the US; it is also being recognised as a parasite responsible for human eye infections. In dogs, nodular eye lesions with gravid females and production of microfilariae may develop [1]. The zoonotic significance of *O. lupi* was first highlighted in 2002 in two suspected human cases from Albania and Russia [3] that had occurred close to regions where the parasite had been described in a wolf and dogs [4]. Only recently, further and definitive human infections have been described from 2011 onwards in Turkey [5-7], Iran [8], Tunisia [7], and the US

[9,10]. The clinical picture in humans is characterised by the development of a bulbar subconjunctival nodule [5-7,10]. In one case also multiple eye nodules were observed [8]. An extradural infection with spinal cord compression was seen in a 22-month-old girl [9]. The presumed arthropod vector for *O. lupi* is unknown, but might be a simuliid black fly in analogy to the biology of *Onchocerca volvulus* [11], the agent of human river blindness. Besides more infections reported in dogs [1,4], several human eye infections with *O. lupi* have been reported. Symptoms in humans and dogs are strikingly similar, involving the eye and its appendices. As demonstrated by our case and a previously reported one [8], also multiple *O. lupi* nodules can occur during human infection – either in parallel [8] or, as seen in our case, successively. In the patient described here, molecular methods unequivocally identified *O. lupi* as the causative agent. The investigation of skin snips, as taken for the detection of microfilariae in *O. volvulus* infections and in canine *O. lupi* disease, has only been reported in one human case with an *O. lupi* infection [9]. In that case, caused by a gravid female *O. lupi* containing microfilariae, skin snips were negative. In all eight clearly diagnosed human cases we found in the literature, surgical excision led to a complete cure. Only in two cases [9,10] additional anthelminthic drugs (ivermectin and/or albendazole) were administered. In one case dexamethasone was applied after surgery and cryotherapy because of generalised urticaria [8]. The incubation time of the disease is unknown. In one report, a 'fly-bite' on the eye had been described 30 days before manifestation of conjunctivitis and 58 days before pain and swelling [5].

So far, in contrast to canine disease [1,4,12], definitive human *O. lupi* infections have not been described in Europe except for two cases living in Istanbul, Turkey [5,7]. The nematode's 12S rDNA sequence here was identical to a sequence from *O. lupi* in dogs from Portugal, and showed 99% similarities to sequences derived from human cases in Turkey and Iran (2 nt difference each in a stretch of 375 nt and of 395 nt, respectively). The parasite had been detected in a local dog from an animal shelter in Germany in 2002 [12], however, the source of the dog's infection remained unclear. In theory, similar to a recent report on the first autochthonous case of human dirofilariosis in Germany soon after the detection of *D. repens* in German dogs [13], the human *O. lupi* infection reported here could have also been acquired autochthonously in Germany – by a hitherto unknown vector, even though this does not seem very likely. Tunisia and Turkey, countries with reported human infections [5-7] were visited by our patient 11 and 22 months before symptom onset, respectively, and are more likely to have been the places of infection. Due to increasing global travel activities, international migration, and importation of dogs, more cases of human *O. lupi* infections might be diagnosed in the future.

Acknowledgments

We are grateful to Prof. Christian Bogdan, University Clinic of Erlangen, for critical reading of the manuscript.

Conflict of interest

None declared.

Authors' contributions

Patient examination and surgery: AB, BH. Molecular and morphological analyses: JH, DT, ET, BM. Wrote the manuscript: AB, BH, JH, BM, ET, DT.

References

1. Otranto D, Dantas-Torres F, Giannelli A, Latrofa MS, Papadopoulos E, Cardoso L, et al. Zoonotic Onchocerca lupi infection in dogs, Greece and Portugal, 2011-2012. Emerg Infect Dis. 2013;19(12):2000-3. http://dx.doi.org/10.3201/eid1912.130264 PMID:24274145
2. Casiraghi M, Bain O, Guerrero R, Martin C, Pocacqua V, Gardner SL, et al. Mapping the presence of Wolbachia pipientis on the phylogeny of filarial nematodes: evidence for symbiont loss during evolution. Int J Parasitol. 2004;34(2):191-203. http://dx.doi.org/10.1016/j.ijpara.2003.10.004 PMID:15037105
3. Sréter T, Széll Z, Egyed Z, Varga I. Subconjunctival zoonotic onchocerciasis in man: aberrant infection with Onchocerca lupi? Ann Trop Med Parasitol. 2002;96(5):497-502. http://dx.doi.org/10.1179/000349802125001267 PMID:12194710
4. Sréter T, Széll Z. Onchocercosis: a newly recognized disease in dogs. Vet Parasitol. 2008;151(1):1-13. http://dx.doi.org/10.1016/j.vetpar.2007.09.008 PMID:17951007
5. Otranto D, Sakru N, Testini G, Gürlü VP, Yakar K, Lia RP, et al. Case report: First evidence of human zoonotic infection by Onchocerca lupi (Spirurida, Onchocercidae). Am J Trop Med Hyg. 2011;84(1):55-8. http://dx.doi.org/10.4269/ajtmh.2011.10-0465 PMID:21212202
6. Ilhan HD, Yaman A, Morishima Y, Sugiyama H, Muto M, Yamasaki H, et al. Onchocerca lupi infection in Turkey: a unique case of a rare human parasite. Acta Parasitol. 2013;58(3):384-8. http://dx.doi.org/10.2478/s11686-013-0152-8 PMID:23990437
7. Otranto D, Dantas-Torres F, Cebeci Z, Yeniad B, Buyukbabani N, Boral OB, et al. Human ocular filariasis: further evidence on the zoonotic role of Onchocerca lupi. Parasit Vectors. 2012;5(1):84. http://dx.doi.org/10.1186/1756-3305-5-84 PMID:22541132
8. Mowlavi G, Farzbod F, Kheirkhah A, Mobedi I, Bowman DD, Naddaf SR. Human ocular onchocerciasis caused by Onchocerca lupi (Spirurida, Onchocercidae) in Iran. J Helminthol. 2014;88(2):250-5. http://dx.doi.org/10.1017/S0022149X13000060 PMID:23388686
9. Eberhard ML, Ostovar GA, Chundu K, Hobohm D, Feiz-Erfan I, Mathison BA, et al. Zoonotic Onchocerca lupi infection in a 22-month-old child in Arizona: first report in the United States and a review of the literature. Am J Trop Med Hyg. 2013;88(3):601-5. http://dx.doi.org/10.4269/ajtmh.12-0733 PMID:23382171
10. Otranto D, Giannelli A, Scotty Trumble N, Chavkin M, Kennard G, Latrofa MS, et al. Clinical case presentation and a review of the literature of canine onchocercosis by Onchocerca lupi in the United States. Parasit Vectors. 2015;8(1):89. http://dx.doi.org/10.1186/s13071-015-0699-3 PMID:25884672
11. Otranto D, Dantas-Torres F, Papadopoulos E, Petrić D, Ćupina AI, Bain O. Tracking the vector of Onchocerca lupi in a rural area of Greece. Emerg Infect Dis. 2012;18(7):1196-200. http://dx.doi.org/10.3201/eid1807.AD1807 PMID:22709878
12. Hermosilla C, Hetzel U, Bausch M, Grübl J, Bauer C. First autochthonous case of canine ocular onchocercosis in Germany. Vet Rec. 2005;156(14):450-2. http://dx.doi.org/10.1136/vr.156.14.450 PMID:15828728
13. Tappe D, Plauth M, Bauer T, Muntau B, Dießel L, Tannich E, et al. A case of autochthonous human Dirofilaria infection, Germany, March 2014. Euro Surveill. 2014;19(17):2-4. http://dx.doi.org/10.2807/1560-7917.ES2014.19.17.20790 PMID:24821120

Congenital rubella still a public health problem in Italy: analysis of national surveillance data from 2005 to 2013

C Giambi (cristina.giambi@iss.it)[1], A Filia[1], M C Rota[1], M Del Manso[1], S Declich[1], G Nacca[1], E Rizzuto[2], A Bella[1], regional contact points for rubella[3]

1. Communicable Disease Epidemiology Unit, National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome, Italy
2. Communicable Diseases Unit, Directorate General of Health Prevention, Ministry of Health, Rome, Italy
3. The contact points are listed at the end of the article.

Citation style for this article:
Giambi C, Filia A, Rota MC, Del Manso M, Declich S, Nacca G, Rizzuto E, Bella A, regional contact points for rubella. Congenital rubella still a public health problem in Italy: analysis of national surveillance data from 2005 to 2013. Euro Surveill. 2015;20(16):pii=21103. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21103

Article submitted on 17 November 2014 / published on 23 April 2015

In accordance with the goal of the World Health Organization Regional Office for Europe, the Italian national measles and rubella elimination plan aims to reduce the incidence of congenital rubella cases to less than one case per 100,000 live births by the end of 2015. We report national surveillance data for congenital rubella and rubella in pregnancy from 2005 to 2013. A total of 75 congenital rubella infections were reported; the national annual mean incidence was 1.5/100,000 live births, including probable and confirmed cases according to European Union case definition. Two peaks occurred in 2008 and 2012 (5.0 and 3.6/100,000 respectively). Overall, 160 rubella infections in pregnancy were reported; 69/148 women were multiparous and 38/126 had had a rubella antibody test before pregnancy. Among reported cases, there were 62 infected newborns, 31 voluntary abortions, one stillbirth and one spontaneous abortion. A total of 24 newborns were unclassified and 14 women were lost to follow-up, so underestimation is likely. To improve follow-up of cases, systematic procedures for monitoring infected mothers and children were introduced in 2013. To prevent congenital rubella, antibody screening before pregnancy and vaccination of susceptible women, including post-partum and post-abortum vaccination, should be promoted. Population coverage of two doses of measles-mumps-rubella vaccination of ≥95% should be maintained and knowledge of health professionals improved.

Introduction

Rubella is an acute contagious viral illness; if contracted early in pregnancy, it can spread from the mother to her developing baby and result in miscarriage, stillbirth or severe birth defects including deafness, blindness, cataracts, heart defects and mental retardation (congenital rubella). The risk of fetal malformation varies according to the time of onset of maternal infection and is estimated to be 90% for infants born to women infected within the first 10 weeks of pregnancy [1].

Rubella infection can be prevented by a safe and effective vaccine and the main aim of rubella control programmes is to prevent infection in pregnant women. In accordance with the objectives of the World Health Organization (WHO) Regional Office for Europe [2], the Italian national measles and rubella elimination plan aims to eliminate rubella (incidence to less than one case per 1,000,000 live births) and reduce the incidence of congenital rubella cases to less than one case per 100,000 live births by the end of 2015 [3].

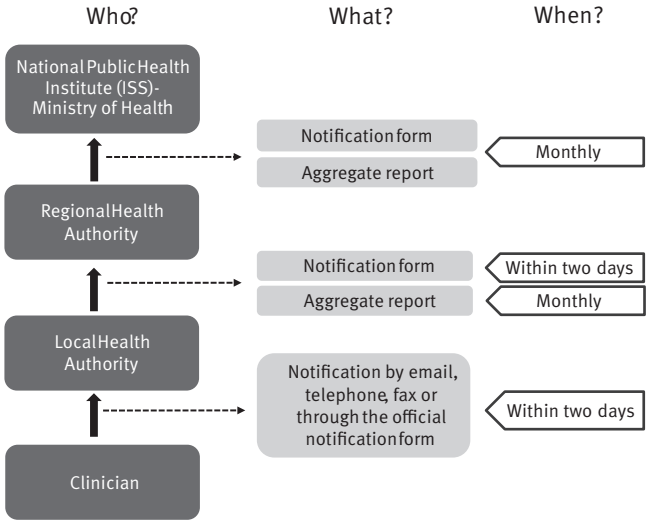
Congenital rubella prevention relies on maintaining high levels of immunity (≥95%) in the general population and on identifying and immunising susceptible women of childbearing age. This strategy allowed the elimination of rubella in the WHO Region of the Americas, where the last confirmed cases of endemic rubella and congenital rubella syndrome (CRS) were reported in 2009 [4].

In Italy, a monovalent rubella vaccine was first available in 1972; vaccination was initially recommended only for adolescent females. The monovalent vaccine was replaced in the early 1990s by the combined measles-mumps-rubella (MMR) vaccine and in 1999 universal vaccination with one dose of MMR vaccine was included in the national immunisation programme. In 2003, when Italy approved the first national measles and congenital rubella elimination plan, a two-dose schedule was adopted in all regions. Currently, a first dose of MMR vaccine is recommended at the age of 12 to 15 months and a second dose at 5 to 6 years of age. MMR vaccination is also offered free of charge to all susceptible adolescents and adults [5].

Uptake of one dose of MMR vaccine remained below 80% until 2002; uptake increased after implementation of the first national elimination plan (2003–07) and national vaccination coverage assessed in children at 24 months of age was 88% in 2013 [6]. Immunisation coverage of adolescents and adults is not routinely

Figure 1

Notification flow for congenital rubella and rubella infections in pregnancy in Italy



measured in Italy; in 2008, an epi-cluster survey conducted in 18 of the 21 Italian regions, found that rubella vaccine coverage was 75% in 16 year-old adolescents [7].

The national elimination plan recommends strengthening surveillance of rubella and congenital rubella cases. In Italy, postnatal rubella has been a notifiable disease since 1934, within a statutory surveillance system including 46 other infectious communicable diseases [8]; however, this system does not collect information on pregnancy status or on congenital rubella cases.

A national surveillance system for congenital rubella and rubella in pregnancy was implemented in 2005 [9]. This system is mandatory, passive, case-based and relies on reporting by clinicians (it is not laboratory based). Data flow is shown in Figure 1. Clinicians must notify suspected cases within two days to the local health authorities, who in turn are responsible for case investigations and monitoring newborns and pregnancy outcomes over time. Separate notification forms are used for congenital rubella and rubella infections in pregnancy and the notification form for congenital rubella also includes a section regarding the mother's history. Forms are forwarded to the regional health authorities who in turn send monthly reports to the Ministry of Health and the National Public Health Institute (Istituto Superiore di Sanità, ISS). Individual data are collected in a central database at the ISS and are regularly analysed. Case classifications are periodically updated based on follow-up data received by local health authorities [10]. A cross-check between the national database and regional archives of statutory notifications is performed yearly.

Surveillance systems for congenital rubella are active in 28 of 29 European Union (EU)/European Economic Area countries that participated in a survey conducted by the European Centre for Disease Prevention and Control (ECDC) in 2012 [11] and information on rubella infections in pregnancy was collected in 25 countries [11]. Although congenital rubella is notifiable at European level, incidence data are not collected by ECDC. They are reported from European countries to the WHO Regional Office for Europe through the WHO/United Nations Children's Fund Joint Reporting Form and are made available on the WHO website on a yearly basis [12]. However, congenital rubella is not included in the list of vaccine-preventable diseases currently monitored at European level by ECDC through TESSy (The European Surveillance System).

In this paper we analyse Italian national surveillance data for congenital rubella and rubella infection in pregnancy from 2005 to 2013, in order to monitor progress towards congenital rubella elimination and provide public health recommendations. Additionally, we discuss strengths and weaknesses of the surveillance system. Given the regional elimination goal, these data may be helpful to other public health actors in Europe.

Methods

Congenital rubella infections

We carried out a descriptive analysis of congenital rubella cases reported to the national surveillance system from 1 January 2005 to 31 December 2013. We classified cases as probable or confirmed according to the 2012 EU case definition for congenital rubella [13]. Cases for whom information was insufficient to confirm or exclude the diagnosis were excluded from the analysis. We calculated the incidence of congenital rubella by year and region, including confirmed and probable cases.

We described newborns with congenital rubella infection in terms of median gestational age, median weight at birth, sex, nationality and clinical manifestations. We also calculated the proportion of cases that satisfy the clinical criteria for CRS [13,14], that is (i) at least two of the category A conditions; or (ii) one category A and one category B condition (where category A conditions include cataract, congenital glaucoma, congenital heart disease, loss of hearing and pigmentary retinopathy, and those in category B include purpura, splenomegaly, microcephaly, developmental delay, meningo-encephalitis, radiolucent bone disease, jaundice that begins within 24 hours after birth).

In order to compare the incidence with the target of less than one case per 100,000 live births, we calculated the incidence of congenital rubella using the WHO Regional Office for Europe case definition (clinical CRS, epidemiologically linked CRS and laboratory-confirmed CRS) [14], which does not fully overlap with the EU case definition. The difference relates to asymptomatic

Table 1

Congenital rubella infections (n = 75) and rubella infections in pregnancy (n = 160) reported by year and case classification, Italy, 2005–13

Year	Congenital rubella[a]			Rubella in pregnancy[b]			
	Probable	Confirmed	Total	Possible	Probable	Confirmed	Total
2005	1	2	3	0	0	6	6
2006	1	0	1	0	0	1	1
2007	1	2	3	1	0	4	5
2008	0	29	29	0	1	76	77
2009	3	10	13	0	0	7	7
2010	0	2	2	0	0	5	5
2011	0	2	2	0	0	4	4
2012	1	18	19	3	7	40	50
2013	0	3	3	0	1	4	5
Total	7	68	75	4	9	147	160

[a] Cases were classified according to the 2012 European Union congenital rubella case definition [13].

[b] Cases were classified according to a modified version [10] of the 2012 European Union rubella case definition [13], that includes among the laboratory criteria for case confirmation a positive rubella IgM result supported by a rubella-specific IgG avidity test showing low avidity.

congenital infections. In particular, an infant born to a mother with confirmed rubella in pregnancy, with laboratory confirmation of infection but no rubella defects is classified as a confirmed case of congenital rubella according to the EU case definition, while the WHO Regional Office for Europe excludes cases without at least one Group A clinical condition [14]. Therefore, we excluded asymptomatic laboratory-confirmed cases to calculate incidence according to the WHO regional case definition.

In order to compare temporal trends of rubella and congenital rubella, we also calculated the incidence of postnatal rubella cases reported to the statutory surveillance system for communicable infectious diseases during 2005 to 2013. Data on postnatal rubella cases are collected in a central database at the Ministry of Health.

Rubella infections in pregnancy

We also carried out a descriptive analysis of rubella infections in pregnancy reported to the national surveillance system during 2005 to 2013. Reported cases included: (i) those notified through the notification form for rubella infection in pregnancy; and (ii) those whose data was obtained from the newborn's notification form (from the section regarding the mother's history), if mother's infection had not been previously notified.

We described cases in terms of median age at infection, nationality, parity, pregnancy trimester of infection, vaccination status, pre-pregnancy testing for rubella susceptibility and clinical manifestations.

Cases were classified as possible, probable or confirmed according to a modified version [10] of the 2012 EU rubella case definition [13], which includes among the laboratory criteria for case confirmation a positive rubella IgM result supported by a rubella-specific IgG avidity test showing low avidity. This criteria was added because when rubella infection is suspected during pregnancy, confirmation of a positive rubella IgM result (e.g. a rubella-specific IgG avidity test) is required [13].

Pregnancy outcomes

We matched data on congenital rubella cases and rubella infections in pregnancy (archived in two separate databases) in order to link pregnant women with their babies. We classified outcomes of pregnancy as live birth (infected, not infected or unknown state of infection), voluntary abortion, miscarriage and stillbirth. We also calculated the proportion of infected women who were lost to follow-up (for whom pregnancy outcome is unknown) and the proportion of infants, born to mothers with a possible, probable, or confirmed infection, who we were unable to classify either because they were lost to follow-up or because of insufficient data.

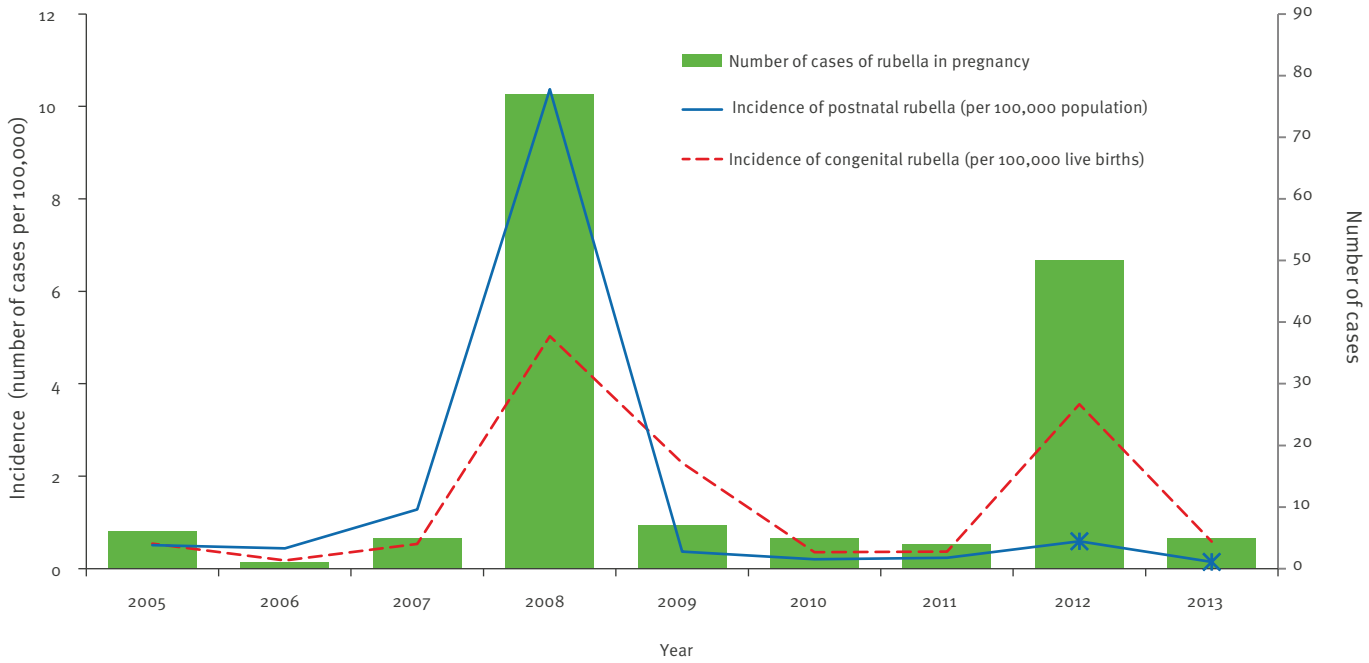
Statistical analysis

We summarised categorical variables using frequencies and proportions, and continuous variables as median and range. We used a chi-squared test or Fisher's exact test to compare proportions. We defined statistical significance as a p value of <0.05.

For calculating the incidence of congenital rubella infections and CRS, we used the number of live births of each year (2005–13) obtained from the Italian National Institute of Statistics (ISTAT) [15]. For calculating the incidence of rubella cases reported to the statutory surveillance system for infectious diseases, we used

Figure 2

Incidence of congenital[a] (n = 75) and postnatal rubella cases[b] (n = 8,421) and number of cases of rubella in pregnancy (n = 160)[c], Italy, 2005–13



The data for incidence of postnatal rubella in 2012 and 2013 (marked with a cross) are provisional, due to the ongoing implementation of a web-based surveillance system for infectious diseases in Italy.

[a] Cased were classified according to the 2012 European Union case definition for congenital rubella [13].

[b] Cases were classified according to clinical criteria for rubella [8].

[c] Cases were classified according to a modified version [10] of the 2012 European Union rubella case definition [13], that includes among the laboratory criteria for case confirmation a positive rubella IgM result supported by a rubella-specific IgG avidity test showing low avidity.

the resident population data of each year (2005–13) obtained from ISTAT [15]. Statistical analysis was performed using Epi Info software version 3.5.4.

Results

Congenital rubella

A total of 75 congenital rubella infections (7 probable and 68 confirmed cases) were reported during 2005 to 2013, according to the 2012 EU congenital rubella case definition [13] (Table 1). We received an additional 59 reports of suspected cases who could not be classified because the available information was insufficient. These were excluded from the analysis.

The median birth weight of 67 of the cases for whom information was available was 2,710 g (range: 913–4,330); 49/75 were male and 5/70 were born to foreign mothers. The median gestational age of cases was 38 weeks (range: 29–42) and 15/64 were born before the 37th week of pregnancy.

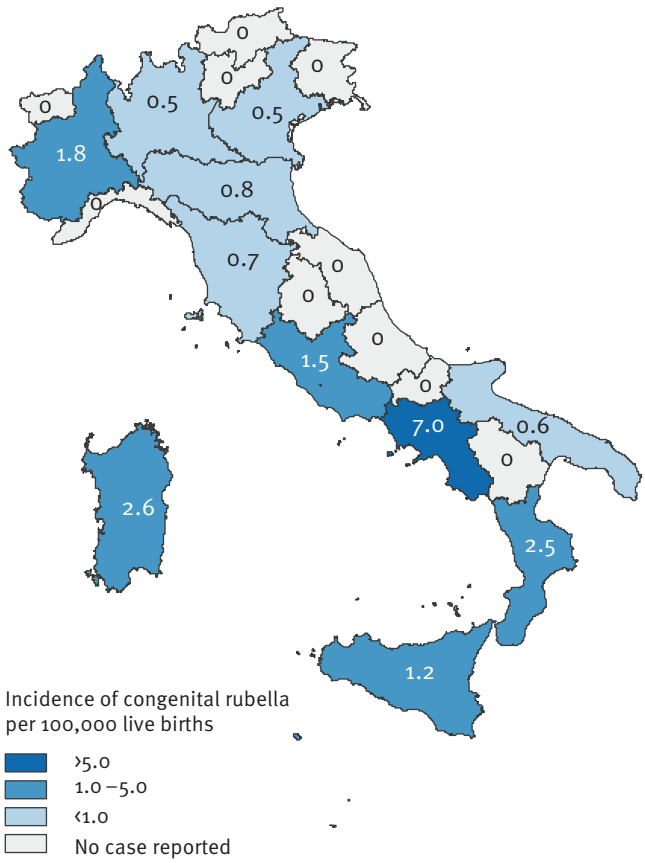
Information on clinical manifestations was available for 73 cases. Of them, 16 were asymptomatic, whereas 57 had at least one clinical manifestation. Among these 57 symptomatic cases, 37 newborns satisfied the clinical criteria for CRS [13,14], 17 had only one group A condition and three had at least one group B condition (but no group A conditions). The most frequently reported condition was congenital heart disease (n = 41), followed by loss of hearing (n = 26), jaundice within 24 hours of birth (n = 18), meningo-encephalitis (n = 11), cataract (n = 12), microcephaly (n = 10), splenomegaly (n = 8), developmental delay (n = 7), purpura (n = 6), and pigmentary retinopathy (n = 1). A total of 20 cases had multiple defects involving the heart, hearing or vision.

The national annual mean incidence in the years studied was 1.5 per 100,000 live births (mean annual number of live births in Italy: 553,389), including probable and confirmed cases according to the 2012 EU case definition. Two incidence peaks of congenital rubella infections occurred in 2008 and 2012, with an incidence of 5.0 and 3.6 per 100,000 newborns, respectively (Figure 2).

Statutory notifications of cases of postnatal rubella also experienced a peak in 2008 and there was a slight increase in the number of reported cases in 2012

Figure 3

Annual mean incidence of congenital rubella infections by region, including probable and confirmed cases[a], Italy, 2005–13 (n = 75)



[a] According to the 2012 European Union congenital rubella case definition [13].

(provisional data) (Figure 2). During 2005 to 2013, a total of 8,421 cases of postnatal rubella were notified, with a median age of cases of 17.5 years (range: 0–88 years).

Of the 21 regions of Italy, 11 reported congenital rubella cases, with regional annual mean incidences (confirmed and probable cases) in the years studied varying from 0.5 to 7.0 per 100,000 live births (Figure 3).

Most cases of congenital rubella reported in 2012 (16/19) were notified by a single region in southern Italy (incidence of 29.2/100,000 live births). In the same year, this region also reported 161 postnatal rubella cases, representing 46% of national cases (n = 353).

The national annual mean incidence of congenital rubella calculated according to the WHO case definition was 1.1 per 100,000 live births. In 2008, 2009 and 2012, it exceeded the threshold fixed by WHO to reach elimination (2.9, 1.8 and 3.2 case per 100,000 live births respectively).

Rubella infections in pregnancy

Overall, 160 rubella infections in pregnancy were reported, of whom 147 were classified as confirmed, nine as probable and four as possible cases according to the modified version [10] of the 2012 EU rubella case definition [13] (Table 1). An additional 105 reports were unclassified because of incomplete data; these were excluded from the analysis.

The median age of the 107 cases for whom information was available was 26 years (range: 16–46). Of these, 23 were foreign-born.

Only three women reported being vaccinated against rubella, but this information was documented in a vaccination card for only one of the cases; the woman had received two vaccine doses in her country of origin, at the age of three and 13 years. However, she was found to have been susceptible to the infection at preconception screening.

Of the 107 cases for whom information on gestational age at infection was available, 45 acquired rubella during the first trimester of pregnancy; 69/148 were multiparous. Only 38/126 women had had a rubella antibody test before pregnancy; among them, 32 stated that they had been found to be susceptible, three were immunised and the test result was missing for three women (Table 2).

Characteristics of Italian and foreign-born infected women were similar but the proportion of multiparous women was significantly higher among the latter, compared with Italian women (68.2 vs 43.2, p = 0.0304).

Notification forms of 51 of the 160 women with rubella infections in pregnancy were not received. In these 51 cases, information on demographic characteristics, clinical manifestations (reported in Table 2) and laboratory results were obtained from the notification forms of suspected congenital rubella of their babies (from the section regarding the mother's history). It indicates that in a large proportion of cases (32%), the infection of the mother had not been reported during pregnancy and information was collected after delivery.

Pregnancy outcomes

Among the 160 women who acquired rubella during pregnancy (two sets of twins were included for this analysis, giving a total of 162 pregnancies), there were 29 uninfected and 62 infected newborns (4 probable and 58 confirmed congenital rubella cases according to EU case definition for congenital rubella). Of the 62 infected newborns, 46 had clinical manifestations (28 of them satisfied the clinical criteria for CRS, 16 had only one group A condition and two had at least one group B condition) and 16 were asymptomatic. Overall, 24 newborns were not classified because of incomplete information (n = 19) or loss to follow-up (n = 5).

A total of 31 voluntary abortions, one stillbirth and one spontaneous abortion were also recorded. Pregnancy outcome was unknown for 14 women who were lost to follow-up (Table 3).

Discussion

The data presented show that the national incidence of congenital rubella during the two epidemic peaks in 2008 and 2012 exceeded the target of less than one per 100,000 live births needed to reach elimination [2]. The incidence was below the WHO threshold in 2013 and provisional data indicate lower values in 2014 (with only one case of congenital rubella reported). However, it is known that rubella infection occurs in epidemic cycles [16] and elimination has not yet been achieved in Italy.

Underestimation of congenital rubella cases is likely for several reasons. Firstly, we found a high percentage of cases lost to follow-up and of unclassified cases. In particular, in 23% (38/162) of cases of infection in pregnancy, the pregnancy outcome was unknown or the newborn was not monitored for final case classification. Additionally, we received 59 reports of suspected congenital rubella cases and 105 reports of suspected rubella infections in pregnancy that could not be classified because of incomplete data, which were excluded from the analysis. Secondly, information on aborted fetuses and stillbirths was not available and it is likely that at least some were infected. Thirdly, the proportion of cases with hearing loss and cataracts is lower than that reported in literature [16,17] and the proportion of cases with congenital heart diseases is higher [17], suggesting incomplete detection of milder cases.

Incidence calculated using the WHO case definition was obviously lower than that using the EU case definition because the former excluded asymptomatic laboratory-confirmed cases. In the framework of the elimination goal, the adoption of a common case definition would facilitate the evaluation of immunisation programmes.

Monitoring of suspected congenital rubella infections over time represents a critical aspect of the surveillance system, because a long follow-up is necessary to definitively classify cases. Laboratory confirmation of congenital infection is not always possible at birth (for instance, when infants are rubella-specific IgM negative at birth, a decrease in rubella-specific IgG levels by the age of 6–12 months allows the infection to be excluded) and also clinical manifestations are not necessarily present at birth.

Pregnancy outcomes of mothers with possible, probable or confirmed rubella infection during pregnancy also need to be monitored in order to detect congenital infections, including spontaneous or voluntary abortions or stillbirths that may occur if the infection is acquired in early pregnancy. No other sources of data for detecting abortions or stillbirths due to rubella infection are available in Italy.

Data from surveillance of rubella infections in pregnancy show that notification forms were not available for 32% (51/160) of the mothers; for these women, data were obtained from notification forms of their newborns, confirming underestimation of cases. Whenever information on mothers is obtained after delivery, it is not possible to obtain laboratory test results and, consequently, to correctly classify cases in a timely manner.

Several actions have been undertaken in Italy to improve the surveillance of congenital rubella and rubella infections in pregnancy. Firstly, at the end of 2013, the Ministry of Health disseminated national recommendations [10] to reinforce the surveillance system. The EU case definition for congenital rubella was adopted, a case definition for rubella in pregnancy was

Table 2

Demographic and clinical characteristics of women who acquired rubella during pregnancy, Italy, 2005–13 (n = 160)

Characteristic	Data	Number of cases (%)
Median age at infection (n = 107)	26 (range: 16–46)	NA
Country of birth (n = 159)	Italy	136 (85.5)
	Foreign country	23 (14.5)
Trimester of pregnancy at time of infection (n = 107)	First	45 (42.1)
	Second	41 (38.3)
	Third	21 (19.6)
Vaccination status (n = 127)	Vaccinated	3 (2.4)
	Unvaccinated	124 (97.6)
Previous pregnancies (n = 148)	0	79 (53.4)
	1	34 (23.0)
	2	25 (16.9)
	≥3	10 (6.8)
Rubella antibody testing before pregnancy (n = 126)	Performed	38 (30.2)
	Not performed	88 (69.8)
Clinical manifestations (n = 148)	Clinical criteria EU case definition fully met[a]	76 (51.4)
	Clinical criteria EU case definition partially met[b]	46 (31.1)
	Asymptomatic, laboratory confirmed	26 (17.6)

EU: European Union; NA: not applicable.

[a] Clinical criteria for 2012 EU rubella case definition [13] fully met: sudden onset of generalised maculo-papular rash AND at least one of the following: cervical adenopathy, sub-occipital adenopathy, post-auricular adenopathy, arthralgia, arthritis.

[b] Clinical criteria for 2012 EU rubella case definition [13] partially met: maculo-papular rash OR cervical adenopathy OR sub-occipital adenopathy OR post-auricular adenopathy OR arthralgia OR arthritis.

Table 3

Pregnancy outcomes of rubella infections acquired in pregnancy by case classification of mothers, Italy, 2005–13 (n = 162)[a]

Pregnancy outcome	Case classification of mothers[b]			Number (%)
	Possible	Probable	Confirmed	
Newborns infected	3	4	55	62 (38.3)
Newborns not infected	1	3	25	29 (17.9)
Newborns with unknown state of infection	0	1	23	24 (14.8)
Voluntary abortion	0	0	31	31 (19.1)
Spontaneous abortion	0	0	1	1 (0.6)
Stillbirth	0	0	1	1 (0.6)
Mothers lost to follow-up	0	1	13	14 (8.6)

[a] 162 outcomes (including two sets of twins) from 160 infected mothers.

[b] Cases were classified according to a modified version [10] of the 2012 European Union rubella case definition [13], that includes, among the laboratory criteria for case confirmation, a positive rubella IgM result supported by a rubella-specific IgG avidity test showing low avidity.

introduced (a modified version of the EU case definition for rubella) and the notification forms were modified, adding new variables to be collected, such as importation status (endemic, imported, import-related cases) and genotyping, which are critical for assessing the elimination of endemic rubella. Additionally, systematic procedures for monitoring infected pregnant women (until the end of pregnancy) and their newborns (at birth, 1, 6, 12, 18 and 24 months) were introduced. However these recommendations have not yet been implemented in all local health authorities. Secondly, an integrated surveillance system for measles and rubella was implemented at the national level in 2013 [18], requiring laboratory investigation of suspected cases of rubella and web-based reporting of cases. It could facilitate the early detection of rubella infections in pregnancy and encourage a timely follow-up. Thirdly, in order to assess under-reporting, an evaluation of the completeness of reporting to the surveillance system is being conducted at the national level, by analysing hospital discharge records for 2010 to 2014 to identify cases discharged with a diagnosis of congenital rubella (*International classification of diseases, ninth revision, clinical modification* (ICD-9-CM) code 771.0) [19].

In the Puglia region, hospital discharge records for 2003 to 2011 were analysed to identify ICD-9-CM codes 647.5 (rubella in pregnancy) and 771.0 (congenital rubella) and individual records of identified cases were retrieved [20]. Delivery-assistance certificate registries were also analysed to retrieve clinical histories of mothers of babies with CRS. One CRS, two congenital asymptomatic rubella infections and four suspected congenital rubella cases were identified, who were not included in the national surveillance database.

Data from laboratories could be an alternative source to assess under-reporting. However, in Italy, diagnostic testing for rubella infection (also in pregnancy) is often performed in private laboratories and building a network involving all these laboratories would be difficult to implement.

In order to prevent congenital rubella, susceptible women need to be identified and vaccinated before pregnancy. The Italian national elimination plan [3] has highlighted the need to reduce to below 5% the percentage of women of childbearing age who are susceptible to rubella. In Italy, the last national seroprevalence survey was conducted in 2004, showing that 11% of women aged 15–19 years and 8% aged 20–39 years were susceptible [21]. This study was conducted before preventive activities were implemented at the national level; however, some local studies published in 2012 have found a continued high percentage of women of childbearing age at risk of rubella infection, varying from 8% to 14% [22,23].

Rubella pre-conception screening is substantially underused in Italy, although it is available free of charge [24]. Data from the Progressi delle Aziende Sanitarie per la Salute in Italia [Progress by Local Health Units towards a Healthier Italy] (PASSI) Italian behavioural risk factor surveillance system showed that in 2010, 38% of 11,450 18–49 year-old women were not aware of their rubella immunisation status [25]. Additionally, a rubella seroprevalence study conducted in 2006 to 2007, targeting a group of pregnant women who had been referred to a prenatal clinic in southern Italy, found that only 55% of 500 pregnant women had undergone screening before pregnancy [23]. In our study, only 30% of infected women had verified their rubella immunity status before pregnancy and most of those found to be susceptible were not vaccinated. According to the national elimination plan, the rubella immunisation status of women of childbearing age should be evaluated whenever possible (e.g. concomitantly with human papilloma virus vaccination, at the 10-yearly anti-diphtheria-tetanus-pertussis booster

dose, at the first Pap test screening visit, at the first vaccination of their newborns, at the first contact of immigrant women with healthcare services), by checking vaccination cards or measuring rubella-specific IgG antibodies, and susceptible women should be promptly offered vaccination. Systematic reporting by laboratories of any negative rubella antibody results to vaccination services could be useful for an active search of seronegative women.

We found that a large proportion (47%) of infected women were multiparous, indicating that they had missed the opportunity to be vaccinated after previous pregnancies. The 2006–07 seroprevalence study mentioned above also found a high proportion of multiparous women: of 71 pregnant women (14.2% of the overall sample) susceptible to rubella, 33.8% had had at least one previous pregnancy [23].

About 14% of infected mothers in our study were not Italian-born, consistent with the rate of newborns from foreign-born mothers during 2005 to 2013 in Italy (9.4–15.1%) [15]. The significantly higher proportion of multiparous women among foreign-born women, compared with those who were Italian, suggests that particular attention needs to be given to this population group, as they may have limited access to healthcare services because of language and culture.

A serosurvey of 2,385 pregnant women, carried out in a region of northern Italy during 2008 to 2013 found that 11.7% of non-Italian women were seronegative for rubella-specific IgG and this proportion was higher than that of Italian women (6.2%, $p<0.01$) [22]. A serosurvey of 489 immigrant women, carried out during 2008 to 2009 in a town in southern Italy, found 17.8% seronegative women; 67% of the overall sample declared having no knowledge of rubella as a potential harm to fetus if the infection is contracted during pregnancy [26].

It is strongly advised to vaccinate all susceptible pregnant women with MMR vaccine during the post-partum (or post-abortum) period, in order to prevent the infection during a future pregnancy. The high proportion of multiparous women among reported cases of rubella in pregnancy shows that post-partum vaccination in Italy is not a routine procedure. Several post-partum vaccination strategies have been proposed in the national elimination plan: (i) immunisation in hospital before discharge; (ii) active call and immunisation at the public vaccination service (the hospital should forward the list of the susceptible women to the immunisation services); and (iii) immunisation at the public vaccination service concomitantly with the first vaccination of the newborn. A qualitative study, carried out in Australia in 2012 to explore the reasons for low maternal vaccine uptake, found that the incorporation of rubella susceptibility detection and maternal vaccination into standard care through a structured process was an important facilitator for immunisation uptake and offered an effective template for other perinatal management, such as pertussis and influenza vaccination [27].

More intensive regional approaches are needed in Italy, as variability of congenital rubella incidence was detected among the regions. In fact, the peak that occurred in 2012 was mostly attributable to a single southern region that notified 84% of all nationally reported cases, with a yearly incidence of 29.2/100,000 live births. A high rate of susceptible women of childbearing age is one explanation for the high incidence in this region, which historically had lower MMR vaccination coverage in children, compared with other regions [28]. The presence of a regional registry of perinatal infections, active since 1996 in this region, may have contributed to improved reporting of cases [29]. Collection of MMR vaccination coverage of adolescents and adults and seroprevalence data would facilitate regional evaluations.

Conclusion

Several actions have been implemented in Italy to strengthen surveillance of congenital rubella and rubella in pregnancy; however, further efforts are needed to ensure that these activities are implemented across the country. In particular, systematic procedures for the follow-up of infected children and mothers should be adopted in all regions.

In order to protect women of childbearing age from rubella infection, routine rubella antibody screening before pregnancy (which is recommended in Italy and offered free of charge) and vaccination of susceptible women, including post-partum and post-abortum vaccination, should be strongly promoted by clinicians.

Healthcare workers (general practitioners, paediatricians, gynaecologists and other specialists) should be sensitised and trained, both for enforcing notification procedures and for evaluating women's rubella immunisation status as a priority task during healthcare visits. Also, information campaigns for the general population are needed to increase awareness of the risk of acquiring rubella infection during pregnancy. Particular attention needs to be focused in high-incidence regions.

Finally, high two-dose MMR vaccination coverage of children should be maintained (≥95%) in order to interrupt viral circulation among the population.
raised among clinicians about the risk of leptospirosis exposure among these groups.

Acknowledgments

Surveillance of congenital rubella and rubella in pregnancy is carried out with financial support of the Italian Ministry of Health – CCM. We wish to thank all the regional and local contact points for rubella, the clinicians and the laboratories that routinely contribute to the notification, investigation, data collection and monitoring of cases. We wish also

to thank Wilma Buffolano, coordinator of the Registry of Perinatal Infections and the Network of the Delivery Clinics (RePuNaRC) for Campania Region, for her helpful support in tracing and following up cases in her region.

Conflict of interest

None declared.

Authors' contributions

Cristina Giambi coordinated surveillance activities for congenital rubella and rubella in pregnancy at the national level, analysed the data, interpreted the results, drafted and edited the manuscript. Antonietta Filia, Maria Cristina Rota and Silvia Declich coordinated surveillance activities, interpreted the results and critically revised the manuscript. Antonino Bella and Martina Del Manso analysed the data, interpreted the results and critically revised the manuscript. Gloria Nacca entered individual reports and follow-up information in the national database. Elvira Rizzuto provided data on postnatal rubella cases and critically revised the manuscript. Regional contact points for rubella coordinated surveillance activities at the regional level and critically revised the manuscript.

Regional contact points for rubella

Di Giacomo M (Abruzzo); Locuratolo F (Basilicata); Natter B (PA Bolzano); Mignuoli A (Calabria); Pizzuti R (Campania); Pascucci MG, Moschella L (Emilia-Romagna); Gallo T., Braida C. (Friuli Venezia Giulia); Vitagliano A, Guerra M (Lazio); Cremonesi I (Liguria); Coppola L, Piatti A (Lombardia); Fiacchini D, Damiani N (Marche); Bagnoli C, Ponzio GV (Molise); Ferrara L (Piemonte); Prato R, Cappelli MG (Puglia); Salotto M (Sardegna); Palermo M (Sicilia); Balocchini E, Gallicchio S (Toscana); Carraro V (PA Trento); Sudano L (Valle d'Aosta); Russo F, Zanella R (Veneto); Tosti A (Umbria).

References

1. Duszak RS. Congenital rubella syndrome--major review. Optometry. 2009;80(1):36-43. http://dx.doi.org/10.1016/j.optm.2008.03.006 PMID:19111256
2. World Health Organization (WHO) Regional Office for Europe. Eliminating measles and rubella. Framework for the verification process in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2012. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/156776/e96153-Eng-final-version.pdf
3. Ministero della Salute [Italian Ministry of Health]. Piano nazionale per l'eliminazione del morbillo e della rosolia congenita 2010-2015. [National Plan for the elimination of measles and congenital rubella 2010-2015]. Rome: Ministero della Salute; 2011. [Accessed 4 Nov 2014]. Italian. Available from: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1519_allegato.pdf
4. United States Centers for Disease Control and Prevention (CDC). National Center for Immunization and Respiratory Disease Division of Viral Diseases. CDC Report: Elimination of Measles, Rubella, and CRS. Documentation and verification of measles, rubella and congenital rubella syndrome elimination in the Region of the Americas. United States National Report, March 28, 2012. Atlanta, GA: CDC; 2012. Available from: http://www.cdc.gov/measles/downloads/Report-elimination-measles-rubella-crs.pdf
5. Italian Ministry of Health. Piano nazionale prevenzione vaccinale 2012-2014. [National Vaccination Prevention Plan 2012-2014]. Gazzetta Ufficiale [Official Bulletin]. 12 Mar 2012; no. 60. [Accessed 4 Nov 2014]. Italian. Available from: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1721_allegato.pdf
6. Ministero della Salute [Italian Ministry of Health]. Malattie infettive e vaccinazioni. Coperture vaccinali. [Infectious diseases and vaccinations. Vaccine coverage]. Rome: Ministero della Salute. [Accessed 4 Nov 2014]. Italian. Available from: http://www.salute.gov.it/malattieInfettive/paginaInternaMenuMalattieInfettive.jsp?id=811&menu=strumentieservizi
7. ICONA Working Group. ICONA 2008: Indagine di copertura vaccinale nazionale nei bambini e negli adolescenti. [ICONA 2008: national vaccination coverage survey among children and adolescents]. Rapporti ISTISAN. 09/29. Rome: Istituto Superiore di Sanità; 2009. [Accessed 4 Nov 2014]. Italian. Available from: http://www.iss.it/binary/publ/cont/09_29_web.pdf
8. Ministero della Salute [Italian Ministry of Health]. Decreto ministeriale 15 dicembre 1990 - Sistema informativo delle malattie infettive e diffusive. [Ministerial decree 15 December 1990 - Informative system for infectious communicable diseases]. Rome: Ministero della Salute; 15 December 1990. Gazzetta Ufficiale [Official Bulletin]. 8 Jan 1991; no. 6. [Accessed 4 Nov 2014]. Italian. Available from: http://www.salute.gov.it/imgs/C_17_normativa_1357_allegato.pdf
9. Ciofi Degli Atti ML, Filia A, Verteramo R, Iannazzo S, Curtale F, Masini L, et al. First cases of rubella infection during pregnancy detected by new reporting system in Italy. Euro Surveill. 2006;11(12):pii=2930.
10. Ministero della Salute [Italian Ministry of Health]. Sorveglianza della rosolia congenita e dell'infezione da virus della rosolia in gravidanza alla luce del nuovo Piano Nazionale di Eliminazione del morbillo e della rosolia congenita 2010-2015. [Surveillance of congenital rubella and rubella infection in pregnancy according to the new National Plan for measles and congenital rubella elimination 2010-2015]. Rome: Ministero della Salute; 17 July 2013. [Accessed 4 Nov 2014]. Italian. Available from: http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=0&codLeg=46583&parte=1%20&serie=
11. European Centre for Disease Prevention and Control (ECDC). Survey on rubella, rubella in pregnancy and congenital rubella surveillance systems in EU/EEA countries. Stockholm: ECDC; 2013. Available from: http://ecdc.europa.eu/en/publications/Publications/survey-rubella-pregnancy-congenital-surveillance-systems-may-2013.pdf
12. World Health Organization (WHO). Rubella (crs) reported cases. Reported incidence time series. Geneva: WHO. [Accessed 4 Nov 2014]. Available from: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencecrs.html
13. European Commission. Commission Implementing Decision of 8 August 2012 (2012/506/EU) amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Official Journal of the European Union. Luxembourg: Publications Office of the European Union. 27.9.2012;L 262. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:262:0001:0057:EN:PDF
14. World Health Organization (WHO) Regional Office for Europe. Surveillance guidelines for measles, rubella and congenital rubella syndrome in the WHO European Region. Update December 2012. Copenhagen: WHO Regional Office for Europe; 2012. Available from: http://www.euro.who.int/__data/assets/pdf_file/0018/79020/e93035-2013.pdf
15. Italian National Institute of Statistics (ISTAT). Popolazione residente, bilancio demografico e cittadinni stranieri.[Resident population, demographic balance and resident foreigners]. Rome: ISTAT. [Accessed 4 Nov 2014]. Available from: demo.istat.it
16. Plotkin SA, Reef SE. Rubella vaccine. In: Plotkin SA, Orenstein W, Offit P, editors. Vaccines. 5th ed.: Saunders Elsevier; 2008. p. 735-71.
17. Dontigny L, Arsenault MY, Martel MJ, Biringer A, Cormier J, Delaney M, et al.; Society of Obstetricians and Gynecologist of Canada. Rubella in pregnancy. J Obstet Gynaecol Can. 2008;30(2):152-68. PMID:18254998
18. Ministero della Salute Italian Ministry of Health. Istituzione di un sistema di sorveglianza integrato per il morbillo e la rosolia alla luce del nuovo Piano Nazionale di Eliminazione del morbillo e della rosolia congenita 2010–2015. [Implementation of an integrated surveillance system for measles and rubella according to the new National Plan for measles and congenital rubella elimination 2010-2015]. Rome: Ministero della Salute; 20 February 2013. Italian. Available from: http://www.sitiappulolucana.it/images/pdf.scaricabili/PNEMoRc%202010-2015%20completo.pdf
19. Centers for Disease Control and Prevention (CDC). International classification of diseases, ninth revision, clinical modification (ICD-9-CM). Atlanta, GA: CDC; 2010. [Accessed 4 Nov 2014]. Available from: http://www.cdc.gov/nchs/icd/icd9cm.htm
20. Cozza V, Martinelli D, Cappelli MG, Tafuri S, Fortunato F, Prato R. Further efforts in the achievement of congenital rubella syndrome/rubella elimination: alternative sources of

information for retrospective case-finding, Puglia Region, Italy, 2003-2011. Hum Vaccin Immunother. 2015;11(1):220-4. http://dx.doi.org/10.4161/hv.36154 PMID:25483539

21. Rota MC, Bella A, Gabutti G, Giambi C, Filia A, Guido M, et al.; Serological Study Group. Rubella seroprofile of the Italian population: an 8-year comparison. Epidemiol Infect. 2007;135(4):555-62. http://dx.doi.org/10.1017/S0950268806007400 PMID:17076939
22. De Paschale M, Manco MT, Paganini A, Agrappi C, Mirri P, Cucchi G, et al. Rubella antibody screening during pregnancy in an urban area of northern Italy. Infect Dis Rep. 2012;4(1)e17.
23. Calimeri S, Capua A, La Fauci V, Squeri R, Grillo OC, Lo Giudice D. Prevalence of serum anti-rubella virus antibodies among pregnant women in southern Italy. Int J Gynaecol Obstet. 2012;116(3):211-3. http://dx.doi.org/10.1016/j.ijgo.2011.10.029 PMID:22233835
24. Italian Ministry of Health. Aggiornamento del d.m. 6 marzo 1995 concernente l'aggiornamento del d.m. 14 aprile 1984 recante protocolli di accesso agli esami di laboratorio e di diagnostica strumentale per le donne in stato di gravidanza e a tutela della maternità. [Procedures to access to laboratory exams and instrumental methods of diagnosis for pregnant women and maternity's protection]. Rome: Ministero della Salute. Ministerial Decree 10 September 1998. Italian. Gazzetta Ufficiale [Official Bulletin]. 20 October 1998, no. 245.
25. Istituto Superiore di Sanità. La sorveglianza Passi. Rapporto nazionale Passi 2010: vaccinazione antirosolia. [PASSI surveillance. PASSI national report 2010: vaccination against rubella]. Italian. [Accessed 4 Nov 2014]. Available from: http://www.epicentro.iss.it/passi/rapporto2010/R2010VaccinazioneAntirosolia.asp
26. Lo Giudice D, Capua A, La Fauci V, Squeri R, Grillo OC, Calimeri S. Congenital rubella syndrome and immunity status of immigrant women living in southern Italy: a cross-sectional, seroepidemiological investigation. Travel Med Infect Dis. 2014;12(3):253-7. http://dx.doi.org/10.1016/j.tmaid.2014.01.003 PMID:24502919
27. Webb H, Street J, Marshall H. Incorporating immunizations into routine obstetric care to facilitate Health Care Practitioners in implementing maternal immunization recommendations. Hum Vaccin Immunother. 2014;10(4):1114-21. http://dx.doi.org/10.4161/hv.27893 PMID:24509790
28. ICONA Working Group. ICONA: Indagine nazionale sulla copertura vaccinale infantile. [ICONA: national survey on pediatric vaccination coverage]. Rapporti ISTISAN. 98/33. Rome: Istituto Superiore di Sanità; 1998. Italian.
29. Buffolano W, Lorenzo E, Lodato S, Parlato A, Pizzuti R, Onlus Rete Punti Nascita Regione Campania, Servizi Epidemiologia e Prevenzione ASL Regione Campania (SEP). Surveillance of congenital rubella: the Campania "Perinatal Infections" Registry experience. Bollettino epidemiologico nazionale (BEN) - Notiziario ISS. 2003;16(5). [Accessed 4 Nov 2014]. Available from: http://www.epicentro.iss.it/ben/2003/maggio2003/4_en.htm

A multi-country *Salmonella* Enteritidis phage type 14b outbreak associated with eggs from a German producer: 'near real-time' application of whole genome sequencing and food chain investigations, United Kingdom, May to September 2014

T Inns (thomas.inns@phe.gov.uk)[1], C Lane[2], T Peters2, T Dallman[2], C Chatt[3], N McFarland[4], P Crook[5], T Bishop[6], J Edge[6], J Hawker[3], R Elson[2], K Neal[3], G K Adak[2], P Cleary[1], on behalf of the Outbreak Control Team[7]

1. Field Epidemiology Services Liverpool, Public Health England, United Kingdom
2. Centre for Infectious Disease Surveillance and Control, Public Health England, United Kingdom
3. Field Epidemiology Services Birmingham, Public Health England, United Kingdom
4. Wessex Public Health England Centre, Public Health England, United Kingdom
5. Field Epidemiology Services Victoria, Public Health England, United Kingdom
6. Food Standards Agency, United Kingdom
7. Members of the team are listed at the end of the article

Citation style for this article:
Inns T, Lane C, Peters T, Dallman T, Chatt C, McFarland N, Crook P, Bishop T, Edge J, Hawker J, Elson R, Neal K, Adak GK, Cleary P, on behalf of the Outbreak Control Team. A multi-country Salmonella Enteritidis phage type 14b outbreak associated with eggs from a German producer: 'near real-time' application of whole genome sequencing and food chain investigations, United Kingdom, May to September 2014. Euro Surveill. 2015;20(16):pii=21098. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21098

Article submitted on 12 November 2014 / published on 23 April 2015

We report an outbreak of *Salmonella* Enteritidis phage type 14b (PT14b) in the United Kingdom (UK) between May and September 2014 where Public Health England launched an investigation to identify the source of infection and implement control measures. During the same period, outbreaks caused by a *Salmonella* Enteritidis strain with a specific multilocus variable-number tandem repeat analysis (MLVA) profile occurred in other European Union Member States. Isolates from a number of persons affected by the UK outbreak, who had initially been tested by MLVA also shared this particular profile. Cases were defined as any person infected with *S.* Enteritidis PT14b, resident in England or Wales and without history of travel outside of this geographical area during the incubation period, reported from 1 June 2014 onwards, with a MLVA profile of 2–11–9-7–4-3–2-8–9 or a single locus variant thereof. In total, 287 cases met the definition. Food traceback investigations in the UK and other affected European countries linked the outbreaks to chicken eggs from a German company. We undertook whole genome sequencing of isolates from UK and European cases, implicated UK premises, and German eggs: isolates were highly similar. Combined with food traceback information, this confirmed that the UK outbreak was also linked to a German producer.

Introduction

The adoption of vaccination and other measures in management of poultry production has led to a reduction in the number of *Salmonella enterica* serovar Enteritidis infections in the United Kingdom (UK) [1,2]. Despite this reduction, there have been several outbreaks of *S.* Enteritidis phage type 14b (PT14b) in the UK which have been associated with chicken eggs originating from outside the UK [3-5].

At the beginning of June 2014, Public Health England (PHE) was alerted to an outbreak of *S.* Enteritidis PT14b in a hospital in central England. Following this, outbreaks of *S.* Enteritidis PT14b cases were detected in the North West and South of England. In addition, PHE was alerted through the Epidemic Intelligence Information System (EPIS) to six Salmonella outbreaks in France associated with eggs from a German producer and an Austrian *Salmonella* outbreak, both countries reporting matching multilocus variable-number tandem repeat analysis (MLVA) profiles of 2–11–9-7–4-3–2-8–9 [6]. Following the detection of an exceedance in the cumulative number of *S.* Enteritidis PT14b cases in England and Wales (Figure 1), some of whom reported the same MLVA profile, PHE launched a national investigation; the first national outbreak control team meeting was held on 6 August 2014. The investigation was undertaken to identify the source of infection and implement control measures to prevent further cases.

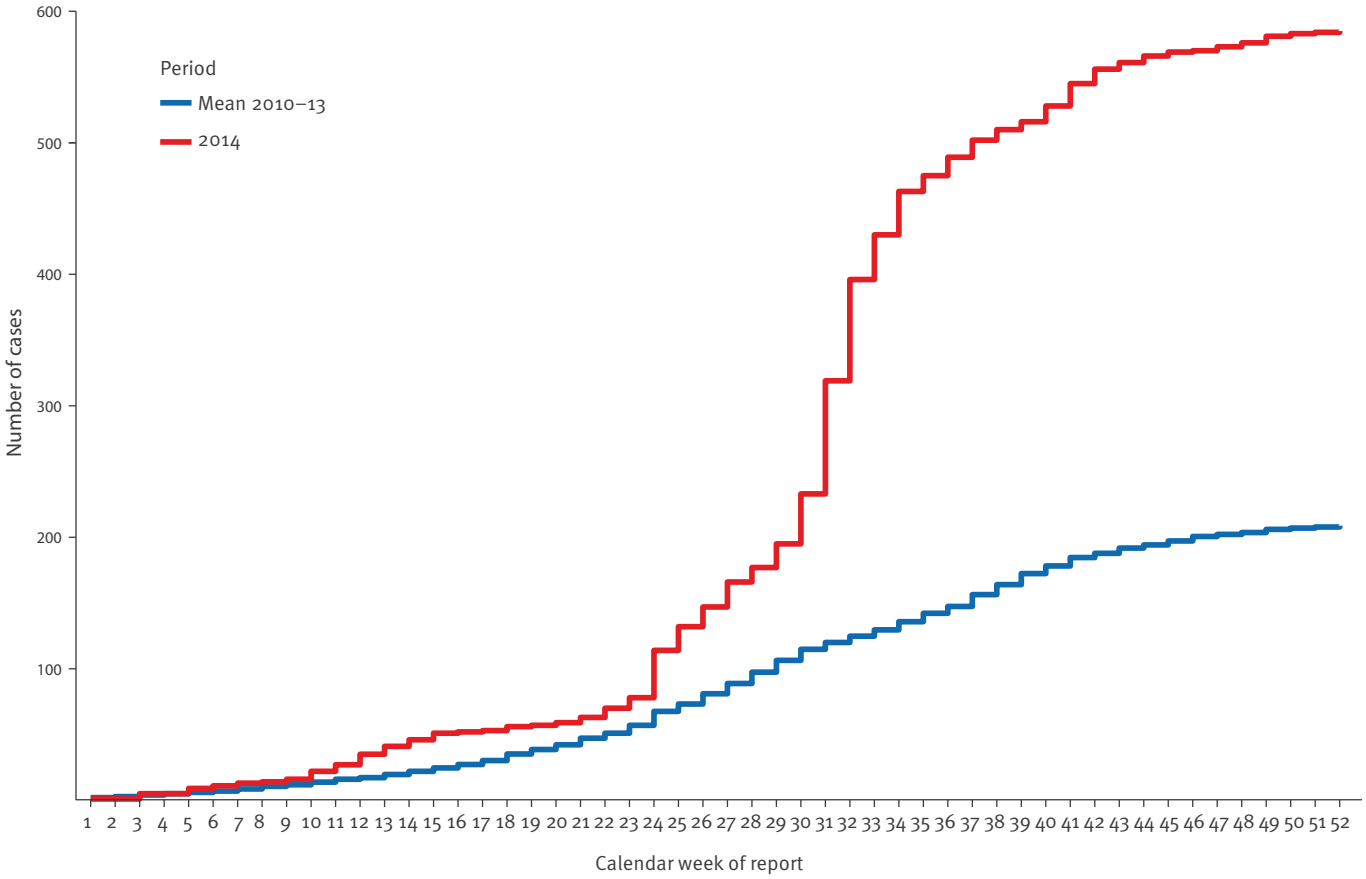
Methods

Epidemiological investigations

Case ascertainment was from statutory notifications of cases of Salmonella infection. A case was defined as any person infected with *S.* Enteritidis PT14b, resident in England or Wales and without history of travel outside of this geographical area during the incubation period (usually up to 72 hours) [7], reported on or

Figure 1

Cumulative count by calendar week, of *Salmonella* Enteritidis PT14b cases in England and Wales, 2014 compared with the 2010–2013 mean



after 1 June 2014, with a MLVA profile of 2–11–9-7–4-3–2-8–9, or a single locus variant thereof (the MLVA outbreak profile). Cases were interviewed using local questionnaires to ascertain foods eaten in the five days before onset of symptoms. These questionnaires differed depending on where in the UK the case was interviewed. Shops, restaurants and other food outlets reported by cases were identified and when a certain premise was related to several cases, environmental or food samples were taken, where possible.

Food traceback investigations

In addition to the information received through EPIS, Rapid Alert System for Food and Feed (RASFF) notifications were issued on 9 July 2014 (France), 31 July 2014 (Austria) and 1 August 2014 (France). These notifications linked *S.* Enteritidis outbreaks in France and Austria to chicken eggs from Company X in Germany. Subsequent updates to the RASFF notifications indicated that the outbreaks were caused by *S.* Enteritidis PT14b. The MLVA results of clinical isolates from France were first reported on 14 August 2014. Food chain investigations involved obtaining information on the supply of eggs from Company X to UK distributors and tracing onward supply from these distributors to other UK companies. In addition, food chain investigations were conducted in England and Wales to trace supplies of chicken and chicken eggs consumed by cases to their source, where possible.

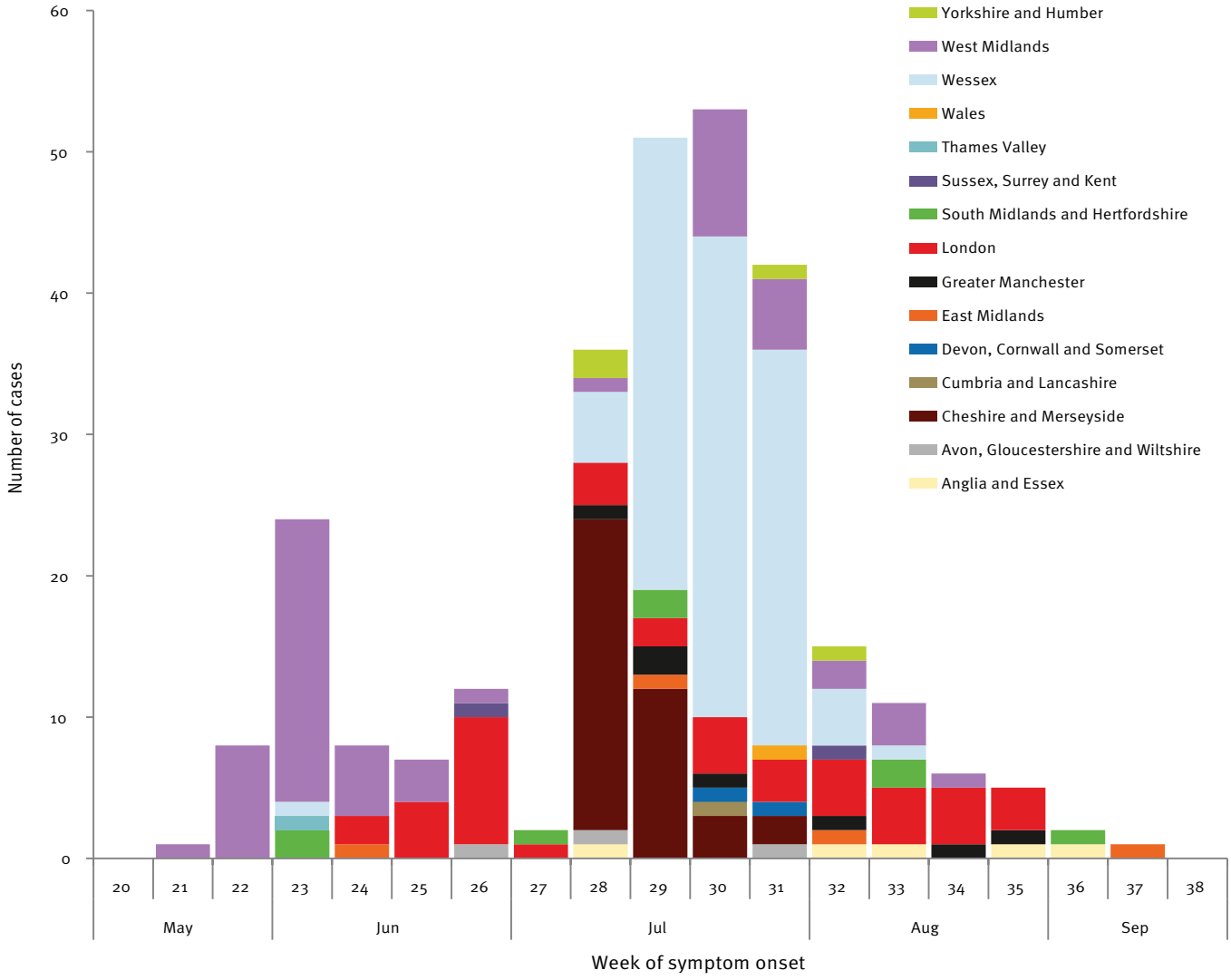
Microbiological investigations

S. Enteritidis strains conformed to the recognised pattern for phage PT14b as described in the current schemes [8]. Isolates were further characterised by MLVA typing [9] and whole genome sequencing (WGS). Sequencing was carried out by the PHE Genome Sequencing Unit using Nextera library preparation and the Illumina HiSeq 2500 in fast run mode according to manufacturers' instructions.

High quality Illumina reads were mapped to the *S. enterica* Enteritidis reference genome (GenBank accession number: AM933172) using BWA-MEM [10]. Single nucleotide polymorphisms (SNPs) were then identified using GATK2 in unified genotyper mode [11]. The core genome is defined as nucleotide positions that are shared between the reference strain and all other strains in the analysis. Core genome positions that had a high quality SNP (>90% consensus, minimum depth 10x, GQ≥30) in at least one strain were extracted and RaxML used to derive the maximum likelihood phylogeny of the isolates [12]. FASTQ reads from all sequences in this study can be found at the PHE Pathogens

Figure 2

Distribution of *Salmonella* Enteritidis phage type 14b, by calendar week of symptom onset and Public Health England centre of residence, England and Wales, week 20–38 2014 (n=284)[a]



[a] Symptom onset dates were not available for three of the 287 outbreak cases.

BioProject at the National Center for Biotechnology Information (accession: PRJNA248792).

International investigations

As international communications had identified that cases had also occurred in other European Union (EU) Member States (Germany and Luxembourg), WGS was undertaken on isolates from outside the UK. This included four isolates from France comprising two from human cases and two from eggs originating from Company X. One human isolate was received from Luxembourg. Six isolates were received from Austria, all from humans. Fourteen isolates were received from Germany; five from humans, one from a cake and eight from eggs from Company X (six from one Company X site, two from another Company X site).

Results

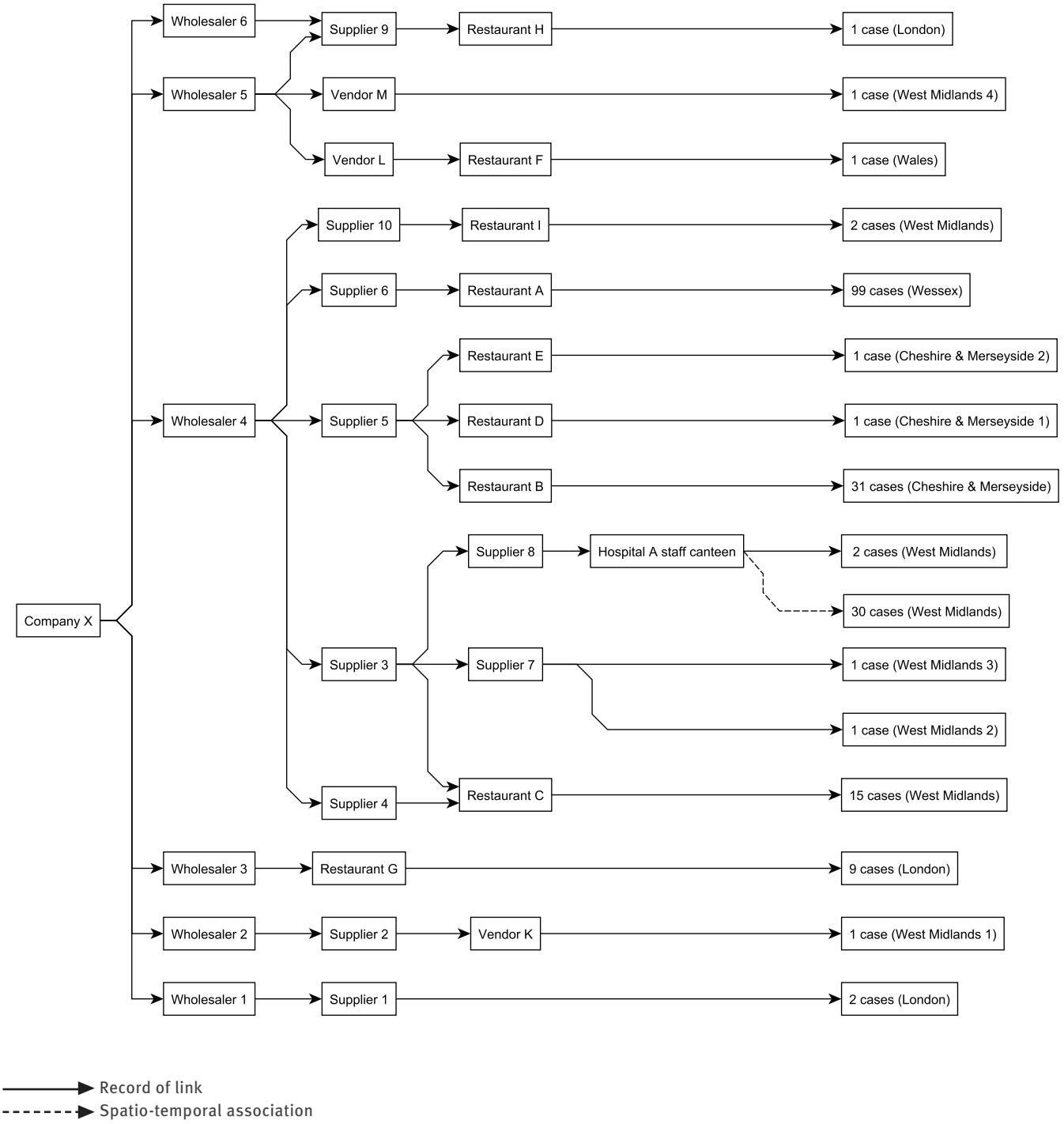
Outbreak description

In total, 287 cases met the definition; ages ranged from <1 to 92 years (median 29), 151 (53%) were male. Seventy-eight (27%) cases were reported to have been hospitalised (of whom 61 were not thought to have acquired their infection while in hospital). Symptom onset dates ranged from 25 May 2014 to 7 September 2014. The week of symptom onset is shown in Figure 2; this also includes information on the residence of cases. A number of outbreak cases were associated with specific premises which are briefly described below.

Between 25 May and 18 June 2014, 32 cases (patients, staff and visitors) were linked to a single hospital in

Figure 3

Egg supply network showing links between Company X and *Salmonella* Enteritidis phage type14b cases in England and Wales, 2014



central England (hospital A), of whom 17 had spent the whole incubation period in the hospital. *Salmonella* infection was considered to be a contributory factor in the cause of death for one patient.

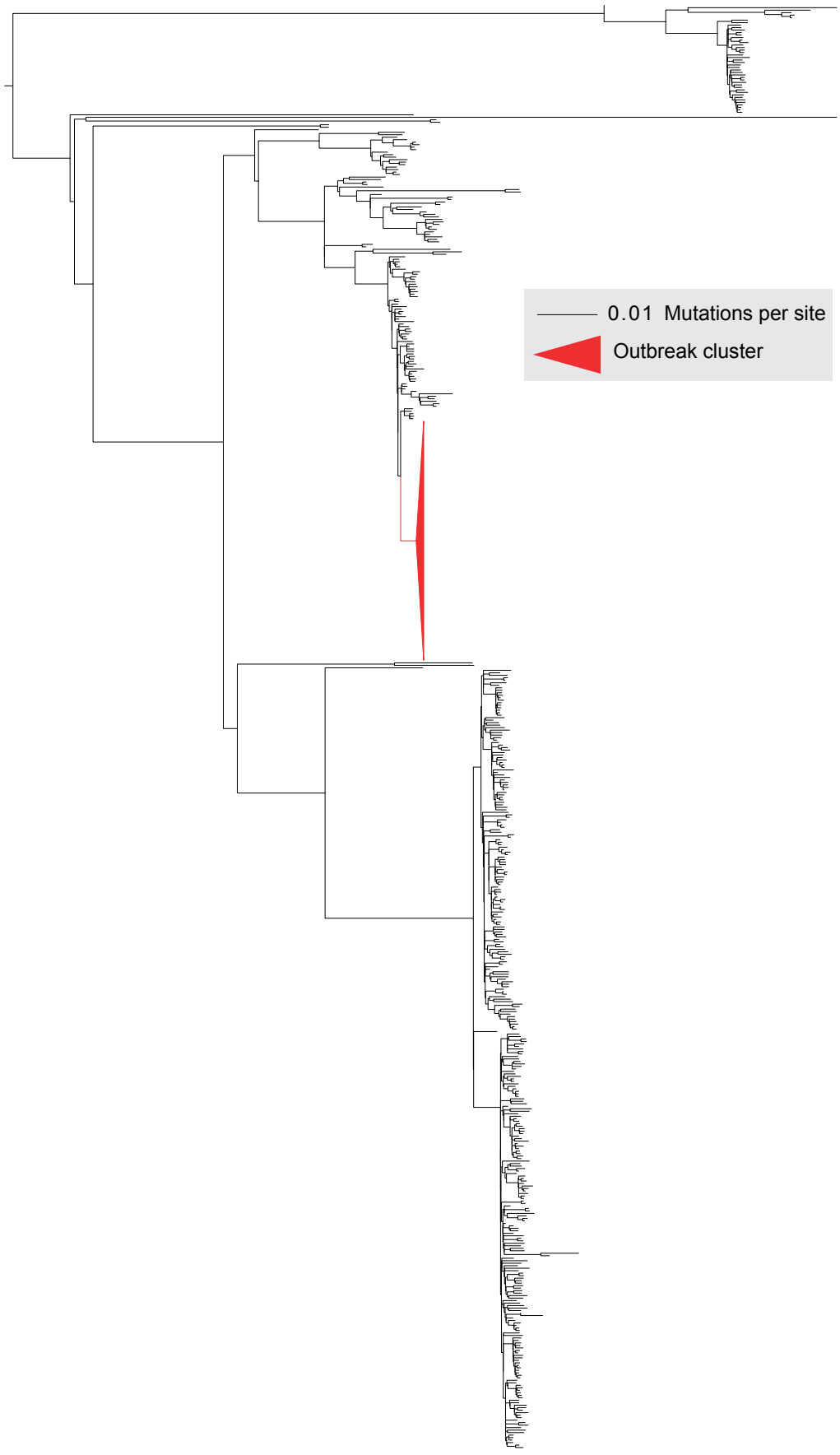
Ninety-nine cases were linked to restaurant A in southern England. Cases reported eating at the restaurant between 11 July and the closure of the restaurant on 24 July to improve food hygiene practices.

Between 8 and 19 July 2014, 31 cases were linked to restaurant B in North West England.

Fourteen cases were linked to restaurant C in central England. Cases reported symptom onsets between 24 July and 6 August 2014. The restaurant closed voluntarily between 7 and 13 August 2014. One further case occurred after this on 1 September.

Figure 4

Phylogeny of *Salmonella* Enteritidis isolates, including representative isolates from England and Wales (n = 484) sequenced between January 2012 and September 2014, together with outbreak isolates from Austria, France, Germany, Luxembourg and the United Kingdom, occurring from May to September 2014 (n = 332)



Following epidemiological and environmental investigations, *Salmonella* was isolated from a catering trolley on one of the wards of hospital A. *Salmonella* was also isolated from food samples (cooked chicken and pork) and an environmental sample (a cleaning cloth) taken at the restaurant B premises. At restaurant C, a dishcloth, a swab from a vegetable preparation sink and a sample of egg-containing vegetarian noodles all tested positive for *Salmonella*. The food and environmental samples from hospital A, restaurants B and C which were positive for *Salmonella* were typed as *S.* Enteritidis PT14b, with the same MLVA profile as cases. Six eggs of Spanish origin were sampled from restaurant C on 12 August 2014; all tested negative for *Salmonella*.

Food chain investigations

In total, 198 of 287 (69%) cases could be plausibly linked to eggs supplied by one company, Company X (Figure 3). Thirty-two cases ate at premises where eggs with a Company X egg stamp number were observed; 166 cases were linked to premises that were plausibly supplied by Company X at the time of exposure according to information from suppliers. Restaurants A, B and C were all supplied with eggs originating from Company X, as was one outlet at hospital A (although most cases did not report eating food from this outlet). It appeared that the majority of cases in England may have acquired the infection via catering services, rather than from eggs obtained from retail establishments.

Company X has four sites, three in Germany, one in the Czech Republic, all operationally independent. All four sites use young chickens (pullets) from two sites, one in Germany and one in the Czech Republic. The last delivery to the UK from all three German sites was on the 17 July 2014; the last delivery of eggs from the Czech Republic site was on 1 September 2014.

Microbiology

The human isolates from France, Austria, Germany and Luxembourg all had the outbreak MLVA profile. The eggs from Company X shared the outbreak MLVA profile. Initial WGS results were available by 26 August 2014 for both UK (including 20 environmental samples and the 287 clinical isolates) and non-UK samples. The WGS results showed that the 332 clinical and environmental samples from Austria, France, Germany, Luxembourg and the United Kingdom clustered phylogenetically into a tight cluster on the *S.* Enteritidis phylogeny (Figure 4). Within the outbreak cluster the minimum SNP distance between strains was 0 and the maximum 23 SNPs. Within the hospital outbreak A and the restaurant outbreaks A, B and C the mode SNP distance was 0 SNPs with no clinical isolate differing by greater than 2 SNPs. Implicated environmental isolates were either identical or a single SNP away from a clinical isolate. Clinical isolates from the rest of Europe clustered within clinical isolates from England and Wales as did all eight isolates from eggs from Company X.

Control measures

Following the reported French outbreaks, investigations at one of the German sites found *Salmonella* in chicken faeces and dust, along with eggs positive for *Salmonella* with the MLVA outbreak profile; investigations at another German site also found eggs positive for the outbreak strain. At both sites public health control measures were taken in August 2014, these included ensuring that affected eggs were properly processed before human consumption.

In the UK, premises associated with clusters were investigated by environmental health officers to ensure compliance with food hygiene guidelines. As the available evidence indicated that potentially affected eggs had been supplied to catering establishments in the UK, on 22 August 2014 the FSA sent letters to UK local authorities which asked them to contact catering establishments in their area and reiterate FSA advice on how to cook and prepare eggs safely. In the letters, the FSA asked local authorities to look in catering establishments for eggs with the three egg stamp numbers relating to Company X's German premises, but no reports of finding these eggs were received. On 22 August 2014, caterers were also reminded of the guidelines for the safe handling of eggs via the FSA website [13]. As the available evidence suggested that the potentially affected eggs had been distributed to catering, rather than retail establishments in the UK, it was not necessary to recall them from consumers. Enhanced infection control procedures were introduced in hospital A to reduce the risk of person to person spread.

Discussion

We present WGS data which provide a clear link between isolates from humans, eggs and environmental samples from premises associated with clusters of cases in an outbreak affecting several EU Member States. This, along with the egg supply network information and information from investigations in other European countries, provides compelling evidence to support the hypothesis that this outbreak was associated with eggs from a German producer (Company X).

This outbreak demonstrated the importance of MLVA which was used to identify this multi-country *Salmonella* outbreak, and the use of WGS which further confirmed the findings. WGS allows improved discrimination between isolates, and adds a new dimension to descriptive epidemiology in the form of phylogenetic relationships [14]. WGS has previously been used for the prospective surveillance of *Salmonella* [15] and to confirm a multi-country *Salmonella* outbreak in Europe [16], but here it was used for the first time in 'near real-time' to define a multi-country Salmonella outbreak and inform public health control measures.

During this investigation, no eggs supplied by Company X were found in the UK for testing; this most likely reflects the delay between egg consumption, symptom onset, phage typing, food history taking and egg sampling. The delay between egg consumption and sampling is usually greater than the shelf life of eggs which is typically 26 days (Mark Jones, AHVLA, personal communication, 24 September 2014), making it inherently unlikely that eggs identified at catering premises during this outbreak investigation were the ones consumed by cases.

An interesting aspect of the WGS results is that within the outbreak cluster there was a maximum genetic distance of 23 SNPs. Within each of the restaurant outbreaks (A-C) and the hospital outbreak, strains differed between 0-2 SNPs. We hypothesise that, while the outbreak cluster formed a monophyletic group, these differences between point source outbreaks were due to eggs that had a degree of *S*. Enteritidis variation at the source of the contamination in the various Company X sites.

We present genetic and food supply information which support the hypothesis that this multinational *S*. Enteritidis PT14b outbreak was associated with eggs from a German producer. This investigation demonstrates the importance of European cooperation when investigating complex food supply networks. Information, both official and informal, from other European countries was important in both detecting the outbreak and ensuring that public health actions in the UK were as timely as possible. We therefore recommend greater use of the RASFF and EPIS systems to exchange intelligence on outbreaks and contaminated foodstuffs both between and within European countries.
Being able to sequence isolates from German eggs made the genetic evidence linking this source to UK cases more compelling. We therefore recommend that EU Members States support measures to create a framework to ensure that public health control measures are enhanced by the exchange of pathogen sequencing information.

Members of the Outbreak Control Team

Bob Adak, Natalie Adams, Debbie Anderson, Philip Ashton, Sooria Balasegaram, Maree Barnett, Tracy Bishop, Louise Brown, Carol Chatt, Paul Cleary, Paul Cook, Paul Crook, Tim Dallman, Elizabeth de Pinna, Joanne Edge, Richard Elson, Ian Fisher, Andrew Fox, Rachel Freeman, Kirsten Glen, Gauri Godbole, Jeremy Hawker, Thomas Inns, Jo Jefferies, Marko Kerac, Geraldine Leong, Chris Lane, Michelle Leung, Keith Neal, Gillian Marsh, Noëleen McFarland, Ruth Moreno, Cam Morgan, Stephen Morton, Ruth Parry, Tansy Peters, Philip Randles, Sarah Reeves, Alex Stewart, Kirsten Stone, Drazenka Tubin-Delic, Roberto Vivancos.

Acknowledgements

We gratefully acknowledge the contribution of Environmental Health Officers in undertaking food traceback investigations. We also acknowledge those involved in the investigations of outbreaks in Hospital A and restaurants A, B and C. We would like to thank Wolfgang Rabsch, Simon Le Hello, Joel Mossong and Christian Kornschober for sending isolates from Germany, France, Luxembourg and Austria, respectively.

Conflict of interest

None declared.

Authors' contributions

Epidemiological investigations were conducted by CL, CC, NM, PCr, JH, RE, KN and PCl. Microbiological investigations were co-ordinated by TD and TP. Food traceback investigations were coordinated by TB and JE. The manuscript was drafted by TI. All authors commented and agreed upon the final manuscript.

References

1. Lane CR, LeBaigue S, Esan OB, Awofisyo AA, Adams NL, Fisher IST, et al. Salmonella enterica serovar Enteritidis, England and Wales, 1945-2011. Emerg Infect Dis. 2014;20(7):1097-104. http://dx.doi.org/10.3201/eid2007.121850 PMID:24960614
2. Hugas M, Beloeil P. Controlling Salmonella along the food chain in the European Union - progress over the last ten years. Euro Surveill. 2014;19(19):20804. http://dx.doi.org/10.2807/1560-7917.ES2014.19.19.20804 PMID:24852953
3. O'Brien S, Gillespie IA, Charlett A, Adak GK, Threlfall EJ, Ward L. National case-control study of Salmonella Enteritidis Phage Type 14b infection in England and Wales implicates eggs used in the catering trade. Euro Surveill. 2004;8(8):pii=2388.
4. Janmohamed K, Zenner D, Little C, Lane C, Wain J, Charlett A, et al. National outbreak of Salmonella Enteritidis phage type 14b in England, September to December 2009: case-control study. Euro Surveill. 2011;16(15):19840. PMID:21507321
5. Harker KS, Lane C, Gormley FJ, Adak GK. National outbreaks of Salmonella infection in the UK, 2000-2011. Epidemiol Infect. 2014;142(3):601-7. http://dx.doi.org/10.1017/S0950268813001210 PMID:23721866
6. European Centre for Disease Prevention and Control (ECDC). European Food Safety Authority (EFSA). Multi-country outbreak of Salmonella Enteritidis infections associated with consumption of eggs from Germany–25 August 2014. Stockholm and Parma: ECDC/EFSA; 2014.
7. Heymann DL, editor. Control of Communicable Diseases Manual. 20th ed. Washington DC: American Public Health Association; 2014.
8. Ward LR, de Sa JDH, Rowe B. A phage-typing scheme for Salmonella enteritidis. Epidemiol Infect. 1987;99(2):291-4. http://dx.doi.org/10.1017/S0950268800067765 PMID:3315705
9. Hopkins KL, Peters TM, de Pinna E, Wain J. Standardisation of multilocus variable-number tandem-repeat analysis (MLVA) for subtyping of Salmonella enterica serovar Enteritidis. Euro Surveill. 2011;16(32):11. PMID:21871223
10. Li H, Durbin R. Fast and accurate long-read alignment with Burrows-Wheeler transform. Bioinformatics. 2010;26(5):589-95. http://dx.doi.org/10.1093/bioinformatics/btp698 PMID:20080505
11. McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, et al. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res. 2010;20(9):1297-303. http://dx.doi.org/10.1101/gr.107524.110 PMID:20644199
12. Stamatakis A. RAxML version 8: a tool for phylogenetic analysis and post-analysis of large phylogenies. Bioinformatics. 2014;30(9):1312-3. http://dx.doi.org/10.1093/bioinformatics/btu033 PMID:24451623
13. Food Standards Agency (FSA). FSA advice to caterers on the safe handling of eggs [Accessed 10 Oct 2014]. Available from: http://www.food.gov.uk/news-updates/news/2014/12842/fsa-advice-to-caterers-on-the-safe-handling-of-eggs

14. Lienau EK, Strain E, Wang C, Zheng J, Ottesen AR, Keys CE, et al. Identification of a salmonellosis outbreak by means of molecular sequencing. N Engl J Med. 2011;364(10):981-2. http://dx.doi.org/10.1056/NEJMc1100443 PMID:21345093

15. den Bakker HC, Allard MW, Bopp D, Brown EW, Fontana J, Iqbal Z, et al. Rapid whole-genome sequencing for surveillance of Salmonella enterica serovar enteritidis. Emerg Infect Dis. 2014;20(8):1306-14. http://dx.doi.org/10.3201/eid2008.131399 PMID:25062035

16. Byrne L, Fisher I, Peters T, Mather A, Thomson N, Rosner B, et al.; International Outbreak Control Team. A multi-country outbreak of Salmonella Newport gastroenteritis in Europe associated with watermelon from Brazil, confirmed by whole genome sequencing: October 2011 to January 2012. Euro Surveill. 2014;19(31):6-13. http://dx.doi.org/10.2807/1560-7917.ES2014.19.31.20866 PMID:25138971

Changing hepatitis A epidemiology in the European Union: new challenges and opportunities

C M Gossner (Celine.Gossner@ecdc.europa.eu)[1,2,3], E Severi[1,3], N Danielsson[1], Y Hutin[4], D Coulombier[1]
1. European Centre for Disease Prevention and Control (ECDC), Surveillance and Response Support Unit, Stockholm, Sweden
2. School of Public Health and Primary Care (CAPHRI), Maastricht University Medical Center (MUMC+), Maastricht, the Netherlands
3. These authors contributed equally to the paper
4. European Centre for Disease Prevention and Control (ECDC), Public Health Capacity and Communication, Stockholm, Sweden

Citation style for this article:
Gossner CM, Severi E, Danielsson N, Hutin Y, Coulombier D. Changing hepatitis A epidemiology in the European Union: new challenges and opportunities. Euro Surveill. 2015;20(16):pii=21101. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21101

Article submitted on 24 February 2014 / published on 23 April 2015

This perspective on hepatitis A in the European Union and European Economic Area (EU/EEA) presents epidemiological data on new cases and outbreaks and vaccination policies. Hepatitis A endemicity in the EU/EEA ranges from very low to intermediate with a decline in notification rates in recent decades. Vaccination uptake has been insufficient to compensate for the increasing number of susceptible individuals. Large outbreaks occur. Travel increases the probability of introducing the virus into susceptible populations and secondary transmission. Travel medicine services and healthcare providers should be more effective in educating travellers and travel agents regarding the risk of travel-associated hepatitis A. The European Centre for Disease Prevention and Control (ECDC) endorses the World Health Organization's recommendations on vaccination of high-risk groups in countries with low and very low endemicity and on universal vaccination in countries with intermediate endemicity. Those recommendations do not cover the use of hepatitis A vaccine to control outbreaks. ECDC together with EU/EEA countries should produce evidence-based recommendations on hepatitis A immunisation to control outbreaks. Data about risk behaviours, exposure and mortality are scarce at the EU/EEA level. EU/EEA countries should report to ECDC comprehensive epidemiological and microbiological data to identify opportunities for prevention.

Hepatitis A

This paper is a perspective on hepatitis A in the European Union and European Economic Area (EU/EEA) taking account of epidemiological data on new cases and outbreaks, and on vaccination policies.

Hepatitis A is a common acute viral infection caused by hepatitis A virus (HAV) that affects 120 million people annually worldwide [1]. The virus spreads mostly through the faecal-oral route via person-to-person contact or ingestion of contaminated food or water; in rare cases, transmission can also occur via infected blood. HAV belongs to the family Picornaviridae; six genotypes have been identified, with subtypes A and B of genotypes I, II, and III infecting humans [2].

Young children often have asymptomatic HAV infection. The proportion of symptomatic infection and severe disease increases with age. The incubation period is 30 days ranging from 15 to 50 days. Symptoms include fever, diarrhoea, fatigue, anorexia, nausea, dark-coloured urine and jaundice. Hepatitis A illness ranges from mild to severe and lasts from two weeks to several months. Bi- or multiphasic relapsing hepatitis with a duration of up to 40 weeks may complicate the course in 6 to 10% of symptomatic HAV infections [3] but recovery is complete and no chronic infections have been reported. Immunity after infection is lifelong. HAV infection rarely causes fulminant hepatitis and liver failure (overall case fatality ratio: 0.1 to 0.3%). Patients with underlying chronic liver disease and people older than 50 years have higher case fatality ratios (1.8%) [4].

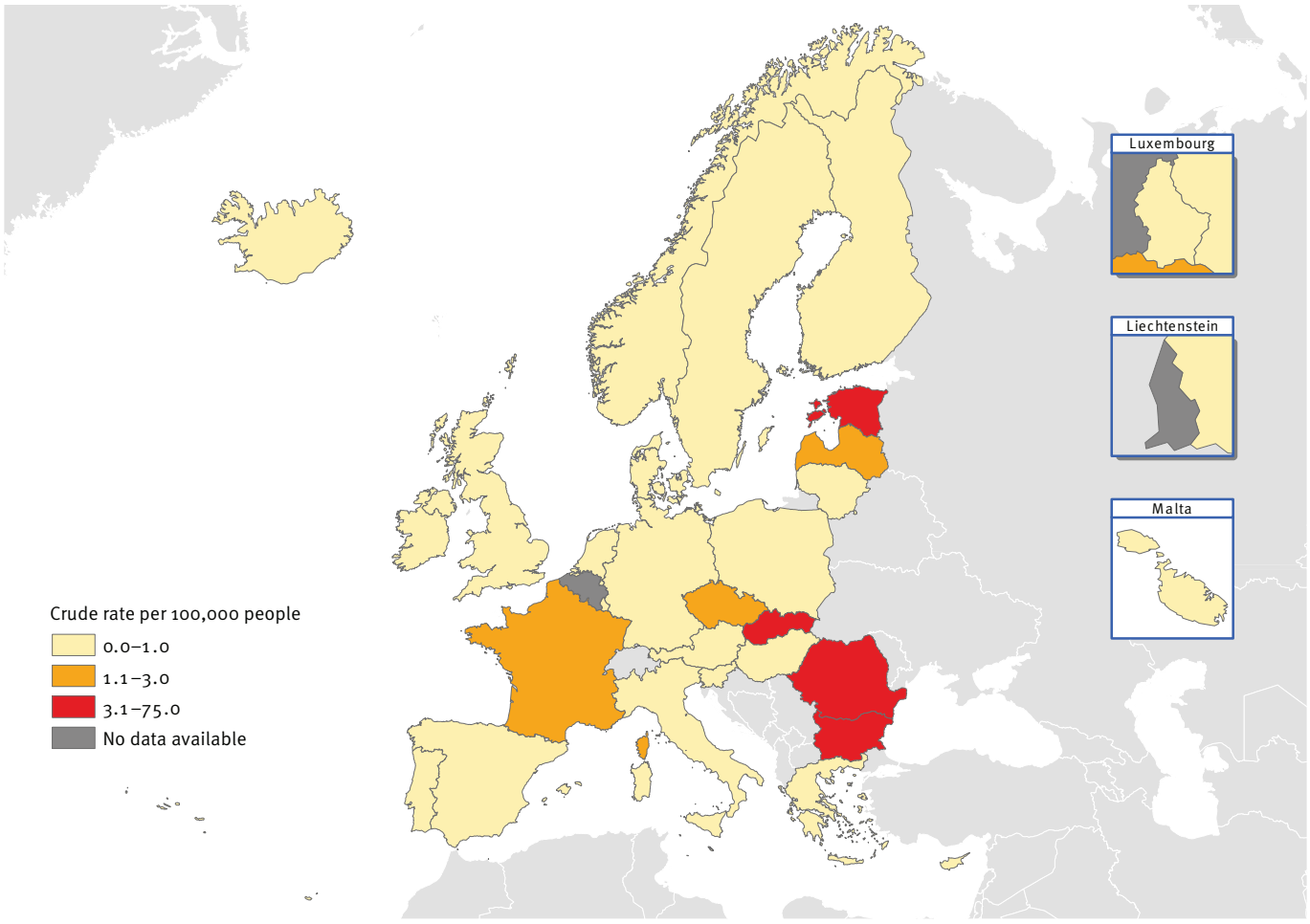
HAV survives in the environment and resists many common food preservation methods including drying or freezing [5]. Hence, food can be a vehicle of HAV transmission. Contamination with HAV early in the production chain of commercial food products can result in large, prolonged and geographically dispersed outbreaks [6,7].

Geographical distribution

The annual risk of infection with HAV is associated with indicators of socioeconomic development, hygiene and access to safe water. Because few countries report notification rates, the World Health Organization (WHO) estimates the level of endemicity based on the age-specific seroprevalence estimates of HAV antibodies in the population. Seroprevalence varies widely among countries [1]. In areas with high endemicity (e.g. Sub-Saharan Africa and parts of South-East Asia) at least 90% of people have antibodies against HAV by

Figure 1

Distribution of hepatitis A crude notification rates in EU/EEA countries, 2011



EEA: European Economic Area; EU: European Union.

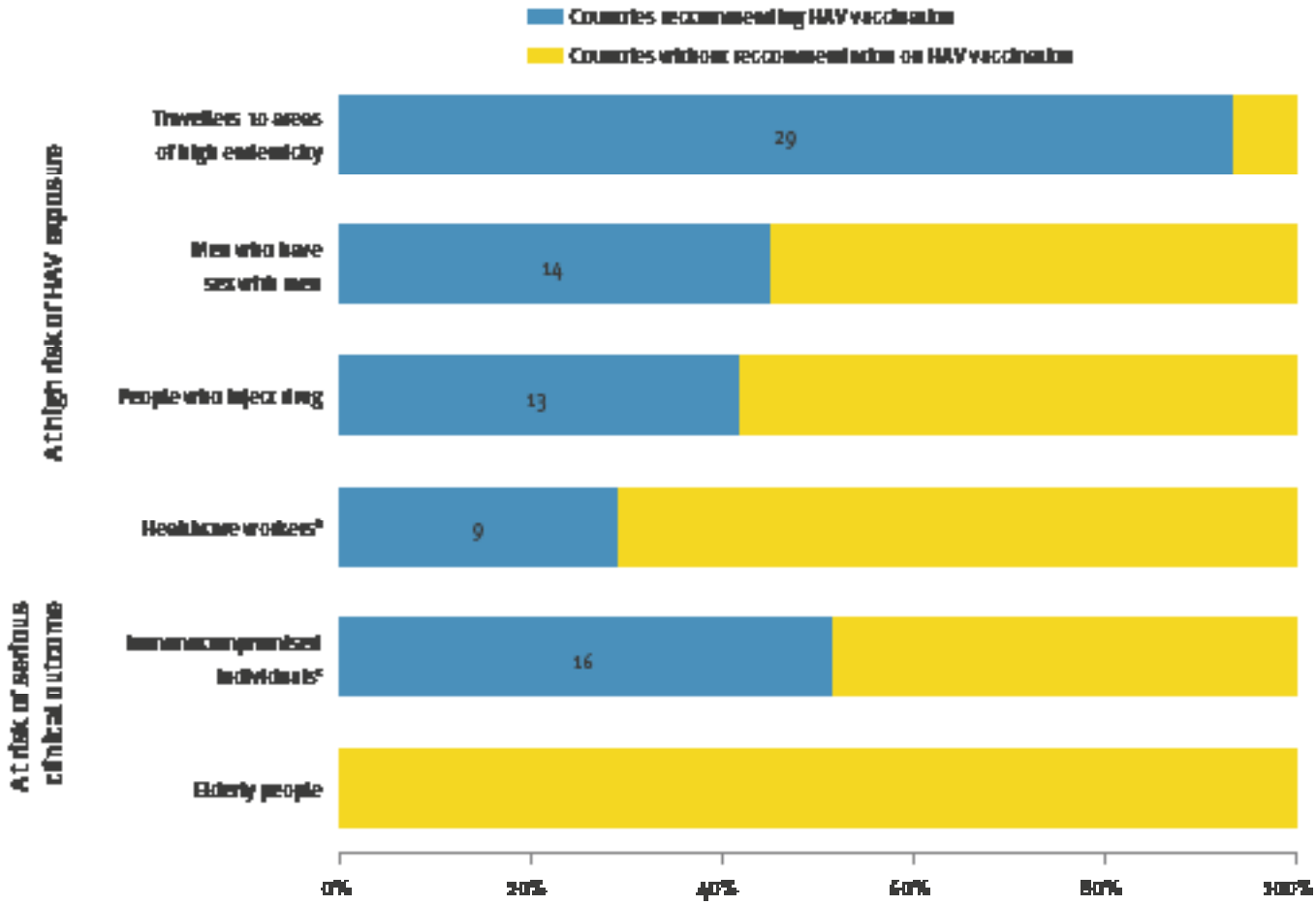
age 10 years. Outbreaks are rarely reported from these areas because most children have asymptomatic infections and the majority of adults are immune. Areas of intermediate endemicity are defined as those with at least 50% seroprevalence by age 15 years, with less than 90% by age 10 years, and include southern and eastern parts of the European Union (EU), China, Latin America, northern Africa, the Middle East and Russia. In these areas, a larger proportion of the population reaches adulthood uninfected, leading to higher susceptibility in older age groups and recurrent outbreaks of symptomatic disease. Finally, in areas with low endemicity (seroprevalence of at least 50% by age 30 years and less than 50% by age 15) and very low endemicity (less than 50% seroprevalence by age 30 years) such as western and northern parts of the EU and European Economic Area (EEA), Australia, Canada, Japan, and the United States (US), virus circulation is limited and the proportion of susceptible individuals is large in all age groups.

Epidemiology of hepatitis A in the EU/EEA

The notification rate in the EU/EEA has fallen between 1997 and 2011, from 10.0 to 2.5 per 100,000 population [8,9]. In 2011, of the 28 EU/EEA countries reporting to The European Surveillance System (TESSy), 21 reported notification rates of up to one per 100,000 population while four central and eastern EU Member States reported notification rates above three per 100,000 population (Figure 1). Male cases accounted for 56%. Children aged five to 14 years were most affected and there was a peak in reported cases in September and October as people returned from holidays and family visits in endemic countries [9-11]. Most countries that report cases to TESSy do not include information about risk behaviour and exposure, preventing analysis on risk factors. From 2005 to 2012, the reported proportion of cases infected abroad ranged from 49 to 80% in Sweden (average: 65%) [12] and was estimated at 37% in Germany and 36% in France in the same time period [13,14]. In France, 50% of hepatitis A cases resulted from secondary transmission from a primary case: 80% of these occurred through a household contact [14]. Case reports to TESSy do not consistently include

Figure 2

EU/EEA countries recommending hepatitis A virus vaccination to groups defined by the WHO as at high risk for exposure or at risk of serious clinical outcome, 2013 (n = 30[a])



EEA: European Economic Area; EU: European Union; HAV: hepatitis A virus; HIV: human immunodeficiency virus; WHO: World Health Organization.

[a] Data from Cyprus were not available.

[b] Some countries recommend HAV vaccination only for specific groups of healthcare workers (e.g. laboratory staff).

[c] Countries recommending HAV vaccination to HIV patients and/or chronic liver disease patients have been included in this category.

Source: Epidemic Intelligence Information System for Vaccine Preventable Diseases, websites of National Public Health Institutes and Ministries of Health in the European Union and European Economic Area.

outcome information which makes it impossible to monitor case fatality ratios or the proportion of cases with complications.

Risk groups and vaccination in EU/EEA

Susceptible individuals from the EU/EEA countries at higher risk of exposure to HAV include travellers to areas of high endemicity, people visiting friends and family in high endemicity areas, expatriates living in these areas, marginalised groups living under poor sanitary conditions, people who inject drugs, men who have sex with men [1] and, very rarely, recipients of blood and blood products [15]. The number of travellers from the EU/EEA to destinations with high hepatitis A endemicity is increasing. As a result, those destinations may appear less exotic and individuals may be less prone to consult travel medicine clinics before departure.

Inactivated hepatitis A vaccines are safe and effective for both pre- and post-exposure prophylaxis [16]. The WHO recommends routine childhood vaccination in countries with intermediate endemicity, including southern and eastern EU countries, but not in high endemicity countries. In western and northern EU/EEA countries, where endemicity ranges from low to very low, the WHO recommendation is to vaccinate only high-risk groups [1]. Some EU countries with intermediate endemicity recommend universal vaccination at the national level (e.g. Greece since 2008 [17]) or at the regional level (e.g. Catalonia, Spain [18] or Apulia, Italy [19] since 1998). Most EU/EEA countries have issued recommendations at least for some risk groups (Figure

2) but those are not necessarily associated with programmes, budgeted resources and coverage monitoring [20,21]. An economic evaluation conducted in the US estimated that the universal hepatitis A vaccination for children implemented in 2006 in the US led to herd immunity and has been a cost saving intervention for the first three years after introduction and cost-neutral over the first 10 years of the programme [22]. Information campaigns and increased access through removal of financial barriers can increase uptake in the EU/EEA countries. For example, Denmark and Norway provide hepatitis A vaccine free of charge to people with chronic liver diseases and people who inject drugs [17]. The WHO does not provide recommendations on the use of hepatitis A vaccination for outbreak control: although immunisation has been reported to be effective in controlling outbreaks in small communities, there is still lack of evidence on the wide-spread use of vaccination to control large outbreaks [1].

Outbreaks in the EU/EEA in the past decade

Several hepatitis A outbreaks have been reported in the EU/EEA in the past decade. Some have affected high risk groups while others have spread in the general population. We divided the outbreaks in three groups, depending on the mode and setting of infection.

Travel-related outbreaks were defined as those affecting EU/EEA residents while abroad, regardless of the mode of transmission. From November 2012 to June 2013, over 100 travellers to Egypt from 14 EU/EFTA countries were infected with HAV of sub-genotype IB [23,24]. Similar outbreaks among European travellers to Egypt were reported in 2004 [25] and 2008 [21]. For all these outbreaks, a food- and/or waterborne transmission was plausible.

Community-wide outbreaks were defined as those for which the primary mode of transmission was person-to-person contact, including among people who use drugs. These outbreaks often start within high-risk groups and later spread to the general community (e.g. in Latvia in 2008 [26]). Also religious groups, migrants and ethnic minorities have been affected (e.g. the Orthodox Jewish community in London 2011 [27]).

Food-borne outbreaks were defined as those for which consumption of contaminated food in the EU/EEA was the primary vehicle of infection. From 2009 to 2011, three clusters of HAV infection with sub-genotype IB in France, the Netherlands and the United Kingdom were associated with consumption of semi-dried tomatoes from Turkey [6,7,28]. In the first half of 2013, two different outbreaks of hepatitis A associated with consumption of frozen berries were reported, one in Denmark, Finland, Norway and Sweden (sub-genotype IB) [29] and the other in Italy and Ireland (sub-genotype IA) [30]. In several outbreaks associated with fresh food products, investigations pointed to food handlers involved in harvesting or preparation of the products as the source of contamination, for example in 2004 in Belgium [31].

Why do we see outbreaks in the EU and what to expect in the future?

The susceptible proportion of the EU/EEA population is growing fast as a result of declining HAV incidence. HAV vaccine uptake has not been high enough to compensate for the fall in natural immunity. On the one hand, as disease severity increases with the patient's age, increasing numbers of susceptible adults could potentially result in more severe disease, and eventually in higher case fatality ratios. On the other hand, the lower rates could also compensate for the higher case fatality ratios and the overall mortality might not increase or decrease.

'Seeding events', when HAV is introduced to a population with low immunity via a food- or travel-associated primary case, may lead to community transmission. However, person-to-person transmission is uncommon. In the outbreak in Denmark, Finland, Norway and Sweden in 2013, associated with consumption of frozen berries, only 10% of cases were secondary cases [29].

Self-controls by the industries and official controls by the food safety authorities Regulatory controls and industry auto-controls are unlikely to completely prevent the importation of HAV-contaminated foods from highly endemic countries into the EU/EEA.* The infective dose is presumably low [32] and it is technically challenging to detect HAV contamination in food products [33]. Because the virus is resistant to many preservation methods, contaminated preserved products (e.g. frozen fruits and dried vegetables) may remain on the market over long periods of time and result in slowly propagating multinational outbreaks in which the cases are widely dispersed in time and space.

Investigations of food-borne hepatitis A outbreaks are challenging. Cases may have difficulties remembering what they ate four weeks before onset of symptoms, and the opportunities to sample implicated food for testing are often limited. If the suspected vehicle is a mixed food item (e.g. mixed berries), it may be impossible to identify the contaminated ingredient.

Unvaccinated EU/EEA travellers visiting endemic countries are at risk of infection. If infected abroad, they expose their close contacts to secondary transmission after returning home. Healthcare providers and travellers underestimate the risk of hepatitis A in tourist destinations. Twenty per cent of returning travellers with hepatitis A had not been vaccinated against hepatitis A despite receiving pre-travel medical advice [34].

Better surveillance and increased international collaboration within the EU/EEA region may partially explain the increased number of multinational outbreaks

reported since 2012. Increasing availability and affordability of molecular characterisation techniques has made it possible to link apparently sporadic cases and to associate them with slowly evolving multinational outbreaks. Through the pooling of epidemiological and microbiological information at the EU/EEA level, the Epidemic Intelligence Information System (EPIS) for Food and Waterborne Disease and for Vaccine Preventable Diseases of the European Centre for Disease Prevention and Control (ECDC) facilitate communication among disease experts in the EU/EEA countries and allow rapid identification of the multicountry dimension of reported outbreaks [35]. In linking geographically and temporarily dispersed cases, RNA sequencing techniques for HAV isolates have facilitated investigations of multicountry outbreaks. Improved surveillance in the EU/EEA may lead to the identification of more outbreaks at an earlier stage in the future.

Conclusions and recommendations

Hepatitis A notification rates have declined in the past two decades in the EU/EEA and this has resulted in a growing proportion of adults who are susceptible to HAV infection. Higher mean age at the time of infection could result in more symptomatic infection and more severe disease. Unfortunately, HAV data reports to TESSy do not include information that would allow assessing the impact of this epidemiological shift on disease severity and case fatality ratio [1]. There are gaps in the vaccination uptake among high-risk groups in low and very low endemicity countries [20,24], and among populations living in intermediate endemicity areas. In addition, international recommendations on vaccination strategies for outbreak control are lacking. Travel continues to cause imported cases and secondary transmission. Outbreaks provide valuable information on missed opportunities for prevention.

On the basis of these conclusions, we recommend improving our knowledge on the epidemiology of hepatitis A as well as prevention efforts: Firstly, ECDC should work closely with the EU Member States to ensure better reporting of cases through TESSy, including information on mode of transmission, risk behaviours and deaths. Secondly, EU/EEA countries should follow WHO recommendations and consider (i) including hepatitis A vaccination in routine childhood vaccination schedules in regions with intermediate endemicity and (ii) vaccinating individuals at high risk of infection in countries with low and very low endemicity. Thirdly, ECDC together with the EU/EEA countries should also consider examining the evidence of the effectiveness of hepatitis A vaccine use in controlling outbreaks in the EU/EEA.* Fourthly, travel medicine services and healthcare providers must educate travellers and travel agents regarding the risks of travel-associated hepatitis A, emphasising that staying in all-inclusive luxury resorts does not protect travellers from infection because food and water might be contaminated [21-25]. Finally, Member States and ECDC should gather information from outbreaks to identify missed opportunities for prevention. Useful actions are (i) timely reporting of signals of multinational outbreaks though EPIS, (ii) prompt sharing of epidemiological and microbiological data on human and food safety, and (iii) sharing of testing protocols and interpretation frameworks for sequencing results.

Acknowledgments

We are very grateful to all colleagues in the EU/EEA countries providing data to TESSy, EPIS-FWD and EPIS-VPD. We warmly thank Denisa Janta, Adriana Pistol, Maria Koliou, Koen De Schrijver and Dragoslav Domanovic for their support in providing relevant information for this article.

Conflict of interest

None declared.

Authors' contributions

Céline Gossner and Ettore Severi have collected and analysed the data, and drafted the manuscript. Niklas Danielson, Yvan Hutin and Denis Coulombier have substantially contributed to the drafting and revision of the manuscript.

*Erratum

The sentence "Self-controls by the industries and official controls by the food safety authorities Regulatory controls and industry auto-controls are unlikely to completely prevent the importation of HAV-contaminated foods from highly endemic countries into the EU/EEA." was corrected to read "Self-controls by the industries and official controls by the food safety authorities are unlikely to completely prevent the importation of HAV-contaminated foods from highly endemic countries into the EU/EEA." on 7 July 2015.

References

1. WHO position paper on hepatitis A vaccines – June 2012. Wkly Epidemiol Rec. 2012;87(28/29):261-76. PMID:22905367
2. Desbois D, Couturier E, Mackiewicz V, Graube A, Letort MJ, Dussaix E, et al. Epidemiology and genetic characterization of hepatitis A virus genotype IIA. J Clin Microbiol. 2010;48(9):3306-15. http://dx.doi.org/10.1128/JCM.00667-10 PMID:20592136
3. Schiff ER. Atypical clinical manifestations of hepatitis A. Vaccine. 1992;10(Suppl 1):S18-20. http://dx.doi.org/10.1016/0264-410X(92)90534-Q PMID:1475999
4. Heymann DL, editor. Control of communicable diseases manual. 19th ed. Washington: American Public Health Association; 2008.
5. Baert L, Debevere J, Uyttendaele M. The efficacy of preservation methods to inactivate foodborne viruses. Int J Food Microbiol. 2009;131(2-3):83-94. http://dx.doi.org/10.1016/j.ijfoodmicro.2009.03.007 PMID:19349089
6. Fournet N, Baas D, van Pelt W, Swaan C, Ober H, Isken L, et al. Another possible food-borne outbreak of hepatitis A in the Netherlands indicated by two closely related molecular sequences, July to October 2011. Euro Surveill. 2012;17(6):20079. PMID:22340976
7. Petrignani M, Harms M, Verhoef L, van Hunen R, Swaan C, van Steenbergen J, et al. Update: a food-borne outbreak of hepatitis A in the Netherlands related to semi-dried tomatoes in oil, January-February 2010. Euro Surveill. 2010;15(20):19572. PMID:20504389
8. European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report on communicable diseases in Europe. Report on the status of communicable diseases

in the EU and EEA/EFTA countries. Stockholm: ECDC; 2007. Available from: http://ecdc.europa.eu/en/publications/Publications/0706_SUR_Annual_Epidemiological_Report_2007.pdf

9. European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report 2013. Reporting on 2011 surveillance data and 2012 epidemic intelligence data. Stockholm: ECDC; 2013. Available from: http://www.ecdc.europa.eu/en/publications/Publications/Annual-Epidemiological-Report-2013.pdf
10. Sane J, de Sousa R, van Pelt W, Petrignani M, Verhoef L, Koopmans M. Risk of hepatitis A decreased among Dutch travelers to endemic regions in 2003 to 2011. J Travel Med. 2014. [Epub ahead of print].
11. Tjon G, Xiridou M, Coutinho R, Bruisten S. Different transmission patterns of hepatitis A virus for two main risk groups as evidenced by molecular cluster analysis. J Med Virol. 2007;79(5):488-94. http://dx.doi.org/10.1002/jmv.20821 PMID:17385681
12. Public Health Agency of Sweden. Hepatit A. [Hepatitis A]. Solna: Folkhälsomyndigheten. [Accessed: 25 Mar 2013]. Swedish. Available from: http://www.folkhalsomyndigheten.se/amnesomraden/statistik-och-undersokningar/sjukdomsstatistik/hepatit-a/
13. Robert Koch Institute (RKI). Infektionsepidemiologisches Jahrbuch für 2007 [Annual epidemiological report on notifiable infectious diseases for 2007]. Berlin: RKI; 2008. German. Available from: http://www.rki.de/DE/Content/Infekt/Jahrbuch/Jahrbuch_2007.pdf?__blob=publicationFile
14. Institut de Veille Sanitaire (InVS). Hépatite A. Données épidemiologiques 2006-2012. [Hepatitis A. Epidemiological data 2006-2012]. [Accessed: 13 Dec 2013]. French. Available from: http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-declaration-obligatoire/Hepatite-A/Donnees-epidemiologiques
15. Perevoscikovs J, Lenglet A, Lucenko I, Steinerte A, Payne Hallström L, Coulombier D. Assessing the risk of a community outbreak of hepatitis A on blood safety in Latvia, 2008. Euro Surveill. 2010;15(33):19640. PMID:20739001
16. Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med. 1992;327(7):453-7. http://dx.doi.org/10.1056/NEJM199208133270702 PMID:1320740
17. European Centre for Disease Prevention and Control (ECDC). Epidemic Intelligence Information System for Vaccine Preventable Diseases. Stockholm: ECDC. [Accessed: 13 Dec 2013].
18. Martínez A, Broner S, Torner N, Godoy P, Batalla J, Alvarez J, et al. Hepatitis A outbreaks in the vaccination era in Catalonia, Spain. Hum Vaccin. 2011;7(sup1) Suppl;205-10.
19. Chironna M, Prato R, Sallustio A, Martinelli D, Tafuri S, Quarto M, et al. Hepatitis A in Puglia (South Italy) after 10 years of universal vaccination: need for strict monitoring and catch-up vaccination. BMC Infect Dis. 2012;12(1):271. http://dx.doi.org/10.1186/1471-2334-12-271 PMID:23098290
20. Faber MS, Stark K, Behnke SC, Schreier E, Frank C. Epidemiology of hepatitis A virus infections, Germany, 2007-2008. Emerg Infect Dis. 2009;15(11):1760-8. http://dx.doi.org/10.3201/eid1511.090214 PMID:19891863
21. Couturier E, Roque-Afonso AM, Letort MJ, Dussaix E, Vaillant V, de Valk H. Cluster of cases of hepatitis A with a travel history to Egypt, September-November 2008, France. Euro Surveill. 2009;14(3):14. PMID:19161726
22. Armstrong GL, Billah K, Rein DB, Hicks KA, Wirth KE, Bell BP. The economics of routine childhood hepatitis A immunization in the United States: the impact of herd immunity. Pediatrics. 2007;119(1):e22-9. http://dx.doi.org/10.1542/peds.2006-1572 PMID:17200247
23. European Centre for Disease Prevention and Control (ECDC). Outbreak of hepatitis A virus infection in travellers returning from Egypt. Rapid risk assessment. Stockholm: ECDC; April 2013. Available from: http://www.ecdc.europa.eu/en/publications/Publications/RRA-Outbreak-hepatitis-A-virus-infection-travellers-returning-from-Egypt.pdf
24. Sane J, MacDonald E, Vold L, Gossner C, Severi E, Outbreak Investigation Team. Multistate foodborne hepatitis A outbreak among European tourists returning from Egypt--need for reinforced vaccination recommendations, November 2012 to April 2013. Euro Surveill. 2015;20(4):21018. http://dx.doi.org/10.2807/1560-7917.ES2015.20.4.21018 PMID:25655054
25. Frank C, Walter J, Muehlen M, Jansen A, van Treeck U, Hauri AM, et al. Major outbreak of hepatitis A associated with orange juice among tourists, Egypt, 2004. Emerg Infect Dis. 2007;13(1):156-8. http://dx.doi.org/10.3201/eid1301.060487 PMID:17370535
26. Perevoscikovs J, Lucenko I, Magone S, Brila A, Curikova J, Vennema H. Community-wide outbreak of hepatitis A in Latvia in 2008 - an update. Euro Surveill. 2009;14(3):19092. PMID:19161728
27. Edelstein M, Turbitt D, Balogun K, Figueroa J, Nixon G. Hepatitis A outbreak in an Orthodox Jewish community in London, July 2010. Euro Surveill. 2010;15(37):19662. PMID:20929646
28. Gallot C, Grout L, Roque-Afonso AM, Couturier E, Carrillo-Santisteve P, Pouey J, et al. Hepatitis A associated with semidried tomatoes, France, 2010. Emerg Infect Dis. 2011;17(3):566-7. http://dx.doi.org/10.3201/eid1703.101479 PMID:21392466
29. Nordic Outbreak Investigation Team C. Joint analysis by the Nordic countries of a hepatitis A outbreak, October 2012 to June 2013: frozen strawberries suspected. Euro Surveill. 2013;18(27):20520. http://dx.doi.org/10.2807/1560-7917.ES2013.18.27.20520 PMID:23870076
30. European Centre for Disease Prevention and Control (ECDC). European Food Safety Authority. Update: outbreak of hepatitis A virus infection in Italy and Ireland. Rapid outbreak assessment. Stockholm: ECDC; July 2013. Available from: http://ecdc.europa.eu/en/publications/Publications/ROA-update_HAV_Italy_Ireland-final.pdf
31. Robesyn E, De Schrijver K, Wollants E, Top G, Verbeeck J, Van Ranst M. An outbreak of hepatitis A associated with the consumption of raw beef. J Clin Virol. 2009;44(3):207-10. http://dx.doi.org/10.1016/j.jcv.2008.12.012 PMID:19179106
32. US Food and Drug Administration. (US FDA). Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins Handbook, Hepatitis A Virus. Silver Spring: US FDA; 2014. Available from: http://www.fda.gov/Food/FoodborneIllnessContaminants/CausesOfIllnessBadBugBook/ucm071294.htm
33. US Food and Drug Administration. (US FDA). BAM 26B: Detection of Hepatitis A Virus in Foods. Silver Spring: US FDA; 2015. Available from: http://www.fda.gov/Food/FoodScienceResearch/LaboratoryMethods/ucm374006.htm
34. Leder K, Torresi J, Libman MD, Cramer JP, Castelli F, Schlagenhauf P, et al.GeoSentinel Surveillance Network. GeoSentinel surveillance of illness in returned travelers, 2007-2011. Ann Intern Med. 2013;158(6):456-68. http://dx.doi.org/10.7326/0003-4819-158-6-201303190-00005 PMID:23552375
35. Gossner CM, de Jong B, Hoebe CJPA, Coulombier D, and European Food and Waterborne Diseases Study Group. Event-based surveillance of food- and waterborne diseases in Europe: A six-year review of urgent inquiries, 2008-2013. Euro Surveill. 2015. Forthcoming.

Strengths and limitations of assessing influenza vaccine effectiveness using routinely collected, passive surveillance data in Ontario, Canada, 2007 to 2012: balancing efficiency versus quality

R D Savage (rachel.savage@mail.utoronto.ca)[1,2], A L Winter[1], L C Rosella[1,2], R Olsha[1], J B Gubbay[1,3], D M Skowronski[4,5], N S Crowcroft[1,2,3]

1. Public Health Ontario, Toronto, Ontario, Canada
2. Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
3. Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
4. British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada
5. School of Population & Public Health, University of British Columbia, British Columbia, Canada

Citation style for this article:
Savage RD, Winter AL, Rosella LC, Olsha R, Gubbay JB, Skowronski DM, Crowcroft NS. Strengths and limitations of assessing influenza vaccine effectiveness using routinely collected, passive surveillance data in Ontario, Canada, 2007 to 2012: balancing efficiency versus quality. Euro Surveill. 2015;20(16):pii=21100. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21100

Article submitted on 28 March 2014 / published on 23 April 2015

Prompt evaluation of annual influenza vaccine effectiveness (IVE) is important. IVE is estimated in Ontario using a test-negative design (TND) within a national sentinel surveillance network (SPSN). To explore alternative approaches, we applied the screening method (SM) during five seasons spanning 2007 to 2012 to passive surveillance data to determine whether routinely collected data could provide unbiased IVE estimates. Age-adjusted SM-IVE estimates, excluding 2008/09 pandemic cases and cases with missing immunisation status, were compared with TND-IVE estimates in SPSN participants, adjusted for age, comorbidity, week of illness onset and interval to specimen collection. In four seasons, including the 2009 pandemic, the SM underestimated IVE (22–39% seasonal; 72% pandemic) by 20 to 35% relative to the TND-IVE (58–63% seasonal; 93% pandemic), except for the 2010/11 season when both estimates were low (33% and 30%, respectively). Half of the cases in the routine surveillance data lacked immunisation information; imputing all to be unimmunised better aligned SM-IVE with TND-IVE, instead overestimating in four seasons by 4 to 29%. While the SM approach applied to routine data may offer the advantage of timeliness, ease and efficiency, methodological issues related to completeness of vaccine information and/or case ascertainment may constitute trade-offs in reliability.

Introduction

Estimates of influenza vaccine effectiveness (IVE) are vital to measuring the impact of annual immunisation efforts and ideally can provide timely information to guide the response to epidemics and pandemics. Starting in 2004, IVE has been monitored in several Canadian provinces through application of a test-negative design (TND) whereby vaccination status is compared among test-positive vs test-negative specimens systematically collected from patients presenting with influenza-like illness (ILI) to designated practitioners within a national sentinel physician surveillance network (SPSN) [1-9]. The TND approach has been validated theoretically and in relation to per-protocol analysis of the same randomised controlled trial datasets, generating IVE estimates within ranges published by other observational and clinical trial designs [10-14]. Importantly, by standardising for healthcare-seeking behaviour and indication to request ILI testing, this design reduces potential selection biases that may arise from differential testing of patients with ILI at the discretion of a clinician in a passive surveillance system, and additionally allows for collection and adjustment of relevant confounding variables.

The screening method (SM) is another commonly used approach for estimating IVE that compares immunisation status of influenza cases to that of an external reference group such as the general population [15,16]. Key advantages of the SM include timeliness, ease and efficiency given that individual-level information is only required for cases, for whom information is routinely collected as part of public health surveillance in jurisdictions where influenza is reportable, such as Ontario. Despite this, valid individual-level data on cases' immunisation status and confounding variables, along with timely population-level coverage data, is difficult to obtain and may result in biased estimates. In light of these competing considerations, the objective of this study was to evaluate whether the SM approach applied to routinely collected surveillance data could be a reliable and timely alternative

for annual IVE estimation relative to the TND approach applied to SPSN data in Ontario, Canada.

Methods

Context

Since 2000, Ontario has provided publicly funded trivalent inactivated influenza vaccine (TIV) to all people six months and older who live, work or attend school in Ontario [17]. Particularly recommended recipients of the seasonal vaccine include those defined by the National Advisory Committee on Immunization (NACI) as at high risk for influenza-related complications owing to underlying health conditions or age, as well as Aboriginal peoples, those capable of transmitting influenza to high-risk individuals and those who provide essential community services [18]. During the 2009/10 pandemic, an influenza A(H1N1)pdm09 AS03-adjuvanted monovalent vaccine was available, along with a limited supply of non-adjuvanted vaccine and seasonal TIV [6].

The majority (≥60%) of influenza testing is performed by Public Health Ontario (PHO) laboratories; respiratory samples from ambulatory settings undergo culture-based testing only, while samples from inpatient, institutional and outbreak settings are tested by PCR [19]. Laboratory-confirmed cases detected by PHO and other laboratories are reported to regional public health units in Ontario, who then use the integrated Public Health Information System (iPHIS) to report cases, including a minimum set of required epidemiological information obtained through case follow-up, to provincial health authorities; iPHIS therefore captures all influenza cases reported to public health authorities.

The Sentinel Physician Surveillance Network (SPSN), in contrast, is an active surveillance system that exists in the five most populous provinces of Canada, including Ontario, and is designed to assess vaccine effectiveness. As previously described [1-9], this system builds on routine public health infrastructure, namely a sentinel network of primary healthcare practitioners used to monitor weekly ILI consultations at a national and provincial level. Participating sentinel practitioners are encouraged to offer influenza testing to all patients who present within one week of ILI onset meeting a standard case definition. Samples are then tested by real-time RT-PCR for influenza at provincial reference laboratories. Epidemiological information is obtained from consenting patients using a standard questionnaire at the time of specimen collection. Since these data are collected for all patients, including those who may ultimately test negative for influenza, the SPSN surveillance protocol is conducted with annual research ethics board review and approval.

Screening method

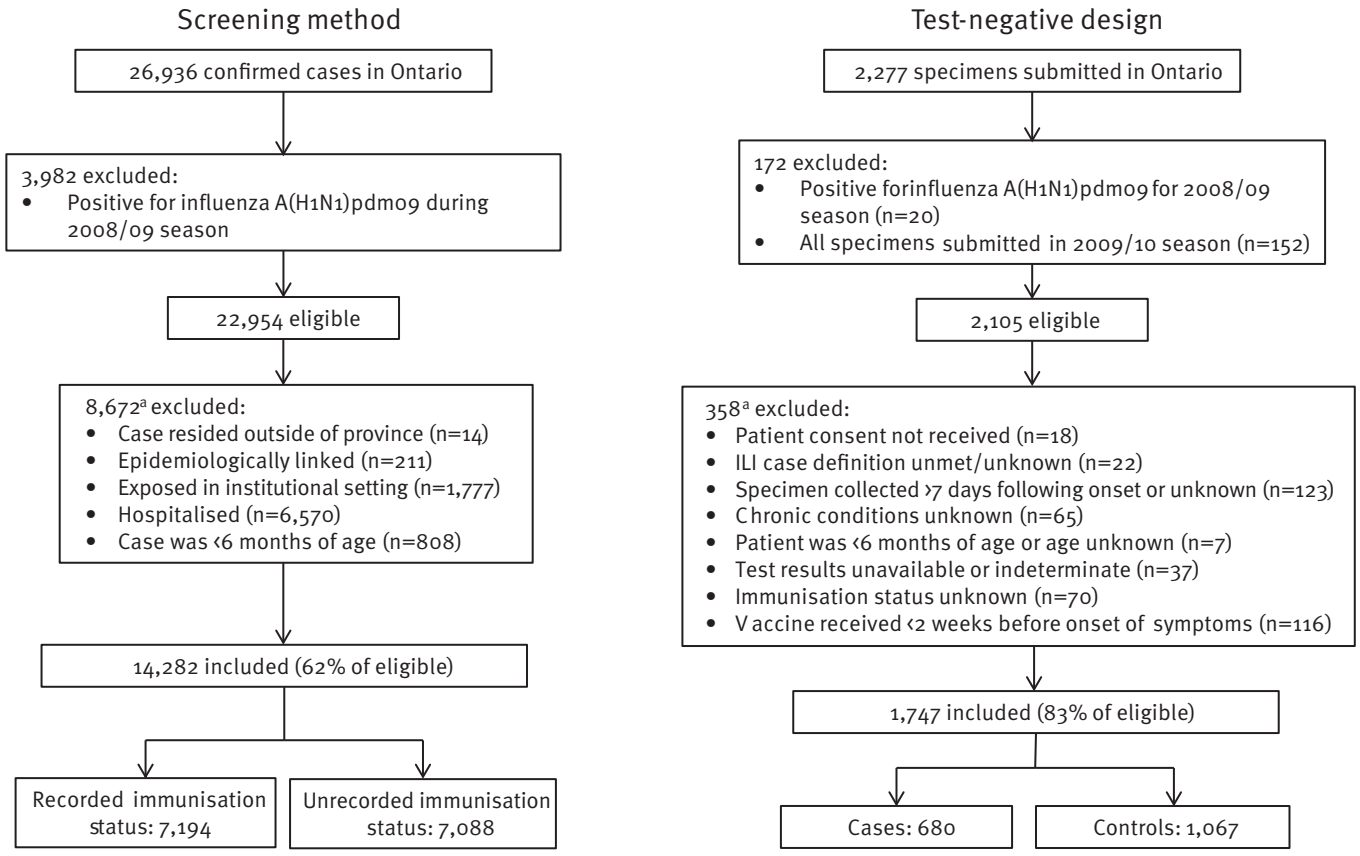
Data on laboratory-confirmed influenza cases for five influenza seasons from 2007/08 to 2011/12 were extracted on 10 January 2013 from iPHIS. Immunisation status, identified by self-report, is a requested but not mandatory field in iPHIS that is captured in a general 'relevant immunisations up to date for client' field. Data entry guidelines stipulate that 'relevant' refers to receipt of the influenza vaccine recommended for the current season at least 14 days before symptom onset and with the correct dosing requirements. The accuracy of this field was examined through comparison with free-text case notes, where available in a non-mandatory comments field, to calculate agreement (measured using the kappa statistic), and by examining potential misclassification of immunisation status in ineligible cases (i.e. infants younger than six months). Vaccine coverage in the general population was derived from Ontario-specific data from the annual Canadian Community Health Survey (CCHS); respondents are interviewed throughout the year about immunisation during the prior 12 months. The CCHS uses a multistage, stratified cluster design and provides cross-sectional data representative of 98% of the Canadian population 12 years and older [20]. For children younger than 12 years, an Ontario influenza vaccination coverage survey conducted in 2007 was used and, in the absence of annual data, applied to all subsequent years [21]. Vaccine coverage estimates for these two age groups were weighted according to the age distribution in Ontario and summed to produce overall population-weighted coverage estimates.

IVE was calculated as (PPV – PCV) / [PPV × (1-PCV)] × 100, where PPV was the proportion of the population vaccinated and PCV was the proportion of cases vaccinated [22]. All IVE estimates were stratified by influenza season, defined as 1 September to 31 August to be consistent with Ontario's respiratory virus surveillance programme. Cases with laboratory-confirmed influenza A(H1N1)pdm09 in the 2008/09 season were excluded in order to examine homologous IVE only. Cases were also excluded from analysis if they were ineligible for influenza immunisation (younger than six months), reported as epidemiologically linked (but not laboratory-confirmed), exposed to influenza in an institutional setting, hospitalised or if they resided outside of Ontario. Both institutionally exposed and hospitalised cases were excluded to ensure comparability of study populations, as the SPSN only includes cases in the community. IVE was calculated using data from cases with a recorded (yes/no) immunisation status only; cases with an unknown/missing status were excluded. IVE estimates were adjusted for age (6 months–11 years, 12–49, 50–64 and ≥ 65 years) and confidence intervals (CI) were calculated using methods described by Farrington in 1993 [15].

Mid-season IVE estimates were also calculated for two seasons. Mid-season was defined as 1 September 2010 to 15 January 2011 for the 2010/11 season, and 1 September 2011 to 15 March 2012 for the 2011/12 season, based on the mid-point of the month after which the peak of the influenza epidemic occurred for the

Figure

Flowchart of study participants by methodological approach, influenza vaccine effectiveness, Ontario, 2007–2012



ILI: influenza-like illness.

[a] Exclusion categories are not mutually exclusive and so totals indicated in brackets will not sum to the total patients excluded.

respective season (5 January and 12 March, respectively, based on case reported dates). The mid-point of the month was used instead of the peak date to be more reflective of the earliest time point that a mid-season analysis would be conducted, recognising that the peak would only be identified by public health officials once it had passed. For the 2010/11 season, PPV was determined based on CCHS survey respondents interviewed between September and December 2010; for the 2011/12 season, coverage was based on respondents interviewed between September 2011 and February 2012. In this analysis, no adjustments were made for age.

Cases with recorded (yes/no) and unrecorded (unknown/missing) immunisation status were compared for demographic characteristics such as age, sex, geographic region of residence and underlying illness or chronic condition to determine if differential misclassification was introduced by excluding cases with an unrecorded status. In iPHIS, underlying illness or chronic condition refers to any self-reported chronic medical condition that puts the individual at greater risk of acquiring the disease or having a more severe outcome. Sensitivity analyses were run, for a range of scenarios, to assess the potential impact of missing data on IVE estimates.

Test-negative design

SM-IVE estimates were compared with TND-IVE estimates derived by the SPSN. Ontario-specific data were used for all seasons except 2007/08 and the 2009/10 pandemic. Patients were considered immunised if the vaccine was given at least two weeks before ILI onset. For the current analysis, immunisation status was compared in test-positive (cases) and test-negative patients (controls). IVE was calculated as (1 – OR) × 100 using logistic regression, where OR represents the odds ratio adjusted for age (6 months–11 years, 12–49, 50–64 and ≥ 65 years), presence/absence of specific chronic conditions (including one or more of heart/pulmonary/renal/metabolic/blood/cancer/immune-compromising

Table 1

Study population characteristics by data source used for influenza vaccine effectiveness estimation, Ontario, 2007–2012

	iPHIS[a] (n = 7,194)		CCHS[b]		SPSN (n = 1,747)			
	Cases				Cases (n = 680)		Controls (n = 1,067)	
	n	%	n	%	n	%	n	%
Age								
6 months–11 years	2,302	32.0	NA		126	18.5	183	17.2
12–49 years	2,983	41.5	50,013	61.2	419	61.6	576	54.0
50–64 years	660	9.2	25,339	23.3	95	14.0	215	20.1
≥ 65 years	1,240	17.3	26,307	15.5	40	5.9	93	8.7
Chronic/underlying illness[c]	765	24.0	38,164	30.3	94	13.8	197	18.5
Vaccinated	1,791	24.9	42,534	35.8	113	16.6	295	27.7

CCHS: Canadian Community Health Survey; iPHIS: Ontario's integrated Public Health Information System for reportable diseases; NA: not available; SPSN: Sentinel Physician Surveillance Network.

[a] Age unknown for nine cases, and 4,005 cases were not asked about whether they had a chronic illness or underlying condition. Cases with missing data have been excluded from denominators in proportion calculations.

[b] Proportions weighted for the survey design are presented.

[c] Definition varied across data source.

conditions, conditions that compromise the management of respiratory secretions and increase risk of aspiration, or morbid obesity), specimen collection interval (≤ 4 days or > 4 days from symptom onset) and time (week of illness onset). Influenza seasons were defined as 1 November to 30 April. A delay in obtaining the ethics board's approval in Ontario in 2009/10 meant that a substantial proportion of Ontario specimens in that season did not have influenza A(H1N1) pdm09 vaccination status recorded [6]. Published pooled Canada-wide estimates for 2009/10 were therefore used for comparison [6]. Similarly, pooled Canada-wide estimates are presented for 2007/08 as Ontario did not participate in the study until January 2008 [4]. All statistical analyses were conducted using Stata version 12 (StataCorp, College Station, TX).

Ethical approval for the Ontario arm of the SPSN data collection was provided by the University of Toronto. Approval from the research ethics committee was not required to use iPHIS data for the SM analysis as PHO has a legislated mandate "*to develop, collect, use, analyse and disclose data, including population health, surveillance and epidemiological data (…) in a manner that informs and enhances healthy public policy and public health planning, evaluation and action*" [23].

Results

Study population

Screening method

After excluding 3,982 laboratory-confirmed cases of influenza A(H1N1)pdm09 from the 2008/09 season, a total of 22,954 cases were identified in the study period (Figure). The number of confirmed cases reported in Ontario ranged by season from 3,636 to 6,062 (5,168 in 2007/08; 3,636 in 2008/09; 4,143 in 2009/10; 6,062 in 2010/11; and 3,945 in 2011/12). After applying exclusion criteria, 14,282 cases were included in the analysis; 7,194 (50.4%) cases had a recorded immunisation status (yes/no), while status was unrecorded for 7,088 (49.6%) of cases.

Test-negative design

Excluding the 20 patients who tested positive for influenza A(H1N1)pdm09 during the 2008/09 season and the 152 patients from the 2009/10 season, 2,105 patients with a specimen submitted in Ontario were available for analysis (Figure). Overall, 365 eligible specimens were submitted in 2008/09, 802 in 2010/11 and 938 in 2011/12. After applying study exclusion criteria, 1,747 participants were included in the analysis; 680 (38.9%) tested positive for influenza (cases) and 1,067 tested negative (controls).

Characteristics of included study participants are shown in Table 1 by data source. For all data sources used for IVE estimation (iPHIS and CCHS for SM, and SPSN for TND), individuals aged 12–49 years comprised the largest proportion of cases/study participants; however, iPHIS data included a higher proportion of children (< 12 years) and adults 65 years and older relative to the SPSN. A higher proportion of cases in iPHIS reported the presence of a chronic or underlying illness and being vaccinated against influenza than cases in the SPSN. Comparisons of chronic disease prevalence across study populations should be made with caution, however, as definitions vary across sources.

Table 2

Unadjusted and adjusted estimates of influenza vaccine effectiveness by influenza season, comparing screening method and test-negative design, Ontario, 2007 to 2012

Method	Influenza season	Cases n	Cases vaccinated[a] %	Controls n	Controls[b] vaccinated %	Unadjusted IVE % (95% CI)	Adjusted[c] IVE % (95% CI)	Difference between methods[d]
Screening method	2007/08	1,951	27	NA	35	29 (22 to 36)	37 (30 to 44)	Ref
	2008/09	1,727	20	NA	34	49 (43 to 55)	39 (31 to 46)	Ref
	2009/10	468	12	NA	40	80 (74 to 85)	72 (63 to 79)	Ref
	2010/11	1,554	27	NA	31	18 (9 to 27)	33 (24 to 41)	Ref
	2011/12	1,494	29	NA	30	7 (–4 to17)	22 (11 to 31)	Ref
Test-negative design	2007/08[e]	689	14	736	28	60 (48 to 70)	60 (45 to 71)	23
	2008/09	114	19	146	36	58 (25 to 77)	63 (30 to 81)	24
	2009/10[e]	209	1	343	17	95 (80 to 99)	93 (69 to 98)	21
	2010/11	341	16	362	21	29 (–4 to 52)	30 (–6 to 54)	–3
	2011/12	225	16	559	30	53 (30 to 69)	58 (34 to 73)	36

CI: confidence interval; IVE: influenza vaccine effectiveness; NA: not applicable; Ref: reference value.

[a] Denominator for proportion calculation comprises cases with known immunisation status.

[b] 'Controls vaccinated' for the screening method refers to the proportion of the population vaccinated (PPV), which is based on population-based, provincial survey data.

[c] Adjusted for age (<12, 12–49, 50–64 and ≥ 65 years), comorbidity (yes/no), specimen collection interval (≤4 days or >4 days) and time (week of illness onset) for the test-negative design, and adjusted for age only (<12, 12–49, 50–64 and ≥ 65 years) in the screening method.

[d] The difference between methods is calculated as the difference between adjusted IVE estimates in the test-negative design relative to the screening method.

[e] National estimate provided due to limited Ontario sample size.

Validity of immunisation status in routine surveillance data

Immunisation-related, free-text case notes, written by the public health professional who investigated the case, were available in a comments field in iPHIS for 164 (2.3%) of 7,194 cases with a recorded immunisation status. Agreement between recorded immunisation status and status documented in case notes was able to be assessed in 151 cases of this convenience sample of 164 cases and was found to be high (kappa = 0.88: 95% CI: 0.80–0.96). Review of case notes, available for 19 cases with an unrecorded immunisation status, revealed that 10 cases should have been recorded as unimmunised and the remainder as immunised; these cases remained excluded in IVE calculations.

Among the 808 cases younger than six months who were ineligible to receive the influenza vaccine, 26 of 471 (5.5%) with recorded immunisation status were classified as immunised.

Influenza vaccine effectiveness with screening method by season

For the three study seasons (2008/09, 2010/11, 2011/12) for which Ontario-specific SPSN data were available for comparison, unadjusted point estimates of IVE based on the screening method ranged from 7% (95% CI: –4 to 17%) during the 2011/12 season to 49% (95% CI: 43–55%) in 2008/09 (Table 2). After adjustment for age, this range narrowed from 22% (95% CI: 11–31%) in 2011/12 to 39% (95% CI: 31–46%) in 2008/09. For the 2007/08 season for which only national SPSN data were available for comparison, age-adjusted SM-IVE was 37% (95% CI: 30–44%), substantially lower than the 60% (95% CI: 45–71%) identified through TND analysis of SPSN data. Similarly during the 2009 pandemic, the age-adjusted SM-IVE in Ontario was 72% (95% CI: 63–79%) whereas the national TND-IVE for the adjuvanted monovalent pandemic vaccine was estimated at 93% (95% CI: 69–98%).

For the 2010/11 season, the mid-season IVE was estimated at –11% (95% CI: –33 to 8%), based on a PCV of 22% for 678 cases and a PPV of 21%, which was substantially lower than the unadjusted full-season estimate of 18% (95% CI: 9–27%). For the 2011/12 season, the mid-season IVE estimate of 13% (95% CI: –3 to 27%), based on a PCV of 24% for 715 cases and a PPV of 27%, was similar to the unadjusted full-season estimate of 7% (95% CI: –4 to 17%).

Comparison of cases with recorded vs unrecorded immunisation status

Relative to unimmunised cases and those with an unrecorded status, immunised cases were more likely to be 65 years or older (52.9% compared with 5.5% and 14.1%, respectively, p value < 0.001), female (62.6% compared with 51.6% and 52.6%, p value < 0.001) and

Table 3

Comparison of laboratory-confirmed influenza cases from routine surveillance data (iPHIS) with known (n = 7,194) and unknown (n = 7,088) immunisation status, by key characteristics, Ontario, 2007 to 2012

Characteristic	Known status, vaccinated		Known status, unvaccinated		Unknown status		p value[a]
	n	%	n	%	n	%	
Age group[b]							<0.001
6 months–11 years	240	13.5	2062	38.2	2,263	32.0	
12–49 years	385	21.6	2598	48.1	3,132	44.4	
50–64 years	215	12.0	445	8.2	668	9.5	
≥ 65 years	945	52.9	295	5.5	999	14.1	
Sex[c]							<0.001
Female	1,117	62.6	2780	51.6	3,702	52.6	
Male	668	37.4	2611	48.4	3,341	47.4	
Chronic/underlying illness[d]							<0.001
Yes	302	44.2	463	18.5	487	31.6	
No	381	55.8	2043	81.5	1052	68.4	

iPHIS: Ontario's integrated Public Health Information System for reportable diseases.

[a] Pearson's chi-squared test.

[b] 35 cases with unknown age.

[c] 63 cases with other or unknown sex.

[d] 9,554 cases not asked about whether they had a chronic illness or underlying condition. Cases with missing data have been excluded from denominators in proportion calculations.

to have reported chronic or underlying illness (44.2% compared with 18.5% and 31.6%, p value < 0.001) (Table 3). Unimmunised cases were generally more similar to cases with an unrecorded immunisation status in terms of age and sex than to immunised cases. The proportion of cases with an unrecorded immunisation status varied substantially by public health unit (range: 12.4–85.2%); however, this proportion was relatively consistent by season (range: 41.6–45.2%) with the exception of the pandemic year (81.3% in 2009/10) (data not shown), suggesting that particular caution should be applied in the interpretation of the SM-IVE for the pandemic year.

Influenza vaccine effectiveness with test-negative design method by season

For the three study seasons (2008/09, 2010/11, 2011/12) for which Ontario-specific TND data were available, unadjusted point estimates of overall IVE ranged from 29% (95% CI: −4 to 52%) in 2010/11 to 58% (95% CI: 25–77%) in 2008/09 (Table 2). These estimates were only slightly increased with adjustment for age, comorbidity, week of illness onset and interval to specimen collection to 30% (95% CI: −6 to 54%) and 63% (95% CI: 30–81%), respectively.

Sensitivity analyses

Restricting the seasons to align with the TND-IVE analysis period (1 November to 30 April for all seasons excluding 2009/10) left SM-IVE estimates either unchanged or increased them slightly (≤ 6%) (data not shown).

An additional sensitivity analysis was performed to evaluate the potential impact of missing data on SM-IVE estimates (Table 4). Unadjusted IVE estimates were substantially altered under both extremes (scenario 1: all cases with unrecorded status were considered immunised; scenario 2: all cases with unrecorded status were considered unimmunised). In scenario 3, where all cases with unrecorded status were assigned the same immunisation distribution as cases with known status, and in scenario 4, where cases with missing data were assigned the average population vaccine coverage estimate for the study time period, SM-IVE estimates became lower still, moving farther away from adjusted TND-IVE estimates. In the more likely scenario that cases with an unrecorded status were unimmunised, SM-IVE estimates became more similar to adjusted TND-IVE estimates exceeding the latter by a range of 4–29% in four of five seasons (Tables 2 and 4).

Discussion

In this analysis, we highlight the differences between SM-IVE estimates based on routinely collected, passive surveillance data to gauge influenza vaccine performance compared with an active and systematic method using a TND approach applied to SPSN data. Although the SM approach offers the advantage of ease and efficiency in using existing surveillance data, we demonstrate the potentially important trade-off of reliability. In four of five study seasons, including the 2009 pandemic, the SM underestimated IVE by an

Table 4

Sensitivity analyses of the potential impact of missing immunisation data on influenza vaccine effectiveness estimates in four different scenarios, Ontario, 2007–2012 (n = 14,282)

Season	PPV	Scenario 1		Scenario 2		Scenario 3	Scenario 4	Scenario 3	Scenario 4
		PCV	IVE	PCV	IVE	PCV	IVE	PCV	IVE
2007/08	35	60	−183	15	67	26	35	31	18
2008/09	34	54	−128	12	73	22	46	25	33
2009/10	40	83	−665	2	97	22	56	29	39
2010/11	31	57	−196	16	59	26	24	31	3
2011/12	31	59	−214	16	57	27	18	31	2

CCHS: Canadian Community Health Survey; iPHIS: Ontario's integrated Public Health Information System for reportable diseases; PCV: proportion of cases vaccinated (iPHIS); PPV: proportion of population vaccinated (CCHS); IVE: influenza vaccine effectiveness.

Scenario 1: all cases with unknown or missing status classified as immunised. Scenario 2: all cases classified as unimmunised. Scenario 3: cases allocated to the same immunisation distribution as cases with known status for all seasons combined (coverage: 25%). Scenario 4: cases assigned the same distribution as the average CCHS estimate for the study time period (coverage: 34%).

absolute difference of ca 20–35% relative to the TND-IVE, except for the 2010/11 season when estimates by both approaches were comparably low. The TND-IVE estimates from Canada, including those cited here, were within the expected range of other studies and comparable to a recently published meta-analysis for which overall pooled IVE has been estimated at 59% (95% CI: 51–67%) [24]; lower TND-IVE estimates for the 2010/11 season were also comparable to IVE estimates from the United States, reported as 31% (95% CI: −7 to 55%) [25].

Inaccuracies and missing data in routine surveillance data may result in misclassification and bias, which may have contributed to the lower SM-IVE estimates. Firstly, immunisation status was not reported for half of all eligible cases in iPHIS. Given that vaccinated cases may be more likely to recall their immunisation status, it is likely that iPHIS data selectively bias unvaccinated individuals to be recorded as missing or unknown. Comparison of cases for key confounding variables supports this hypothesis: unvaccinated cases were more similar in age and sex to cases with an unrecorded status than to vaccinated cases. The proportion of cases with an unrecorded immunisation status who reported a chronic or underlying condition was 31.6%, between that of immunised (44.2%) and unimmunised (18.5%) cases, suggesting that this group may comprise both immunised and unimmunised cases. We cannot, however, rule out that this finding may be attributable to the high proportion of missing data. Our sensitivity analysis demonstrated that in the scenario assuming that cases with an unrecorded immunisation status were not vaccinated, SM-IVE estimates increased and became more similar, if somewhat exceeding TND-IVE estimates. This exceedance provides further support that in reality, cases with an unrecorded immunisation status are likely to include also a small proportion of immunised cases. Still, our decision to exclude cases with missing data in SM-IVE calculations probably overrepresented vaccinated cases, contributing to an artificially high proportion of vaccinated cases in the SM approach (25% vs 17% in the TND), which biased IVE estimates downwards. Although the issue of unvaccinated individuals registering as missing is likely to affect also SPSN, the use of a standardised questionnaire completed by a motivated physician who knows the patient and may have administered the vaccine themselves, meant that less than 5% of cases were excluded. This issue is therefore unlikely to have had a significant impact within the SPSN system.

Secondly, iPHIS data capture persons tested and reported in the public health system without standardisation for testing indication or illness severity, unlike the SPSN. In Ontario, specimens are more likely to be collected from hospitalised patients and those at elevated risk for severe disease [19]. We found that cases captured in iPHIS were more likely to report having a chronic condition or underlying illness than cases from the SPSN. Therefore, iPHIS data are more prone to selection bias by capturing cases at the more severe end of the disease spectrum. Because persons with chronic or underlying conditions are more likely to be vaccinated and less likely to respond to vaccine, it is possible that this also led to the higher proportion of cases vaccinated in iPHIS and to lower SM-IVE estimates. Finally, we cannot discount the role of recall bias in iPHIS data since immunisation status was recorded after the influenza test results were known, an added difference from the SPSN.

We do not anticipate that differences in the diagnostic methods used by the two systems (PCR for SPSN vs both PCR and culture for iPHIS) explain the variation we observed in IVE estimates. While culture methods are less sensitive than PCR, both methods are highly specific [26]. Orenstein et al. have shown that although poor test sensitivity can underestimate IVE as true cases that tend to be distributed in the non-vaccinated

group are not detected; test specificity has a greater impact on IVE by increasing the number of false positives in both vaccinated and non-vaccinated groups [10].

Arguably the greatest potential of routine surveillance data lies in the timeliness and efficiency with which this system can accrue a large number of cases, drawing as it does on specimens submitted from all province-wide practitioners. In Ontario, influenza cases are required to be entered into iPHIS within five days of case report to local public health authorities [27]; swift data upload further supports in-season estimates. While our mid- and full-season SM-IVE estimates were similar for 2011/12, we noted a discrepancy for the 2010/11 season (–11% vs 18%). It is unclear whether this discrepancy reflects a true phenomenon or is a result of the aforementioned issues with routine surveillance data. During the 2010/11 season, the vaccine was shown to have suboptimal IVE against a genetic variant of influenza A(H3N2) [7] which was the predominant circulating strain; the latter part of the season, however, also included circulation of influenza A(H1N1) pdm09 for which IVE was moderate, which may have led to an improved IVE estimate when the full season was considered. While this analysis demonstrates retrospectively the capacity of routine data for in-season IVE calculation; in practice, the timeliness of population-based influenza vaccine coverage estimates from CCHS would be a limiting factor. It should be noted that the SPSN has been used successfully to generate interim IVE estimates [9,28]; however, this requires early and intense activity to enable sufficient accrual of sample size and statistical power for IVE estimation within the more limited network of sentinel practitioners and their ILI testing indication.

We identified data quality issues that need to be addressed not only for IVE estimation but also for accurately monitoring immunisation coverage; both activities are vital for guiding effective public health response. The proportion of cases with missing immunisation data varied substantially by health unit as data collection procedures are not standardised nor is immunisation status a mandatory field in iPHIS, suggesting that organisational practices can be modified to improve completeness. Contributing factors for this variation in practice should be investigated to identify and minimise barriers.

Linkage of case-level data to physician billing claims for influenza vaccination recorded in the database of the Ontario Health Insurance Plan (OHIP) may be a strategy to improve completeness of this field and additionally offer data on the timing of immunisation in the absence of an immunisation registry. Kwong et al. recently successfully linked laboratory testing data with the OHIP database to ascertain influenza immunisation status and subsequently estimate IVE in elderly adults [29]. This strategy, however, may lead to misclassification of those vaccinated outside of doctor's offices, e.g. in work, school and community-based clinics, as unvaccinated [30]. Linkage to health administrative data may similarly improve completeness of data on important covariates, e.g. chronic conditions. Lastly, immunisation data captured in iPHIS have not been validated against physician billing or medical records. In a subset of cases, we found strong agreement with free-text data entered into case notes, which was encouraging regarding the accuracy of the immunisation field. These findings, however, should be interpreted cautiously as they were based on a small convenience sample. Additionally, the question of the reliability of the immunisation field does not address the larger concern regarding missing data. Further work is needed to improve the quality of this information, particularly if immunisation registries are considered in the future for vaccine and programme evaluation.

Conclusions

As health organisations search for efficiency, this study highlights potential pitfalls inherent in using readily available, routine surveillance data for the purpose of IVE estimation. Improved data quality, particularly related to immunisation status and its timing as well as important covariates, is needed. Further work is merited to explore whether linkage with health administration data or ideally a vaccine registry could offer solutions to current data limitations. Fundamentally, valid estimation of vaccine effectiveness through any observational design requires consistent and systematic case finding, ascertainment of vaccination status and comparability of study groups, which ultimately may not be possible to achieve through passive surveillance systems alone. These methodological considerations apply not only within Ontario but also in other regions where annual IVE estimation is of interest. Given the significant implications of IVE findings on public perceptions and prevention measures, ensuring timely and reliable results remains an important goal.

Acknowledgments

The authors thank Michael Lebenbaum for his contribution to the analysis. Funding for the Sentinel Physician Surveillance Network study of vaccine effectiveness was provided by the Canadian Institutes of Health Research (CIHR) - Institute of Infection and Immunity, grant TPA-90193.

Conflict of interest

None declared

Authors' contributions

RDS participated in the study's design, extracted data, performed the analysis and drafted the manuscript. AW and LCR participated in the study's design, assisted in the analysis and interpretation of the data and helped draft the manuscript. RO extracted data, provided coordination for the Ontario arm of the sentinel study, and assisted in the interpretation of the data. JG provided medical oversight for specimen testing, and assisted in the interpretation of the data. DMS provided medical oversight for the sentinel study,

assisted in the analysis and interpretation of the data and helped draft the manuscript. NSC conceived of the study, assisted in the analysis and interpretation of the data and helped draft the manuscript. All authors read, provided feedback on and approved the final manuscript.

References

1. Skowronski DM, Gilbert M, Tweed SA, Petric M, Li Y, Mak A, et al. Effectiveness of vaccine against medical consultation due to laboratory-confirmed influenza: results from a sentinel physician pilot project in British Columbia, 2004-2005. Can Commun Dis Rep. 2005;31(18):181-91. PMID:16669132
2. Skowronski DM, Masaro C, Kwindt TL, Mak A, Petric M, Li Y, et al. Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: results from the 2005-2006 season of dual A and B vaccine mismatch in Canada. Vaccine. 2007;25(15):2842-51. Available from: http://dx.doi.org/10.1016/j.vaccine.2006.10.002 PMID:17081662
3. Skowronski DM, De Serres G, Dickinson J, Petric M, Mak A, Fonseca K, et al. Component-specific effectiveness of trivalent influenza vaccine as monitored through a sentinel surveillance network in Canada, 2006-2007. J Infect Dis. 2009;199(2):168-79. Available from: http://dx.doi.org/10.1086/595862 PMID:19086914
4. Janjua NZ, Skowronski DM, De Serres G, Dickinson J, Crowcroft NS, Taylor M, et al. Estimates of influenza vaccine effectiveness for 2007-2008 from Canada's sentinel surveillance system: cross-protection against major and minor variants. J Infect Dis. 2012;205(12):1858-68. Available from: http://dx.doi.org/10.1093/infdis/jis283 PMID:22492921
5. Skowronski DM, De Serres G, Crowcroft NS, Janjua NZ, Boulianne N, Hottes TS, et al.; Canadian SAVOIR Team. Association between the 2008-09 seasonal influenza vaccine and pandemic H1N1 illness during Spring-Summer 2009: four observational studies from Canada. PLoS Med. 2010;7(4):e1000258. Available from: http://dx.doi.org/10.1371/journal.pmed.1000258 PMID:20386731
6. Skowronski DM, Janjua NZ, De Serres G, Hottes TS, Dickinson JA, Crowcroft N, et al. Effectiveness of AS03 adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009. BMJ. 2011;342(feb03 1):c7297. http://dx.doi.org/10.1136/bmj.c7297 PMID:21292718
7. Skowronski DM, Janjua NZ, De Serres G, Winter AL, Dickinson JA, Gardy JL, et al. A sentinel platform to evaluate influenza vaccine effectiveness and new variant circulation, Canada 2010-2011 season. Clin Infect Dis. 2012;55(3):332-42. Available from: http://dx.doi.org/10.1093/cid/cis431 PMID:22539661
8. Janjua NZ, Skowronski DM, De Serres G, Winter A, Dickinson JA, Mahmud SM, et al. Component-Specific Estimates of 2011-12 Influenza Vaccine Effectiveness Based on the Canadian Sentinel Surveillance System. 10th Canadian Immunization Conference, Vancoouver, BC 3-5 December 2012:P001.
9. Skowronski DM, Janjua NZ, De Serres G, Dickinson JA, Winter AL, Mahmud SM, et al. Interim estimates of influenza vaccine effectiveness in 2012/13 from Canada's sentinel surveillance network, January 2013. Euro Surveill. 2013;18(5):20394. PMID:23399422
10. Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. Int J Epidemiol. 2007;36(3):623-31. Available from: http://dx.doi.org/10.1093/ije/dym021 PMID:17403908
11. De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Euro Surveill. 2013;18(37):20585. Available from: http://dx.doi.org/10.2807/1560-7917.ES2013.18.37.20585 PMID:24079398
12. Frey S, Vesikari T, Szymczakiewicz-Multanowska A, Lattanzi M, Izu A, Groth N, et al. Clinical efficacy of cell culture–derived and egg- derived inactivated subunit influenza vaccines in healthy adults. Clin Infect Dis. 2010;51(9):997-1004. Available from: http://dx.doi.org/10.1086/656578 PMID:20868284
13. Monto AS, Ohmit SE, Petrie JG, Johnson E, Truscon R, Teich E, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. N Engl J Med. 2009;361(13):1260-7. Available from: http://dx.doi.org/10.1056/NEJMoa0808652 PMID:19776407
14. Fleming DM, Andrews NJ, Ellis JS, Bermingham A, Sebastianpillai P, Elliot AJ, et al. Estimating influenza vaccine effectiveness using routinely collected laboratory data. J Epidemiol Community Health. 2010;64(12):1062-7. Available from: http://dx.doi.org/10.1136/jech.2009.093450 PMID:19910645
15. Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol. 1993;22(4):742-6.http://dx.doi.org/10.1093/ije/22.4.742 PMID:8225751
16. Valenciano M, Kissling E, Ciancio BC, Moren A. Study designs for timely estimation of influenza vaccine effectiveness using European sentinel practitioner networks. Vaccine. 2010;28(46):7381-8. Available from: http://dx.doi.org/10.1016/j.vaccine.2010.09.010 PMID:20851086
17. Ontario Ministry of Health and Long-Term Care. Influenza Vaccine Fact Sheet. Toronto: Queen's Printer for Ontario. [Accessed: 20 Apr 2015]. Available from: http://www.health.gov.on.ca/en/pro/programs/publichealth/flu/uiip/uiip_flu_fact_sheet.pdf
18. National Advisory Committee on Immunization. Statement on Seasonal Influenza Vaccine for 2013-2014. Canada Communicable Disease Report. 2013;39. Available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/13vol39/acs-dcc-4/index-eng.php
19. Influenza and other respiratory viral testing for the 2013-2014 influenza season (November 4, 2013 to May 5, 2014). Labstract - November 2013; Toronto: Public Health Ontario. [Accessed: 29 Jan 2014]. Available from: http://www.publichealthontario.ca/en/eRepository/LAB_SD_070_Influenza_respiratory_viral_testing_2013-14_season.pdf
20. Statistics Canada. Canadian community health survey - annual component (CCHS). Ottawa: Queen's Printer for Canada. [Accessed: 19 Nov 2013]. Available from: http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3226&Item_Id=118913
21. Moran K, Maaten S, Guttmann A, Northrup D, Kwong JC. Influenza vaccination rates in Ontario children: implications for universal childhood vaccination policy. Vaccine. 2009;27(17):2350-5. Available from: http://dx.doi.org/10.1016/j.vaccine.2009.02.017 PMID:19428850
22. Seyler T, Bella A, Puzelli S, Donatelli I, Rizzo C. Screening method working group. Estimating pandemic vaccine effectiveness in two Italian regions using the screening method, 2009-2010. Vaccine. 2012;30(2):109-11. Available from: http://dx.doi.org/10.1016/j.vaccine.2011.11.013 PMID:22100893
23. Ontario Agency for Health Protection and Promotion Act. SO 2007, c 10. Toronto: Queen's Printer for Ontario. [Accessed: 20 Apr 2015]. Available from: http://www.ontario.ca/laws/statute/07010
24. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(1):36-44. Available from: http://dx.doi.org/10.1016/S1473-3099(11)70295-X PMID:22032844
25. Ohmit SE, Petrie JG, Malosh RE, Cowling BJ, Thompson MG, Shay DK, et al. Influenza vaccine effectiveness in the community and the household. Clin Infect Dis. 2013;56(10):1363-9. Available from: http://dx.doi.org/10.1093/cid/cit060 PMID:23413420
26. Weinberg GA, Erdman DD, Edwards KM, Hall CB, Walker FJ, Griffin MR, et al. Superiority of reverse-transcription polymerase chain reaction to conventional viral culture in the diagnosis of acute respiratory tract infections in children. J Infect Dis. 2004;189(4):706-10. Available from: http://dx.doi.org/10.1086/381456 PMID:14767825
27. Ontario Ministry of Health and Long-Term Care. Infectious disease protocol, 2013: Appendix A: Disease-specific chapters (Influenza). Toronto; Queen's Printer for Ontario; 2009. Available from: http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/influenza_chapter.pdf
28. Skowronski D, Chambers C, Sabaiduc S, De Serres G, Dickinson J, Winter A, et al. Interim estimates of 2013/14 vaccine effectiveness against influenza A(H1N1)pdm09 from Canada s sentinel surveillance network, January 2014. Euro Surveill. 2014;19(5):20690. Available from: http://dx.doi.org/10.2807/1560-7917.ES2014.19.5.20690 PMID:24524234
29. Kwong JC, Campitelli MA, Gubbay JB, Peci A, Winter AL, Olsha R, et al. Vaccine effectiveness against laboratory-confirmed influenza hospitalizations among elderly adults during the 2010-2011 season. Clin Infect Dis. 2013;57(6):820-7. Available from: http://dx.doi.org/10.1093/cid/cit404 PMID:23788243
30. Kwong JC, Manuel DG. Using OHIP physician billing claims to ascertain individual influenza vaccination status. Vaccine. 2007;25(7):1270-4. Available from: http://dx.doi.org/10.1016/j.vaccine.2006.10.004 PMID:17079057

European Immunization Week 2015: 10th anniversary

Eurosurveillance editorial team (eurosurveillance@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Citation style for this article:
Eurosurveillance editorial team. European Immunization Week 2015: 10th anniversary. Euro Surveill. 2015;20(16):pii=21102. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21102

Article published on 23 April 2015

The 10th anniversary of the European Immunization Week (EIW) is celebrated between 20 and 25 April 2015 all over Europe [1].

This year, EIW focuses on the need for renewed commitment to immunisation at political, professional and personal levels.

Various activities at national level are organised this week under the banner of EIW and they vary greatly from country to country. In some areas supplementary immunisation activities against diseases such as polio, rubella and measles are conducted, while in others, awareness-raising campaigns are being launched, and media engagement sought. EIW is also used in some areas as background for publication of a strategic document.

Every year, EIW promotes the core message that the immunisation of every child is vital to prevent diseases and protect life. This initiative is led and coordinated by the World Health Organization Regional Office for Europe (WHO/Europe) and implemented by the countries of the European Region. For one week in April, countries across the Region unite under the EIW slogan – Prevent. Protect. Immunize. – and carry out activities to inform and engage key target audiences and to address challenges regarding immunisation. These activities include training sessions for healthcare workers, dissemination of informational materials, workshops, press conferences and round table discussions with political decision makers.

More information on the activities around the EIW is available on the campaign site [1].

On the occasion of the 10th anniversary of the EIW, the European Centre for Disease Prevention and Control (ECDC) is releasing a new set of data, tools, blogs and updates to support public health authorities in their work against vaccine preventable diseases. ECDC has launched surveillance data on measles and rubella from the European Union / European Economic Area (EU/EEA) countries through the Surveillance Atlas of Infectious Diseases [2]. The interactive tool shows, amongst other things: confirmed cases for the past 12 months, notification rates, age and sex distribution, vaccination status, complication rates.

References

1. World Health Organization Regional Office for Europe (WHO/Europe). European Immunization Week (EIW) campaign site. Copenhagen: WHO/Europe. [Accessed 23 Apr 2015]. Available from: http://eiw.euro.who.int/
2. European Centre for Disease Prevention and Control (ECDC). Surveillance Atlas of Infectious Diseases. Stockholm: ECDC. [Accessed 23 Apr 2015]. Available from: http://ecdc.europa.eu/en/data-tools/atlas/Pages/atlas.aspx