Impact factor 5.49

Eurosurveillance

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

Vol. 19 | Weekly issue 18 | 08 May 2014

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Laboratory-confirmed case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in Malaysia: preparedness and response, April 2014

J Premila Devi (premilausm@yahoo.com)[1], W Noraini[1], R Norhayati[1], C Chee Kheong[1], A S Badrul[1], S Zainah[1], K Fadzilah[1], I Hirman[1], S Lokman Hakim[1], A Noor Hisham[1]
1. Ministry of Health Malaysia

Citation style for this article:
Premila Devi J, Noraini W, Norhayati R, Chee Kheong C, Badrul AS, Zainah S, Fadzilah K, Hirman I, Lokman Hakim S, Noor Hisham A. Laboratory-confirmed case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in Malaysia: preparedness and response, April 2014. Euro Surveill. 2014;19(18):pii=20797. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20797

Article submitted on 25 April 2014 / published on 08 May 2014

On 14 April 2014, the first laboratory-confirmed case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection was reported in Malaysia in a man in his mid-fifties, who developed pneumonia with respiratory distress, after returning from a pilgrimage to Saudi Arabia. The case succumbed to his illness three days after admission at a local hospital. The follow-up of 199 close contacts identified through contact tracing and vigilant surveillance did not result in detecting any other confirmed cases of MERS-CoV infection.

Here we report a laboratory-confirmed case of Middle East respiratory syndrome (MERS-CoV) in a patient returning to Malaysia from an Umrah pilgrimage in Saudi Arabia.

Case report and travel history

Case report

On 9 April 2014, a man aged in his mid-fifties, on treatment for diabetes, presented at the emergency department of a public hospital in Malaysia with complaints of cough, fever and shortness of breath. Clinical investigation showed the patient to be afebrile with a temperature of 36.7°C and radiographic evidence of pneumonia. The next day, the patient was hospitalised, and because he had been travelling to Saudi Arabia 13 days prior, he was managed in an isolation room for suspected possible MERS-CoV infection. The staff of the local hospital and caring for the patient complied with infection prevention and control procedures according to national guidelines [1]. The patient was treated for a provisional diagnosis of community-acquired pneumonia. As bacteriological (culture of blood samples) investigation yielded negative results, the patient was treated with oseltamivir. On 10 April 2014, due to worsening of his condition he was intubated. However, the patient developed consecutive multi-organ failure and his condition further deteriorated. On 13 April 2014, throat samples were taken and he passed away on the same day.

Laboratory investigation

Diagnosis of MERS-CoV was confirmed by polymerase chain reaction (PCR) in the hospital laboratory on 14 April 2014. A real-time reverse-transcription PCR (rRT-PCR) screening assay targeting upstream of the envelope gene (upE assay) and a rRT-PCR confirmatory assay targeting the open reading frame (ORF)1a yielded positive results. On 15 April 2014 sample was sent to the Institute for Medical Research (IMR), Kuala Lumpur, for sequencing of genes that code for the nucleocapsid (N) and RNA-dependent RNA polymerase (RdRp) proteins of the MERS-CoV [2].

Travel history

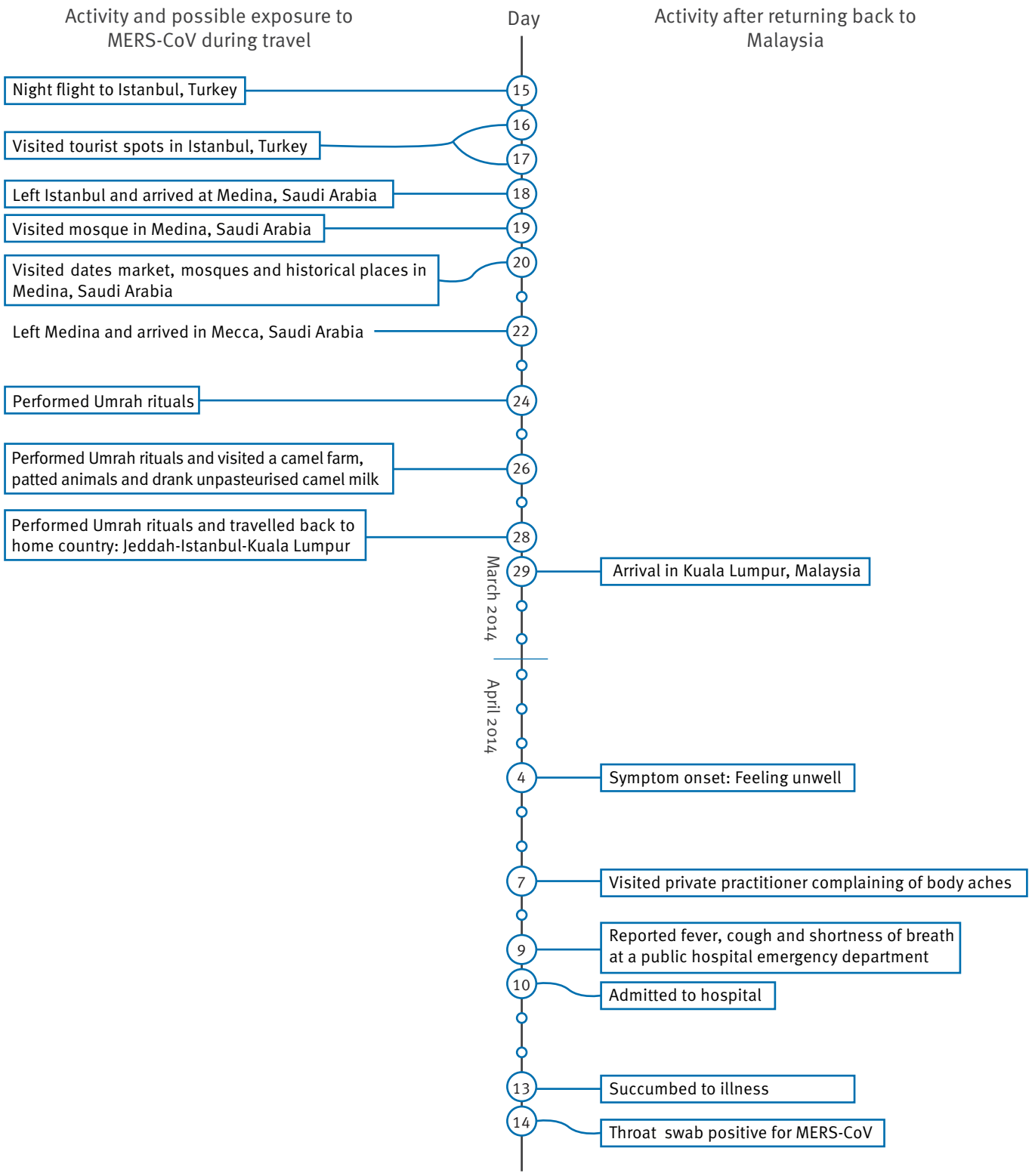
The travel history of the case was obtained from interviewing a relative who travelled with him. The interview was carried out using the standard questionnaire recommended by the World Health Organization (WHO) [3]. The case travelled to Saudi Arabia from 15 to 28 March 2014 to perform the Umrah pilgrimage with a group of 17 fellow pilgrims. Following the Umrah rituals on 26 March, he visited a camel farm in Saudi Arabia, where he patted camels and consumed unpasteurised camel milk sold by vendors at the farm. On 28 March, the case and his travel group boarded a flight from Jeddah, Saudi Arabia, to Istanbul, Turkey, and took another connecting flight from Istanbul to Malaysia where they arrived on 29 March 2014. The case was well during his travel and went back to his village on same day of arrival. The patient started feeling unwell on 4 April 2014, and sought treatment in a private clinic on 7 April 2014. At the private clinic he complained of body aches and was given analgesics. A brief timeline of the case's travel, possible exposure to the virus, healthcare contacts and diagnosis is detailed in the Figure.

Background on Middle East respiratory syndrome coronavirus

Coronaviruses are enveloped RNA viruses classified in alpha, beta and gamma genera that can be found globally in birds, humans and other mammals [4]. MERS-CoV

Figure

Timeline of possible exposure to Middle East respiratory syndrome coronavirus (MERS-CoV), travel, healthcare contacts and diagnosis of a case of MERS-CoV, Malaysia, March–April 2014



is a novel virus among the genus betacoronavirus [5]. The first case was identified in Saudi Arabia in June 2012, followed by another case from Qatar that was treated in the United Kingdom. Subsequently, a hospital cluster of pneumonia among healthcare workers in Jordan was traced retrospectively to this virus [5,6]. As of 24 April 2014, 254 laboratory-confirmed cases of MERS-CoV including 93 deaths, involving 12 countries, have been notified to the WHO [7].

Most MERS-CoV cases have been reported from Saudi Arabia, a country that hosts two important Muslim pilgrimages, the Hajj and the Umrah.The Hajj occurs during the month of Dhulhijjah that is the twelfth month of the Islamic Hijri calendar year. Any adult Muslim of a sane mind, able body and with means to bear the expenses must perform Hajj once in his/her lifetime. Hajj is not obligatory for children, the sick, and those who cannot bear the costs. The Umrah pilgrimage is a non-mandatory lesser pilgrimage made by Muslims to Mecca, which may be performed at any time of the year.

Ministry of Health, Malaysia: preparedness and response for Middle East respiratory syndrome coronavirus

Due to the large number of visitors to Saudi Arabia from Muslim countries around the world, in the context of the Hajj and the Umrah, such countries are potentially at risk for MERS-CoV importation. Malaysia contributes approximately 22,000 to 23,000 pilgrims annually to the Hajj and this figure may vary according to the quota given by the Saudi Arabian government. Bumiputera Travel and Tour Agents Association of Malaysia (BUMITRA) reported that Malaysia also has an annual average of 200,000 Umrah pilgrims.

The Ministry of Health (MoH) in Malaysia works closely with BUMITRA for the Umrah pilgrims. Tour agencies organise a pre-departure talk for Umrah pilgrims including information on MERS-CoV, advice for preparation before the pilgrimage, in particular prevention and control measures to be taken during and after the pilgrimage. For Hajj pilgrims, MoH works with the Hajj Pilgrimage Fund Board, a government agency dedicated to providing lectures, medical examinations and vaccines to the Hajj pilgrims. During the Hajj period, medical teams are sent to Saudi Arabia and will remain there for the entire Hajj period to take care of the medical needs of Malaysia's Hajj pilgrims. In 2013, the medical teams consisted of a total of 250 medical personnel and these were coordinated by MoH through the Hajj Pilgrimage Fund Board.

Since 2013, MoH has distributed health alert cards to travellers including pilgrims and flight crews returning from Middle East countries. Those with mild respiratory symptoms are also given a home assessment tool, consisting of information such as sign and symptoms of MERS-CoV infection, when to seek medical care and simple steps on how to avoid transmission of illness to others.

In Malaysia, any person who presents with fever (defined as body temperature ≥38°C), cough and breathing difficulty and has travelled or returned from Middle East countries within the past 14 days before symptom onset is advised to seek immediate care from the nearest healthcare facilities. In these facilities persons are clinically screened and if they fulfil the criteria for patient under investigation (PUI) for MERS-CoV as defined by WHO [8], they are referred to a hospital for further investigation. At the hospital, these patients receive treatment and samples are taken in order to test for MERS-CoV infection.

Guidance for management of PUI, probable and confirmed MERS-CoV cases as defined by WHO [8] has been disseminated to all the Malaysian healthcare community, including private practitioners [9]. The guidance emphasised the importance of strict infection prevention and control measures among healthcare workers and continuously monitoring their implementation. Simulation exercises were conducted to test: (i) the preparedness to detect PUI MERS-CoV cases and further management; (ii) laboratory capacities and capabilities; (iii) infection control procedures at all levels; and (iv) risk communication of various MoH facilities.

Additional means to detect cases of MERS-CoV infection are the surveillance systems for respiratory infections already in place, such as the Malaysia Influenza Surveillance System (MISS) operating since September 2003 [10]. The surveillance of influenza-like illness (ILI) and severe acute respiratory infection (sARI) involves nationwide sentinel sites and assists in detecting any unusual trends associated with respiratory infections.

Notification of MERS-CoV was made compulsory for any PUI MERS-CoV to the national Crisis Preparedness and Response Centre (CPRC) on 1 November 2012. As of 9 April 2014, before the laboratory-confirmed MERS-CoV case reported here, the MoH received a total of 507 PUI MERS-CoV notifications and all test results for MERS-CoV were negative.

In addition to the IMR and the National Public Health Laboratory, 12 of 15 government provincial hospital laboratories and one regional Public Health Laboratory have the capacity and capability to detect and confirm MERS-CoV infection. This is further supported by the availability of private and university laboratories that can provide similar services. There has been no change to the existing case detection algorithm or laboratory assays that would have increased the probability of detecting the first case.

Contact tracing and control measures

As soon as MERS-CoV infection was confirmed in the patient reported here, contact tracing was done. Close

Table

Close contacts of a case of Middle East respiratory syndrome coronavirus (MERS-CoV), Malaysia, March–April 2014 (n=199)

Type of close contact	Total (n=199)	Symptomatic and tested for MERS-CoV (n=79)
Family members[a]	38	29
Healthcare workers	56	11
Person in the same pilgrim group as the case[b]	17	17
Community members	67	13
Passengers on the same flight as the case occupying a seat located either within two rows in the front and back, or lateral to the case in both flights taken to return to Malaysia[c]	15	3
Passengers on board both flights who called CPRC[d]	6	6

CPCR: Malaysian national Crisis Preparedness and Response Centre.

Close contacts presenting with any symptoms in a period of 14 days after their last contact with the case were tested for MERS-CoV, while close contacts who remained asymptomatic during this period were not tested.

[a] Excluding one family member who was in the same pilgrim group as the case.

[b] Including nine passengers on the same flights as the case who were sitting within two rows in the front and in the back of the case, or whose seat was lateral to the case.

[c] These 15 passengers were not part of the same pilgrim group as the case and consisted of 12 Malaysians and three foreigners.

[d] Passengers on the same flights, who were from a different pilgrim group and not seated lateral to the case or within two rows back or front of the case, but who called CPRC due to symptoms.

contacts consisted of family members, community members (including friends), members from the same pilgrim group, and healthcare workers who had contact with the case. Fellow passengers sitting within two rows in the front and back or seated lateral to the case on both return flights to Malaysia were also considered close contacts. Samples were also taken from some of the symptomatic passengers who were also on board the same flights as the case and had contacted CPRC. Samples were taken as these individuals could have had contact at any time while boarding or while in transit in Istanbul.

A total of 199 close contacts were identified and placed on surveillance for 14 days starting from the last day of contact with the case. Throat swab samples were taken from 79 of them who were symptomatic. Samples were taken only once. Results from the samples taken were negative. Close contacts who were asymptomatic were given home assessment tools and those who remained asymptomatic were not tested. Among the 199 close contacts, 24 consisted of the passengers on board the same flights, who were sitting within two rows in the front, the back or lateral to the case and another six who had contacted CPRC due to symptoms. Twenty-one of these 24 passengers were from Malaysia and were contacted by the Malaysian health department.

It was quite difficult to reach the remaining three close contact passengers, who were not from Malaysia. We noticed that as not all airlines have the details of passengers, this is a limitation for contact tracing of passengers. However, MoH has managed to get the contact details of the three passengers and is currently in the process of contacting them. MoH also published press statements in local newspapers advising passengers of both flights to contact the CPRC. Details on the type of close contacts and number of samples taken are given in Table.

As this is the first MERS-CoV infection in Malaysia, the community measures taken in the vicinity of the patient were rather extensive. In addition to the activities carried out by the MoH, a local member of the Parliament took the initiative to advise the community from the same village as the case to seek medical attention if they became ill with respiratory symptoms. A local service point of screening was set up and those manning the service point provided information on MERS-CoV infection to the villagers.

Strategic health communication represents a big part of our efforts to increase the public awareness and to overcome public anxiety. Official press statements were released through the office of the Minister and Director General of Health. Subsequently, there were daily engagements with the public to provide regular updates through daily press statements, the MoH website and social media (e.g. CPRC Facebook). The public was educated on MERS-CoV, informed on MoH's preparedness and response and provided with travel health advice through regular interviews or talk shows on local television and radio stations.

Discussion and conclusion

The relative paucity of MERS-CoV cases to date is consistent with the disease epidemiology, which over the last two years accounts for approximatively 250 cases

in 10 countries and the majority of cases in Saudi Arabia. Cases outside the Middle East are mostly imported cases and mainly healthcare workers tending for the cases and family members, i.e. very close contacts, become secondary cases. Muslim countries specifically are at risk of importation of the virus, because a large number of visitors to Saudi Arabia come from these countries. As such, it appears inevitable that Malaysia will detect imported cases over time.That we managed to detect our first case in Asia is due to our vigilant surveillance system.

Although our case had travelled to Saudi Arabia with a group of 17 fellow pilgrims, none of them appear to have been affected by MERS-CoV. To date, it is still unclear how humans acquire MERS-CoV and what kind of exposures represent a potential risk for getting ill. As some other cases of MERS-CoV infection, the case reported here had an underlying condition [11]. Although limited human-to-human and nosocomial transmission has been reported [12], he did not have any contact with the local healthcare system during his journey in Saudi Arabia. He was nevertheless visiting the country at a time when a sharp increase in MERS-CoV cases was occurring [13]. Some studies have shown that camels on the Arabian Peninsula are frequently infected with MERS-CoV [14,15] and high viral loads found in camel nasal and conjunctival swabs suggest possible zoonotic transmission by the respiratory route [16]. It has also been reported that MERS-CoV can survive in raw camel milk [17]. In light of this, the fact that the case reported here was in close contact with camels and drank unpasteurised camel milk may be of relevance, although a clear route of transmission cannot be established.

This incident has highlighted the importance of preparedness and response mechanisms for early detection and prompt activation of prevention and control measures. The areas, which we can improve are to further educate Umrah pilgrims on the need for prevention during the journey and the need to seek early treatment at goverment clinics when they fall ill upon returning home. Private clinics in Malaysia may not be as vigilant on the criteria for screening of PUI and this should be addressed. Would there be evidence for a sustained human-to-human transmission in the future and secondary cases, the MoH of Malaysia may consider a need to quarantine close contacts.

Acknowledgments

The authors would like to thank the Director General of Health Malaysia for his permission to publish this paper and the World Health Organization for all its support. The authors are grateful to local health authorities, all related Divisions in the MoH Malaysia and other agencies involved in responding to this incident.

Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: Premila Devi Jeganathan, Wan Noraini Wan Mohamed Noor, Norhayati Rusli, Badrul Hashim Abdul Samad, Zainah Saat. Provided comments and revised the manuscript: Chong Chee Kheong, Fadzilah Kamaludin, Hirman Ismail, Lokman Hakim Sulaiman, Noor Hisham Abdullah.

References

1. Ministry of Health Malaysia. Policies and procedures of infection control. 2nd edition. Putrajaya: Ministry of Health Malaysia; 2010. Available from: http://www.moh.gov.my/images/gallery/Polisi/infection_control.pdf
2. World Health Organization (WHO). Laboratory Testing for Middle East Respiratory Syndrome Coronavirus. Geneva: WHO; Sep 2013. Available from: http://www.who.int/csr/disease/coronavirus_infections/MERS_Lab_recos_16_Sept_2013.pdf?ua=1
3. World Health Organization (WHO). Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Initial Interview Questionnaire of Cases. Guide for the interviewer. Geneva: WHO. [Accessed 05 May 2014]. Available from: http://www.who.int/csr/disease/coronavirus_infections/MERS_case_investigation_questionnaire.pdf
4. Danielsson N, on behalf of the ECDC Internal Response Team, Catchpole M. Novel coronavirus associated with severe respiratory disease: Case definition and public health measures . Euro Surveill. 2012;17(39):pii=20282.
5. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 367(19):1814-20. http://dx.doi.org/10.1056/NEJMoa1211721
6. Hijawi B, Abdallat M, Sayaydeh A, Alqasrawi S, Haddadin A, Jaarour N et al. Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation. East Mediterr Health J. 2013; 19 Suppl 1:S12-8.
7. World Health Organization (WHO). WHO risk assessment: Middle East respiratory syndrome coronavirus (MERS-CoV). 24 April 2014. Geneva: WHO; Apr 2014. Available from: http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140424.pdf?ua=1
8. World Health Organization (WHO). Revised interim case definition for reporting to WHO - Middle East respiratory Syndrome coronovirus (MERS-CoV). Interim case definitions as of 3 July 2013. Geneva: WHO. [Accessed 05 May 2014]. Available from: http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/
9. Ministry of Health, Malaysia. Makluman StatusTerkini Mengenai Kejadian Jangkitan MERS-CoV Dan Langkah Kesiapsiagaan Kementerian Kesihatan Malaysia (BIL. 02/2013) [Accessed 05 May 2014]. Malaysian. Available from: http://htan.moh.gov.my/v1/htdocs/Makluman%20Status%20Terkini%20Mengenai%20Kejadian%20Jangkitan%20MERS-CoV%20Bil.%2002_2013%20(0gos%202013).pdf
10. Ministry of Health Malaysia. Malaysia Influenza Surveillance System (M.I.S.S): Clinical and Laboratory Surveillance. Putrajaya: Ministry of Health Malaysia; Sep 2004, Available from: http://h1n1.moh.gov.my/NIPPP/MISS%20-Clinical%20Lab%20Surveillance.pdf
11. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis. 2013;13(9):752-61. http://dx.doi.org/10.1016/S1473-3099(13)70204-4
12. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med. 2013;369(5):407-16. http://dx.doi.org/10.1056/NEJMoa1306742
13. European Centre for Disease Prevention and Control (ECDC). Updated rapid risk assessment. Severe respiratory disease associated with Middle East respiratory syndrome coronavirus (MERS-CoV), Ninth update, 24 April 2014. Stockholm: ECDC; Apr 2014. Available from: http://www.ecdc.europa.eu/en/publications/Publications/Middle-East-respiratory-syndrome-coronavirus-risk-assessment-25-April-2014.pdf
14. Reusken CB, Haagmans BL, Müller MA, Gutierrez C, Godeke GJ, Meyer B, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. Lancet Infect Dis.

2013;13(10):859-66.
http://dx.doi.org/10.1016/S1473-3099(13)70164-6

15. Perera RA, Wang P, Gomaa MR, El-Shesheny R, Kandeil A, Bagato O, et al. Seroepidemiology for MERS coronavirus using microneutralisation and pseudoparticle virus neutralisation assays reveal a high prevalence of antibody in dromedary camels in Egypt, June 2013. Euro Surveill. 2013;18(36):pii=20574.
http://dx.doi.org/10.2807/1560-7917.ES2013.18.36.20574
16. Nowotny N, Kolodziejek J. Middle East respiratory syndrome coronavirus (MERS-CoV) in dromedary camels, Oman, 2013. Euro Surveill. 2014;19(16):pii=20781.
http://dx.doi.org/10.2807/1560-7917.ES2014.19.16.20781
17. van Doremalen N, Bushmaker T, Karesh WB, Munster VJ. Stability of Middle East respiratory syndrome coronavirus in milk [letter]. Emerg Infect Dis. 2014;20(7). [Epub ahead of print].
http://dx.doi.org/10.3201/eid2007.140500

Influenza at the animal–human interface: a review of the literature for virological evidence of human infection with swine or avian influenza viruses other than A(H5N1)

G S Freidl[1,2], A Meijer[1], E de Bruin[1], M de Nardi[3], O Munoz[3], I Capua[3], A C Breed[4], K Harris[4], A Hill[4,5], R Kosmider[4], J Banks[4], S von Dobschuetz[5,6], K Stark[5], B Wieland[5,] K Stevens[5], S van der Werf[7], V Enouf[7], K van der Meulen[8], K Van Reeth[8], G Dauphin[6], M Koopmans (marion.koopmans@rivm.nl)[1,2], FLURISK Consortium[9]

1. National Institute for Public Health and the Environment (RIVM), Centre for Infectious Diseases Research, Diagnostics and Screening (IDS), Bilthoven, the Netherlands
2. Department of Viroscience, Erasmus Medical Center, Rotterdam, the Netherlands
3. Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe), OIE/FAO and National Reference Laboratory for Newcastle Disease and Avian Influenza, OIE Collaborating Centre for Diseases at the Human–Animal Interface, Padova, Italy
4. Animal Health and Veterinary Agency (AHVLA), Surrey, United Kingdom
5. Royal Veterinary College (RVC), London, United Kingdom
6. United Nations Food and Agricultural Organization (FAO), Rome, Italy
7. Institut Pasteur, Paris, France
8. Universtiy of Ghent, Ghent, Belgium
9. http://www.izsvenezie.it/index.php?option=com_content&view=article&id=1203&Itemid=629

Citation style for this article:
Freidl GS, Meijer A, de Bruin E, de Nardi M, Munoz O, Capua I, Breed AC, Harris K, Hill A, Kosmider R, Banks J, von Dobschuetz S, Stark K, Wieland B, Stevens K, van der Werf S, Enouf V, van der Meulen K, Van Reeth K, Dauphin G, Koopmans M, FLURISK Consortium. Influenza at the animal–human interface: a review of the literature for virological evidence of human infection with swine or avian influenza viruses other than A(H5N1). Euro Surveill. 2014;19(18):pii=20793. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20793

Article submitted on 01 August 2013/ published on 08 May 2014

Factors that trigger human infection with animal influenza virus progressing into a pandemic are poorly understood. Within a project developing an evidence-based risk assessment framework for influenza viruses in animals, we conducted a review of the literature for evidence of human infection with animal influenza viruses by diagnostic methods used. The review covering Medline, Embase, SciSearch and CabAbstracts yielded 6,955 articles, of which we retained 89; for influenza A(H5N1) and A(H7N9), the official case counts of t he World Health Organization were used. An additional 30 studies were included by scanning the reference lists. Here, we present the findings for confirmed infections with virological evidence. We found reports of 1,419 naturally infected human cases, of which 648 were associated with avian influenza virus (AIV) A(H5N1), 375 with other AIV subtypes, and 396 with swine influenza virus (SIV). Human cases naturally infected with AIV spanned haemagglutinin subtypes H5, H6, H7, H9 and H10. SIV cases were associated with endemic SIV of H1 and H3 subtype descending from North American and Eurasian SIV lineages and various reassortants thereof. Direct exposure to birds or swine was the most likely source of infection for the cases with available information on exposure.

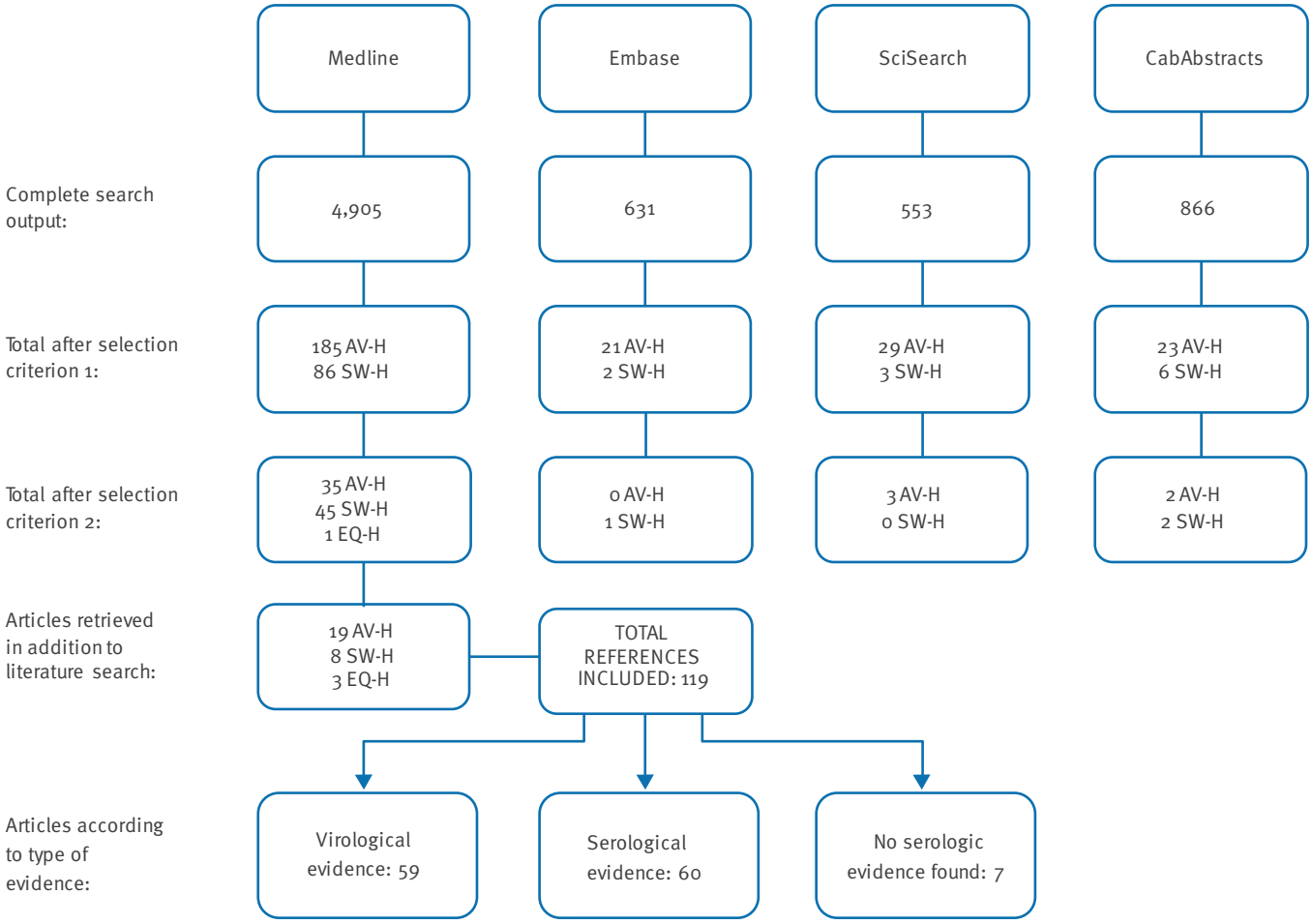
Introduction

Influenza virus type A, a member of the family *Orthomyxoviridae*, is an enveloped virus with a negative-sense, single-stranded RNA genome organised in eight gene segments, which encode at least eleven proteins. Antigenic and genetic diversity of two surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), is used to classify type A influenza viruses into subtypes; 18 HA and 11 NA subtypes are known to date [1-5]. Water- and shorebirds were identified as reservoirs harbouring all subtypes, except A(H17N10) and A(H18N11) of which RNA was recently detected in bats from Guatemala and Peru, respectively [2,3]. Reservoir animals typically do not display symptoms. In contrast, the diversity of influenza viruses in mammalian hosts is limited to specific subtypes. Human-adapted seasonal influenza viruses since the beginning of the 20th century have had HA subtypes H1, H2 and H3, combined with NA subtypes N1 and N2.

The segmented nature of the genome facilitates the exchange of genetic material if a host is co-infected with two genetically different type A influenza viruses. This reassortment process, also known as antigenic shift if it involves the gene segment encoding the HA, can result in the generation of viruses with surface antigens against which the human population may not have pre-existing, protective antibodies. Additional flexibility is conferred by the accumulation of mutations during replication, potentially resulting in amino acid substitutions that can affect pre-existing immunity if the HA is involved (antigenic drift), host range, virulence, and other factors [6]. If this results in sustained

Figure 1

Search strategy for the literature review on animal influenza A virus infections in humans



AV: avian; SW: swine; EQ: equine; H: human.

Selection step 1 extracted studies indicating information on human infection with animal influenza viruses in title and abstract. Selection step 2 excluded papers as specified in *Inclusion and exclusion criteria*. Seven articles described virological as well as serological evidence of infection. These references were counted once in the total count and listed twice in the row 'Articles according to type of evidence'. The virological evidence of human infection is presented in this paper. The indirect serological evidence will be described elsewhere.

human-to-human transmission of a virus against which a large proportion of the world's human population is immunologically naïve a pandemic can develop resulting in a large number of human cases occurring simultaneously worldwide [7,8]. Such novel introductions of reassorted viruses were at the root of four influenza pandemics in the last 100 years, and claimed the lives of millions of people, namely the 'Spanish flu' A(H1N1) in 1918, the 'Asian flu' A(H2N2) in 1957, the 'Hong Kong flu' A(H3N2) in 1968, and the recent pandemic caused by influenza A(H1N1)pdm09 in 2009 [9,10]. Influenza A(H1N1)pdm09 has replaced previous human seasonal A(H1N1) viruses [11] and, together with A(H3N2) and influenza B viruses, has been causing seasonal influenza epidemics in humans since 2009. With the emergence of the influenza A(H3N2) pandemic in 1968, influenza A(H2N2) viruses ceased to circulate in humans, but H2 subtypes are still present in birds and were also recently isolated from diseased swine [12,13].

The factors that determine whether an animal influenza virus may acquire the ability to efficiently spread among humans are poorly understood [14]. Reassortment is not a necessary prerequisite for human infection, and there is clear documentation of direct transmission and human disease caused by animal influenza viruses, in particular avian (AIV) and swine (SIV) influenza viruses , such as AIV A(H5N1), A(H9N2) and various H7 subtypes, as well as European avian-like SIV A(H1N1) [15-22]. Early detection and in-depth investigation of such events may provide clues for (future) risk assessment of animal-to-human transmissions.

This review was conducted under the framework of the FLURISK project funded by the European Food Safety

Table 1a

Virological evidence of human infection with avian influenza A viruses, excluding high pathogenicity A(H5N1)

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
1959	1/1	H7N7	Unknown	Culture in embryonated chicken eggs; subtyping with specific antisera	Source unknown; isolated from patient suffering from hepatitis	United States	Campbell et al. 1970 [52]
1977	1/1	H7N7	Keratoconjunctivits	Culture in embryonated chicken eggs	Laboratory technician accidentally infected with fowl plague	Melbourne, Australia	Taylor and Turner 1977 [53]
1979	1/1	H7N7	Conjunctivitis	Virus isolation	Source: experimentally infected harbour seal; Prior to that case, four additional possible cases who performed autopsies on infected harbour seals showed conjunctivitis but virus isolation was not performed	Massachusetts, United States	Webster et al. 1981 [54,60]
1991	11/2 14/3 15/6	H6N1 H4N8 H10N7	Ranging from respiratory and some constitutional symptoms to no symptoms	Culture in embryonated chicken eggs	Experimental infection	United States	Beare and Webster 1991 [75]
1996	1/1	LP H7N7	Conjunctivitis	Culture on rhesus monkey kidney cells	Source: straw contaminated with duck faeces	United Kingdom	Kurtz et al. 1996 [55]
1998	5/5	H9N2	Acute respiratory symptoms	Culture in embryonated chicken eggs, HI and NI assay	Poultry contact	Shantou (n=3), Shaoguan (n=2), China	Guo et al. 1999 [70]
1999	2/2	H9N2	Mild ILI	Cultured by WHO reference laboratory	4- and 1-year-old girl; one patient probably had contact with live poultry	Hong Kong[b]	Peiris et al. 1999 [16]
1999	1/1	H9N2	Fever, cough, bronchitis	MDCK cell culture, HI and NI-assay	2-year-old female with probable poultry contact	Guangzhou, China	Guo et al. 2000 [71]
2003	453/89 (including one fatality)	HP H7N7	Conjunctivitis, ILI (fatality: fever, pneumonia, multi-organ failure, respiratory insufficiency)	Cell culture (used for the first 25 confirmed cases, afterwards RT-PCR used as screening method), typed and subtyped by HI assay (turkey RBC), RT-PCR	Poultry famer and family, cullers, veterinarians, medical personnel, others	Gelderland, North Brabant, Limburg, The Netherlands	Koopmans et al. 2004; Fouchier et al. 2004 [17,56]
2003	1/1	H9N2	Mild ILI	Culture in embryonated chicken eggs. HI and NI assay, sequencing	No history of contact with poultry	Hong Kong[b]	Butt et al. 2005 [66]
2004	2/2	LP and HP H7N3	Conjunctivitis, mild ILI	RT-PCR, cell culture, sequencing	Occupational exposure to infected poultry (Veterinarian, general worker)	British Columbia, Canada	Tweed et al. 2004 [18]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

HI: haemagglutination inhibition; HP: highly pathogenic; ILI: influenza-like illness, LP: low pathogenic; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; PCR: polymerase chain reaction; RBC: red blood cells; RT-PCR: reverse transcription polymerase chain reaction; rtRT-PCR, real-time reverse transcription polymerase chain reaction; WHO: World Health Organization.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[b] Hong Kong Special Administrative Region (SAR), China.

Table 1b

Virological evidence of human infection with avian influenza A viruses, excluding high pathogenicity A(H5N1)

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2004	2/2	H10N7	'Illness' (not further specified)	Virus isolation	Infants with indirect contact to poultry (father of one is poultry merchant)	Egypt	Pan American Health Organization, 2004 [76]
2006	1/1	LP H7N3	Conjunctivitis	PCR (no serological confirmation reported)	Source: infected poultry	United Kingdom	Nguyen-Van-Tam et al. 2006 [57]
2007	4/4	LP H7N2	Conjunctivitis, ILI	Confirmed influenza A[c]	Source: infected poultry	United Kingdom	Editorial team, 2007 [58]
2007	1/1	H9N2	Mild ILI	Information not available	Source: probably a bird market	Hong Kong[b]	United States Centers for Disease Control and Prevention 2008 [67]
2008, 2009	2/2[d]	H9N2	ILI, vomiting, dyspnoea	Rapid test, RT-PCR; MDCK cell culture; immunofluorescence assay; sequencing	Immunocompromised persons (with and without poultry contact)	Shenzhen and Hong Kong[b]	Cheng et al., 2011 [68]
2010	7/ 2	H10N7	Conjunctivitis, rhinorrhoea, sore throat	PCR, partial sequencing of haemagglutinin genes (no virus culture); no evidence of seroconversion	Abattoir workers exposed to infected poultry	New South Wales, Australia	Arzey et al. 2012 [20]
2011	1/1	H9N2[e]	Fever, headache, runny nose, cough, sneezing	Partial sequencing	51-month-old female exposed to slaughtered chickens	Bangladesh	International Centre for Diarrhoeal Disease Research, Bangladesh 2011 [69]
2012	2/2	HP H7N3	Conjunctivitis; no fever or respiratory symptoms	rtRT-PCR (n=2), culture in embryonated chicken eggs (n=1), sequencing (n=1)	32- and 52-year-old female/male poultry worker exposed to infected poultry	Jalisco, Mexico	United States Centers for Disease Control and Prevention 2012 [59]
2013	251/251 (including 56 fatalities)[f]	LP H7N9	Ranging from mild symptoms and recovery to severe respiratory symptoms and death	Virus isolation, PCR	Source: not specified	Shanghai, Beijing, Hong Kong[b], Anhui, Fujian, Jiangsu, Jiangxi, Guangdong, Guizhou, Henan, Hunan, Hebei, Shandong, Zheijang, provinces, China; two cases were imported to Taiwan from mainland China	European Centre for Disease Prevention and Control updated rapid risk assessment [23]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

HI: haemagglutination inhibition; HP: highly pathogenic; ILI: influenza-like illness, LP: low pathogenic; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; PCR: polymerase chain reaction; RBC: red blood cells; RT-PCR: reverse transcription polymerase chain reaction; rtRT-PCR, real-time reverse transcription polymerase chain reaction; WHO: World Health Organization.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[b] Hong Kong Special Administrative Region (SAR), China.

[c] Authors assume that influenza A-positive test suggests influenza A(H7N2) infection because of close temporal-spatial links with influenza A(H7N2)-infected poultry and low seasonal influenza activity at that time.

[d] One patient and her asymptomatic husband showed a titre of 80 in the microneutralisation assay, three and two weeks after onset of illness respectively.

[e] Belongs to G1 lineage.

[f] At the time of writing (31 January 2014) the number of cases was still on the increase.

Table 1c

Virological evidence of human infection with avian influenza A viruses, excluding high pathogenicity A(H5N1)

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2013	1/1	H6N1	ILI, mild pneumonia	Virus isolation, full genome sequencing	20-year-old female; no exposure to poultry	Taiwan	Centers for Disease Control 2013 [79]
2013	1/1	H10N8	Severe pneumonia and death	Not specified	73-year-old immunocompromised female with underlying illness; exposed to live poultry	Jiangxi province, China	ProMED 2013 [77]
2013	1/1	H9N2	Chest infection, low fever, chills and cough	Not specified	86-year-old male with underlying illness; no recent poultry exposure	Shenzhen/Hong Kong[b]	ProMED 2013 [72]
2014	1/1	H9N2	Illness (not further specified); recovered	Not specified	7-year-old male with poultry exposure	Hunan, China	ProMED, 2014 [73]
2014	1/1	H10N8	Sore throat, dizziness, loss of strength, severe pneumonia[g]	Not specified	55-year-old female; visited agricultural market	Jiangxi, China	ProMED 2014 [78]
Total	784/386 (375 when experimentally infected human cases are subtracted)						29

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

HI: haemagglutination inhibition; HP: highly pathogenic; ILI: influenza-like illness, LP: low pathogenic; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; PCR: polymerase chain reaction; RBC: red blood cells; RT-PCR: reverse transcription polymerase chain reaction; rtRT-PCR, real-time reverse transcription polymerase chain reaction; WHO: World Health Organization.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[b] Hong Kong Special Administrative Region (SAR), China.

[g] At the time of writing (31 January 2014) the patient was hospitalised and in critical condition.

Table 2a

Virological evidence of human infection with swine influenza A viruses

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
Not specified	7/3[b] 13/2	swH3N2[c] clH1N1	Mild: coryza	Virus isolation (not further specified)	Experimentally infected humans (intranasal, $10^{5.5}$ egg-infective doses)	Not specified (according to author affiliations: England)	Beare et al. 1972 [45]
1974	1/1 (fatal)	swH1N1[d]	Pneumonia	Culture on WI-38-, HeLa- and rhesus-monkey kidney-cells, inoculation of mice; HI assay (guinea pig RBC)	16-year-old Hodgkin's disease patient living on swine farm	Minnesota, United States	Smith et al. 1976 [42]
1976	20/5 (including 1 fatality)	swH1N1	Acute respiratory illness, pneumonia	Embryonated chicken egg culture, HA assay	Previously healthy soldiers without known exposure to swine	New Jersey, United States	Gaydos et al. 1977 [28]
1976	1/1	swH1N1[e]	Mild ILI	Virus isolation; HI assay	22-year-old swine worker exposed to ill, influenza-positive swine	Wisconsin, United States	United States Centers for Disease Control and Prevention 1976 [29]
1976	1/1	swH1N1[f]	ILI	Virus isolation; HI assay	13-year-old boy living on swine farm	Wisconsin, United States	United States Centers for Disease Control and Prevention 1976 [30]
1979/80	2/2	swH1N1[f]	ILI	Rhesus monkey kidney cell culture; embryonated chicken egg culture; HI assay	20-year-old fell ill after close contact with swine; 6-year-old visitor of livestock show without direct contact with swine	Texas, United States	Dacso et al. 1984 [31]
1982	1/1 (fatal)	swH1N1[f]	Pneumonia	Cynomolgus monkey kidney cells; embryonated chicken egg culture; RNA-oligonucleotide mapping	4-year-old female leukemia patient; no known exposure to swine	Nevada, United States	Patriarca et al. 1984 [32]
1983	3/3	swH1N1	Information not available	Isolation	65-year-old male with occupational exposure to swine; 10-year old female and 27-year-old male with unknown exposure to swine	Russia	Chuvakova et al. 1985 [27]
1986	a) 1/1 b) 2/2	swH1N1[g,h]	a) Pneumonia b) Mild ILI	a) Various cell cultures; embryonated chicken egg culture; HI and NI assay b) Various cell cultures; HI assay, complement fixation assay	a) 29-year-old farmer exposed to ill, influenza-infected pigs b) 50-year-old employee exposed to ill, influenza-infected pigs, and 3-year-old with no known contact with pigs	a) The Netherlands b) Switzerland	De Jong et al 1988 [33]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[b] Number of humans from whom virus could be reisolated.

[c] Swine/Taiwan/7310/70 related to A/Hong Kong/1/68.

[d] Named A/Mayo Clinic/103/74, inhibited by antisera against A/swine/1976/31 and A/swine/Wisconsin/67.

[e] A/New Jersey/8/76.

[f] A/New Jersey/8/76-like influenza virus.

[g] A/Netherlands/386/86, A/Geneva/5521/86, A/Geneva/5200/86.

[h] Highest homology with European swine-influenza viruses.

Table 2b

Virological evidence of human infection with swine influenza A viruses

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
1988	1/1 (fatal)[i]	swLH1N1	Pneumonia	RNA fingerprinting; partial sequencing;	32-year-old pregnant woman exposed to pigs at county fair showing ILI	Wisconsin, United States	McKinney et al. 1990 [34]
1991	1/1 (fatal)	swLH1N1[j]	Pneumonia	Rhesus monkey kidney cell culture; embryonated chicken egg culture; rtRT-PCR; oligonucleotide mapping; HI and NI assay; sequencing; experimental infection of swine	27-year-old animal caretaker exposed to swine showing respiratory symptoms	Maryland, United States	Wentworth et al. 1994 [35]
1992/ 93	2/2	swH3N2[k]	Mild respiratory symptoms	Virus isolation; HI assay; sequencing	1- and 2-year-old with no known exposure to swine	The Netherlands	Claas et al. 1994 [41]
1993	1/1	swH1N1[h]	Pneumonia	Tertiary monkey kidney cell culture; RT-PCR; immunofluorescence assay on MDCK cells; sequencing; HI assay	5-year-old living on swine farm (health status of swine not known)	The Netherlands	Rimmelzwaan et al. 2001 [36]
1994	2/2	swH1N1[l]	Mild ILI	Embryonated chicken egg culture; MDCK cell culture; HI- and NI-assay; sequencing; RT-PCR and other PCR-types; Eexperimental infection of swine	39- and 30-year-old BSL3 laboratory workers exposed to influenza-infected pigs	Wisconsin, United States	Wentworth et al. 1997 [37]
1995	1/1 (fatal)	swH1N1	Severe pneumonia	Virus isolation and subtyping	37-year-old healthy woman working on pig farm (health status of pigs unknown)	Minnesota, United States	Kimura et al. 1998 [38]
1999	1/1[m]	H3N2[n]	Mild ILI	MDCK cell culture; HI and NI assay; RT-PCR; sequencing	10-month-old girl (neither she nor her family had recent contact with pigs)	Hong Kong[o]	Gregory et al. 2001 [39]
2002	1/1	H1N1[p]	ILI	MDCK cell culture; HI assay (also serologically confirmed by HI)	50-year-old farmer (possibly from pigs showing respiratory symptoms)	Switzerland	Gregory et al. 2003 [21]
2004, 2005	1/1 1/1	H1N2[q] H1N1[q]	Mild ILI	MDCK cell culture; HA assay (turkey RBC); HI assay[r]; rapid tests[s]; RT-PCR; sequencing	25- and 4-year-old male; neither had direct contact to pigs (incidental contact with backyard pigs could not be excluded)	Philippines Thailand	Komadina et al. 2007 [85]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[h] Highest homology with European swine-influenza viruses.

[i] Patient's husband developed ILI symptoms one day before the patient (virus isolation not done)

[j] A/Maryland/12/91.

[k] Human-avian reassortants: A/Netherlands/5/93, A/Netherlands/35/93.

[l] Strain was similar to strain used in swine experiment and closely related to Sw/IN and A/WI/3523/88.

[m] Patient showed a titre of 160 by HI assay, the patient's mother a titre of 20, father, brother and grandparents titres of less than 10.

[n] Virus was closely related to viruses circulating in European pigs.

[o] Hong Kong Special Administrative Region (SAR), China.

[p] A/Switzerland/8808/02 (European avian-like lineage).

[q] Swine-like viruses: HA genetically similar to swine viruses circulating in swine in Asia at the time and to viruses that circulated in North America in the 1990s, whereas NA and internal genes were similar to European swine viruses.

[r] Both isolates tested negative against human strains.

[s] To determine whether isolates belong to influenza A or B.

Table 2c

Virological evidence of human infection with swine influenza A viruses

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2005	1/1	trH1N1[t]	Sore throat, runny/ stuffed nose, cough, fever	Cell culture, RT-PCR, sequencing	50-year-old swine farm resident exposed to ill swine (not influenza confirmed)	Iowa, United States	Gray et al. 2007 [92]
2005	1/1[u]	trH1N1[v]	Acute mild respiratory illness; no fever	MDCK cell culture; RT-PCR; sequencing	Vaccinated one month before illness; assisted in butchering swine;	Wisconsin, United States	Newman et al. 2008 [89]
2005	1/1	trH3N2[w]	ILI	Culture on primary rhesus monkey kidney cells; sequencing	Previously healthy swine farmer exposed to influenza-positive pigs	Canada	Olsen et al. 2006 [40]
2006	1/1[x]	sw trH3N2[w]	ILI	HI assay (guinea pig RBC) RT-PCR, sequencing	7-month-old child living on communal farm; no direct exposure to animals, seropositive swine found on farm	Canada	Robinson et al. 2007 [96]
2007	1/1[y]	trH3N2[w]	Parotitis, nasal congestion; no fever, cough or pharyngitis	Virus isolation; HI assay (turkey RBC); sequencing	6-year-old boy living on swine farm (no illness in swine observed)	Canada	Bastien et al. 2009 [95]
2007	26/2[z]	swH1N1[aa]	ILI	Virus isolation; sequencing	People exposed to ill swine at county fair	Ohio, United States	Vincent et al. 2009 [87]; Yassine et al. 2009 [88]
2005–09	a) 10/10 b) 1/1	a) sw trH1N1[bb] b) trH1N2[cc]	Ranging from mild ILI to pneumonia	Rapid point of care test (n=8); Virus culture (n=7); rt RT-PCR (n=6); HI assay; complete genome pyrosequencing	Seven males (age: 16 months–36 years) our females (age: 4–48 years); exposure ranging from unknown contact, close proximity and direct contact with swine (some pigs were ill)	Wisconsin, Missouri, Iowa (n=3), Ohio (n=2), Illinois, Michigan, Minnesota and Texas, United State	Shinde et al. 2009 [93]

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[t] H1 HA, N1 NA, M, NP, NS genes descended from classical swine-, PB1 from human- and PA and PB2 from avian influenza virus lineages

[u] Patient showed a two-fold titre increase in MN assay (not in HI assay) and four family members and the patient's brother-in-law were seronegative by MN and HI assay.

[v] Predominant genotype of subtype H1N1 in North American pigs.

[w] Same genotype as human/classical swine/avian reassortant that emerged in 1998 in North America.

[x] Four of seven household members of the patient and four of 46 other residents of the farm showed serological evidence of infection.

[y] Household members were only serologically screened.

[z] Virus from at least two individuals was isolated and sequenced and turned out to be nearly identical to the swH1N1 isolated from the ill swine; not done for all human cases.

[aa] HA related to H1γ cluster (H1N2-like) of contemporary H1-SIV, NA related to swine N1 phylogenetic cluster and internal genes were from triple-reassortant SIV lineage and group with cluster IV of A(H3N2) viruses.

[bb] H1N1: HA, NA, NP, NS, M (classical swine, North-American lineage), PB2, PA (avian, North American lineage), PB1 (human seasonal H3N2).

[cc] H1N2: HA (human seasonal H1N1), NP, M, NS (classical swine, North-American lineage), PB2, PA (avian, North-American lineage), PB1, NA (human seasonal H3N2).

Table 2d

Virological evidence of human infection with swine influenza A viruses

Year	(Tested)[a]/ confirmed cases	Subtype	Symptoms	Method	Patient information and nature of exposure	Location	Reference
2008	1/1[dd]	SwL trH1N1[ee]	ILI, vomiting, diarrhoea	Rapid test; culture; rRT-PCR; sequencing	19-year-old male exposed to healthy appearing pigs (no physical contact)	South Dakota, United States	Dawood et al. 2011 [90]
2008	1/1	swH1N1[ff]	ILI	MDCK cell culture; immunofluorescence using MAb; PCR; partial sequencing	50-year-old-female with direct contact to asymptomatic pigs	Spain	Adiego Sancho et al. 2009 [22]
2009	1/1[gg]	sw trH3N2	Fever, cough, sore throat	Rapid test; rtRT-PCR; sequencing	12-year-old boy (touched healthy appearing swine at a county fair, pigs were seropositive)	Kansas, United States	Cox et al. 2011 [97]
2009	3/3[hh]	sw trH1N1[ii]	ILI	MDCK cell culture; rtRT-PCR; HI assay (turkey RBC)[jj], sequencing	Swine workers (one was immunized in 2008, other two never received an influenza vaccination)[kk]	Saskatchewan, Canada	Bastien et al. 2010 [91]
2009–11	3/3	swH1N1[ll]	Not specified	Not specified	Three adult, male swine workers exposed to ill, influenza-confirmed pigs	Switzerland	European Centre for Disease Prevention and Control 2012 [86]
Aug- Dec 2011 2012 2013	12/12[mm] 309/309 19/19[oo]	H3N2v[nn]	ILI, vomiting, diarrhoea	Rapid tests; rtRT-PCR; sequencing	50% exposed and 50% not exposed to swine; (11 children, one adult male); Most attending agricultural fair Most attending agricultural fair	Hawaii, Illinois, Indiana, Iowa, Maine, Maryland, Michigan, Minnesota, Ohio, Pennsylvania, Utah, West Virginia, Wisconsin, United States	United States Centers for Disease Control and Prevention 2012 [99],2013 [25]
Total	**455/401**						**33**

Where more than one human case is stated, diagnostic tests were performed for all cases as stated in the Methods section, unless otherwise specified.

BSL: biosafety level; cl: classical swine lineage; HA: haemagglutination; HeLa: Henriette Lacks cervical cancer cells; HI: haemagglutination inhibition; ILI: Influenza-like illness; MAb: monoclonal antibodies; MDCK: Madin Darby canine kidney; MN: microneutralisation; n.a.: not applicable; NI: neuraminidase inhibition; RBC: red blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; rtRT-PCR: real-time reverse transcriptase polymerase chain reaction; sw: swine; SwL: swine-like; tr: triple reassortant; WI-38: human embryo lung fibroblast.

[a] In most cases the number tested reflects only the confirmed cases reported in the reviewed paper where the authors did not report on the true number of suspected cases tested.

[dd] Contacts of the patient and people exposed to swine during the event were serologically screened.

[ee] Distinct from A(H1N1)pdm09 and similar to triple-reassortant swine viruses circulating in the United States shortly before .

[ff] Phylogenetically close to A/Switzerland/8808/02 (European avian-like lineage) [19].

[gg] In addition, 27 of 34 visitors of the county fair participated in a survey: none reported ILI.

[hh] No household members were ill at the time.

[ii] Distinct from A(H1N1)pdm09: NS, NP, M, PA, PB1 and PB2 were similar to a North-American swine triple reassortant and HA and NA were most similar to A/Brisbane/59/2007 (H1N1)-like viruses.

[jj] For antigenic characterisation.

[kk] Mild respiratory illness was present in less than 1% of the swine herd the workers were exposed to (no confirmation whether it was due to influenza A infection).

[ll] Infected with European SIV similar to viruses identified in ill pigs the workers were exposed to.

[mm] Eleven children (including two children attending the same daycare centre) and one adult male.

[nn] Influenza A H3N2 variant (comprises genes from avian, swine and human origin) with M gene derived from A(H1N1)pdm09.

[oo] Case count as available on 31 January 2014.

Authority (EFSA). The main objective of FLURISK is the development of an evidence-based influenza risk assessment framework (IRAF) to assess the potential of animal influenza viruses to cross the species barrier and cause sustained infections in humans. The work presented here aims at describing available evidence for animal-to-human influenza virus transmissions.

Methods

Search strategy

We performed a literature search using Medline, Embase, SciSearch and CabAbstracts. Search terms included 'influenza', 'influenza virus', 'animals', 'swine', 'birds', 'poultry', 'wild bird', 'water bird', 'waterfowl', 'goose', 'duck', 'chicken', 'turkey', 'environment', 'animal-to-human',
'transmission-to-humans', 'interspecies transmission', 'human', 'case', 'seroprevalence', 'serosurveillance', 'prevalence', 'incidence', 'risk factor', 'exposure' and various subtypes of influenza virus; the terms were used alone or in combinations using Boolean operators. Full search details are available from the corresponding author on request. Only articles published in English were included and the search covered all years available in the respective databases, Medline from 1946, Embase from 1947, SciSearch from 1980, CabAbstracts from 1973, all up to February 2012. The search algorithm automatically discarded duplicates. Newly published evidence that came to our attention between February 2012 and January 2014 was also included. Case counts of avian influenza A(H7N9) and A(H5N1) cases were updated on 31 January 2014 based on the latest figures reported by the European Centre for Disease Prevention and Control (ECDC) [23] and by the World Health Organization (WHO) [24]. Case counts of human infections with swine influenza variant A(H3N2)v were retrieved on 31 January 2014 from the website of the United States (US) Centers for Disease Control and Prevention (CDC) as posted on 18 October 2013 [25. Grey literature was searched in a non- systematic way.

Inclusion and exclusion criteria

Included were papers indicating evidence of human infection with animal influenza viruses (selection criterion 1, Figure 1). Two investigators first screened all papers by title and, when necessary, by abstract. All articles meeting this first criterion were reviewed for details of the methods used to diagnose the infection. Experimental and observational studies describing human infection with animal influenza viruses other than influenza A(H5N1) were included. Articles solely describing human infection with A(H5N1) were excluded, and for influenza A(H5N1) and A(H7N9), the official WHO and ECDC statistics from notifications under the International Health Regulations were used for completeness. Commentaries, reviews, articles dealing with influenza in animals only, studies solely assessing human-to-human transmission of an animal influenza virus (i.e. most of the literature on influenza A(H1N1)pdm09), and articles referring to study subjects described in prior original publications were excluded (selection criterion 2, Figure 1). Studies based on serological evidence only were excluded to ensure high specificity of the findings. Papers were screened for information on the time period when the study was conducted, total number of people sampled, patient information, nature of exposure (e.g. occupational, recreational), possible exposure to diseased animals, influenza virus subtypes included in testing, number of virologically confirmed cases, information on vaccination history if stated, methods used for confirmation, geographic region and study design. Available data were extracted and summarised in tables. Grey literature such as ProMED, and reference lists from articles were screened for possible additional relevant papers. Virus detection by culture or (real-time) reverse transcription polymerase chain reaction (rtRT-PCR) and sequencing was considered to be definitive proof of infection, listed as virological evidence (Tables 1 and 2).

Search output and article selection

The initial search yielded 6,955 articles, with 4,905 articles resulting from the Medline search, and the others from additional searches (Figure 1). Search outputs from Embase, SciSearch and CabAbstracts yielded 631, 553 and 866 references, respectively. After screening of titles, abstracts and application of the second selection criterion, a total of 89 publications were selected. The majority of these would also have been identified solely through the Medline search.

Thirty additional studies were retrieved through scanning of reference lists of articles identified via the literature review, were retrieved from grey literature or came to our attention after February 2012. Of these 119, 59 publications and reports described virological evidence for infection of humans and met all other inclusion criteria; 60 papers provided some evidence for human infection, but only based on antibody testing and will therefore be described elsewhere.. Seven publications containing both serological and virological evidence were counted once in the total reference count but were included twice in the subdivision according to type of evidence in Figure 1.

Most studies discussed in a review of case reports of SIV infections in humans by Myers et al. [26] were also identified in our literature search. For completeness of the human case count, virologically confirmed civilian (n=23) and military cases of Fort Dix (n=5), although discussed in detail in the review by Myers et al. [26], were also included in the current review [21,27-42] (Table 2). For two virus-confirmed cases from the review by Myers et al. [26], the reference could not be retrieved or did not provide full confirmation; these cases were therefore excluded from our listing in Table 2 [43,44].

Table 3

Humans naturally infected with avian influenza virus subtypes other than A(H5N1) and swine influenza virus subtypes, 1959–2014 (n=771)

Source virus	Number of human cases infected with										
Avian											
Subtype	LP H6N1	H7N2	HP H7N3	LP H7N3	HP H7N7	LP H7N7	LP H7N9[a]	H9N2	H10N7	H10N8	**Total**
	1	4	3	2	89	4	251	15	4	2	**375**
Swine											
Subtype	H1N1	H1N2	H3N2	H3N2v[b]							**Total**
	47	2	7	340							**396**

HP: highly pathogenic; LP: low pathogenic.

[a] as of 27 January 2014 [23].

[b] as of 18 October 2013 [25].

Results

The evidence for virologically confirmed infections of humans with avian or SIV is listed in Tables 1, 2 and 3. The exposure status of infected patients is summarised in Table 4. A total of 386 cases of human infection with non-A(H5N1) AIV were described, of which 375 were caused by natural infection and 11 were infected experimentally (Table1).

Regarding human infections with SIV, a total of 401 naturally (n=396) and experimentally (n=5) infected cases were detected in the published and grey literature in English. This included, three virologically confirmed SIV A(H1N1) cases originally published in Russian by Chuvakova et al. [27] because they were listed in the review by Myers et al. [26]. The majority of cases (n=340) were naturally infected by a SIV variant A(H3N2)v [25]. Recognised in US swine in 2010, this variant combines seven genes from the contemporary North-American A(H3N2) SIV lineage and has acquired the M gene of the A(H1N1)pdm09 virus [25]. The remaining 56 naturally infected, virologically confirmed human cases were caused by different circulating SIV or SIV reassortants (Table 2). Five persons were experimentally infected with SIV [45]. The majority of AIV- and SIV-infected patients had been exposed to animals (Table 4).

Human infections with avian influenza viruses

Infections with highly pathogenic avian influenza virus A(H5N1)

To date, highly pathogenic avian influenza (HPAI) A(H5N1) viruses are the most frequently diagnosed zoonotic influenza virus infections related to avian exposure [46], although this picture may change in the near future given the recent upsurge in low pathogenic avian influenza (LPAI) A(H7N9) cases. The HPAI A(H5N1) viruses first attracted major attention in the scientific community in 1996, when a large number of domestic waterfowl died in the course of an A(H5N1) outbreak in Guangdong province in southern China. In 1997, HPAI A(H5N1) resurfaced in Hong Kong SAR, China (in the following referred to as Hong Kong); it caused a massive die-off in poultry and crossed the species barrier for the first time, infecting 18 humans, of whom six died [47,48]. From mid-2003 to March 2004, HPAI A(H5N1) spread to seven south-east Asian countries with outbreaks in poultry and waterfowl, and the first confirmed human cases, were reported in Thailand and Vietnam in 2004 [49]. In 2005, HPAI A(H5N1) accounted

Table 4

Exposure status of patients infected with avian influenza virus, excluding 251 A(H7N9) and including 11 experimentally infected cases, and with swine influenza virus, 1959–2014 (n=536)

Source	Number of cases					
	Exposed	Not exposed	Exposure status unknown	Likely exposed (H3N2v)	Other[a]	**Total**
Avian	114	3	5	n.a.	13	**135**
Swine	45	20	2	328	6	**401**

n.a.: not applicable.

[a] Experimental (avian n=11, swine n=5) or laboratory exposure (avian n=2), or human-to-human transmission (swine n=1).

for the death of a large number of migratory waterfowl at Qinghai lake, China. Shortly after this event, the virus rapidly spread to other Asian countries, Africa, Europe, the Middle East, Mongolia and Russia [50]. Over time, the viruses evolved into multiple lineages, some of which persisted and have become endemic in China, Bangladesh, Egypt, India, Indonesia and Vietnam [51].

As of 10 December 2013, the WHO has listed 648 HPAI A(H5N1) infected cases from 15 countries, confirmed according to WHO criteria and covering a time span of 10 years [24]. In total, 59% of the reported cases died [24]. Indonesia, Egypt and Vietnam reported 195, 173 and 125 cases, respectively, accounting for about 75% of the total influenza A(H5N1) human case count. These three countries also reported the majority of fatalities [24].

Infections with H7 subtype avian influenza viruses

In total, we identified 353 human cases with virologically confirmed H7 infection (Table 1). The majority of these cases (n=251) were reported in China, followed by 95 cases in Europe, six in North America and one in Australia [17,18,23,52–59]. In China, all cases were caused by the recently emerged subtype A(H7N9) [23]. Of the remaining 102 cases, 93 cases had influenza A(H7N7), five had influenza A(H7N3) and four influenza A(H7N2) (Table 3). The first two human cases infected with influenza A(H7N7) were reported in 1959 and 1977. One of these patients had keratoconjunctivitis, thought to be caused by the AIV infection [52,53]. This predilection for the ocular mucosa was confirmed when a person involved in an experimental infection of a seal with an avian-like influenza A(H7N7) developed conjunctivitis, and virus was cultured from a conjunctival swab [54,60]. In the United Kingdom (UK) in 1996, LPAI A(H7N7) virus infection was associated with mild conjunctivitis in a woman who cleaned a duck house and mentioned getting a piece of straw in her eye [55].

Among European cases, 89 humans were infected in the course of a large outbreak with HPAI A(H7N7) in poultry in the Netherlands in 2003 [17]. In contrast to the severe consequences in poultry, only mild symptoms were seen in 88 of the infected people. There was one exception. a veterinarian who died of acute respiratory distress syndrome and multiple organ failure. This person had contracted a virus with several mutations, including a known virulence marker in PB2 [56]. Most of these mutations had accumulated during circulation of the virus in poultry, showing that the public health risk may change over the course of an outbreak [61]. In February 2004, a mixed LPAI and HPAI A(H7N3) virus outbreak was reported in poultry in British Columbia, Canada [18]. Enhanced surveillance for influenza-like illness (ILI) and conjunctivitis in the course of this outbreak led to the identification of two poultry workers showing symptoms of unilateral conjunctivitis. Neither had used the recommended goggles or taken prophylactic oseltamivir. Interestingly, both virus types led to human infection: the isolate cultured from the first worker had the LPAI phenotype, whereas the strain retrieved from the second worker was classified as HPAI [19,62,63]. In 2006 and 2012, LPAI A(H7N3) was associated with one patient in the UK and HPAI A(H7N3) with two patients in Mexico. In both instances, exposure to infected poultry was documented and all patients presented with conjunctivitis [57,59]. Finally, LPAI A(H7N2) was reported as the infectious agent causing mild influenza-like symptoms and conjunctivitis in four cases in the UK in 2007 [58].

The assumption that LPAI influenza viruses were mostly associated with mild disease was challenged with the emergence of influenza A(H7N9) viruses in March 2013, when China notified the WHO of three cases infected with LPAI A(H7N9) who were severely ill and eventually died [64]. During the first wave of infections from February to May 2013, 133 human cases were reported and an additional two cases in July and August [23]. Phylogenetic studies concluded that all genes of this newly detected virus were of avian origin [64]. In October 2013, the second wave started and was still ongoing at the time of writing (31 January 2014) [23]. Between February 2012 and 27 January 2014, a total of 251 influenza A(H7N9) cases were reported, 56 of whom died [23]. Infections occurred in Anhui (n=4), Beijing (n=3), Fujian (n=15), Guangdong (n=32), Guizhou (n=1), Hebei (n=1), Henan (n=4), Hong Kong (n=3), Hunan (n=4), Jiangsu (n=31), Jiangxi (n=5), Shandong (n=2), Shanghai (n=42) and Zheijang (n=102). Two cases were imported from mainland China into Taiwan [23]. In response to these events, China culled thousands of birds and closed several poultry markets [65], although only 39 of 48,000 samples representing 1,000 poultry markets tested positive. Most human cases had a history of exposure to birds or live bird markets [23]. As of 31 January 2014, no conclusive evidence of human-to-human transmission has been reported and the ecology of the viruses remains to be resolved.

Infections with H9 subtype avian influenza viruses

In total, we detected 15 human cases infected with AIV A(H9N2) (Table 1, Table 3). Since the mid-1990s, influenza viruses of the H9 subtype have established stable lineages in poultry in Asia and have occasionally infected humans and swine (Table 1) [16,66-69]. As of 31 January 2014, human A(H9N2) cases have only been detected in Asia, particularly in China. Six cases were identified via the literature search [16,66-68]. Of those, three reported poultry exposure and all presented with mild ILI (Table 1). Reviews conducted by Peiris [46] and Cheng et al. [68] identified six additional human infections in China reported in the Chinese literature [70,71]. Three additional cases from Bangladesh, Hunan and Shenzhen, two with and one without poultry exposure, complete the total count of fifteen human cases caused by AIV A(H9N2) [69,72,73] (Table 3). Infections with AIV A(H9N2) viruses gained public health interest when researchers found that strains circulating in Asian poultry had a receptor specificity similar to

human influenza A viruses, which is considered one of the essential features of a human-to-human transmissible virus [74]. So far, however, no sustained human-to-human transmission of A(H9N2) influenza viruses has been reported.

Infections with other avian influenza virus subtypes

Experimental inoculation of human volunteers with influenza strains A(H4N8), A(H6N1) or A(H10N7) resulted in mild clinical symptoms and virus shedding in eleven volunteers [75]. In 2004, the National Influenza Center in Egypt and the WHO Influenza Collaborating Centre in the UK announced the isolation of influenza A(H10N7) virus from two children presenting with fever and cough in Egypt [76]. In Australia, virus of the same subtype could be detected by PCR in two abattoir workers with conjunctivitis who were exposed to infected poultry [20] (Table 3). In December 2013 and January 2014, human infection with A(H10N8) virus was reported for the first time in Jiangxi province, China [77,78]. Both patients were female and had visited a poultry and an agricultural market, respectively, before onset of illness. One of them was immunocompromised and had died whereas the other case was still in critical condition as of 31 January 2014. In 2013, CDC Taiwan reported a human case of AIV A(H6N1) infection causing mild pneumonia, although an avian source could not be identified [79,80] (Table 3).

Human infection with swine influenza viruses

An overview of all studies describing virologically confirmed human SIV cases is given in Table 2. In total, we identified 396 SIV-confirmed patients who were naturally infected (401 including experimental infections) (Table 2). Beare et al. [45] successfully recovered SIV from five of 20 human volunteers after experimental infection: of seven volunteers infected with SIV A(H3N2) related to A/Hong Kong/1/68, three tested virus-positive), and of 13 infected with a classical swine A(H1N1) virus strain, two tested positive. Of the naturally infected cases, 47 were infected with SIV A(H1N1), two with SIV A(H1N2), seven with SIV A(H3N2) and 340 with SIV A(H3N2)v (Table 2, Figure 2). The majority of these cases were reported in North America, 11 in Europe and six in Asia. One of the six Asian cases was infected with SIV A(H3N2) from the European lineage (Figure 2) [39]. SIV epidemiology differs between continents and was extensively reviewed for North America, Europe and Asia [81-84]. In addition to the studies discussed in the review by Myers et al. [26] we identified fourteen studies and reports describing a further 28 human SIV cases; 368 when taking into account 340 cases with SIV A(H3N2)v infection. Details on these studies are described in more detail in the following sections grouped by continent.

Infections with swine influenza A H1 subtype viruses

Asia: A 25 year-old male from the Philippines and a four year-old male from Thailand were infected with swine-like A(H1N2) and A(H1N1), respectively [85]. The isolated viruses carried HA genes most closely related to classical swine viruses circulating in Asia and North America. NA genes were most similar to circulating European SIV. Both cases showed mild ILI and neither of them had direct contact with swine, although occasional contact with backyard swine could not be ruled out.

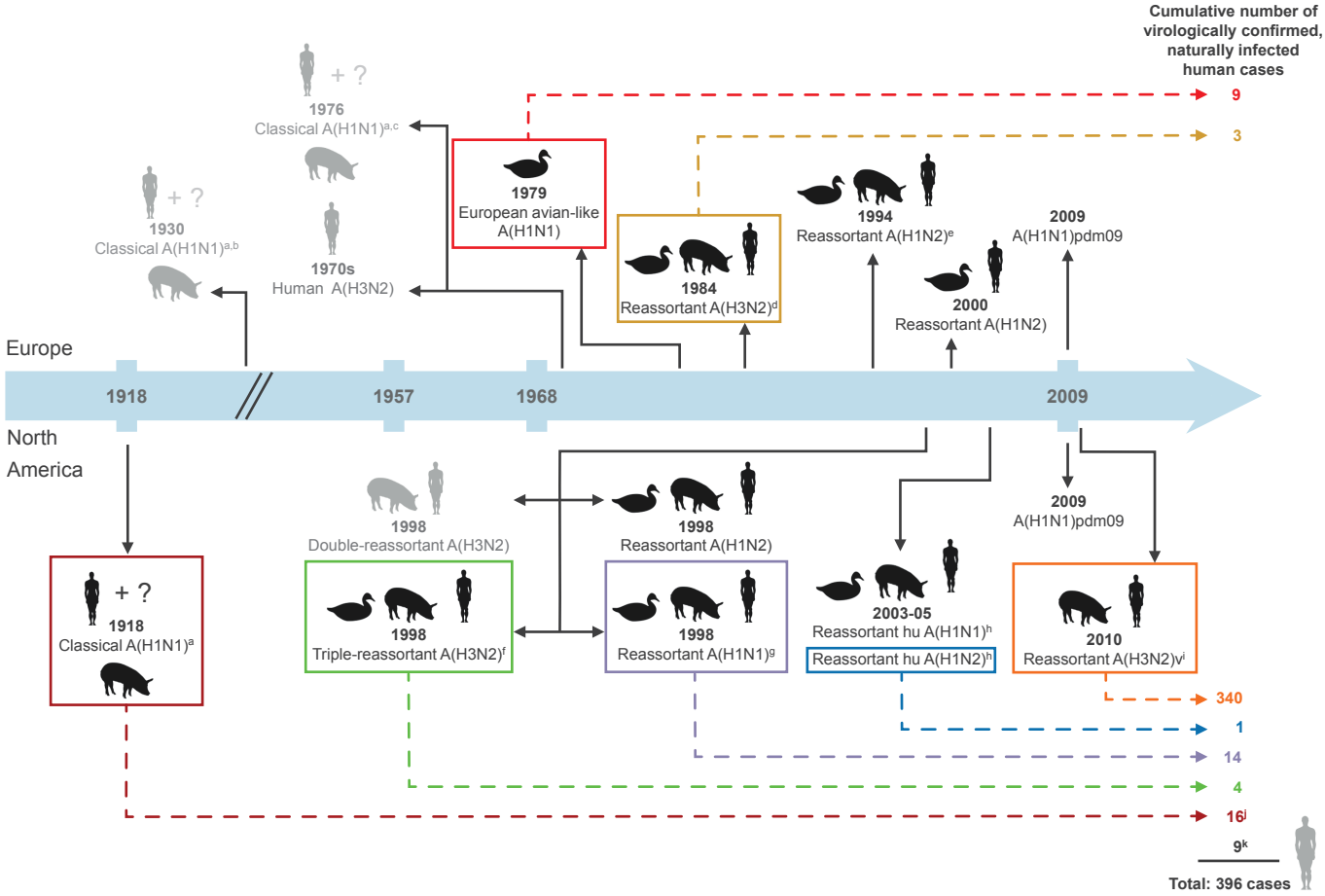
Europe: In Spain, a 50 year-old woman developed ILI after having been closely exposed to swine on a family farm [22]. No symptoms in swine were observed and sequencing of the isolate revealed that it was closely related to avian-like SIV A(H1N1) circulating in swine in western Europe. Three cases from Switzerland were detected who had worked with influenza-confirmed swine [86].

North America: For the US, 19 confirmed cases of SIV A(H1N1) infection were described in the published literature. This number could possibly be higher because Vincent et al. [87] reported on 26 human cases presenting with ILI after exposure to ill swine on a county fair in Ohio. The authors described that isolation and sequencing was performed for at least two of the human cases. Since the exact number of virologically confirmed cases was not given, we only added the two confirmed patients to the overall SIV A(H1N1) count (Table 3). Sequences from swine and human isolates from this outbreak were identical and were similar to triple–reassortant (tr) viruses currently circulating in swine herds in the US [87,88]. Another triple–reassortant A(H1N1) SIV was detected in a 17 year-old male from Wisconsin who assisted in butchering healthy appearing swine [89]. The patient presented with acute, mild respiratory illness without fever. Similarly, Dawood et al. [90] reported infection with trSIV A(H1N1) in a 19 year-old asthmatic male who visited a swine show in South Dakota. Symptoms included fever, ILI, vomiting and diarrhoea. No respiratory illness was observed in swine at this event. A trSIV A(H1N1) was also detected in three infected swine workers in Sasketchewan, Canada [91]. Household members did not report any signs of disease. Mild respiratory illness was reported in less than 1% of the swine; however, no confirmatory test had been conducted in ill swine. Unlike trSIV identified earlier in North America, this isolate contained an HA and a NA belonging to the A/Brisbane/58/2007 A(H1N1) lineage, whereas the remaining genes were derived from trSIV A(H3N2) viruses circulating in North America since 1998. Gray et al. [92] found another trSIV A(H1N1) in the course of a prospective survey, which was isolated from an ill swine farmer exposed to swine showing respiratory symptoms. Routine national influenza surveillance reported another 10 human cases infected with trSIV A(H1N1), distinct from A(H1N1)pdm09, and one case caused by trSIV A(H1N2). The majority of those twelve patients stated exposure to swine prior to disease onset and all made a full recovery [93].

The CDC reported additional human infections with SIV-variant viruses of subtype A(H1N1)v and A(H1N2)v identified in the US since 2005 [94]. These figures have

Figure 2

Timeline of emergence of swine influenza virus lineages circulating in Europe and North America indicating natural human infections from swine



HA: haemagglutinin; NA: neuraminidase; SIV: swine influenza virus; v: variant; hu: human.

Years on main arrow denote human influenza pandemics: A(H1N1) in 1918, A(H2N2) in 1957, A(H3N2) in 1968 and A(H1N1)pdm09 in 2009. Pictograms denote the origin of viral genes. Items in grey font indicate that the virus did not establish itself in the swine population and therefore did not circulate any further. Boxed items indicate infection in humans. Double-ended arrows indicate that four viruses were introduced in 1998 in the swine population.

Superscript letters refer to the genome segment constellation:

[a] Classical SIV A(H1N1) constitutes a reassortant between human A/BM/1918 and unknown virus.

[b] Recent phylogenetic evidence suggests that classical SIVA(H1N1) may have been present in Europe already in the 1930s and not around 1950 as previously assumed [122].

[c] Classical SIV A(H1N1) was re-introduced into Europe via Italy in 1976 and circulated in European countries until it was replaced by avian-like SIV(H1N1) in 1979 (was not replaced in England) [122].

[d] HA and NA from human HongKong/68-like virus, remaining genes from European avian-like swine A(H1N1).

[e] HA from human A(H1N1) (England/80-like), NA from European reassortant swine A(H3N2), remaining genes from European avian-like swine A(H1N1).

[f] HA, NA of human A(H3N2) origin, remaining genes from classical swine A(H1N1) and avian influenza origin.

[g] HA, NA from classical SIV A(H1N1), remaining genes from triple-reassortant or swine A(H1N2).

[h] HA, NA from seasonal human influenza viruses, remaining genes from triple-reassortant swine A(H3N2).

[i] A(H3N2)variant: M gene from A(H1N1)pdm09, remaining genes from triple-reassortant swine A(H3N2), N2 antigenically different from triple-reassortant A(H3N2) from 1998.

[j] Including five virus-confirmed human cases reported from Fort Dix outbreak among soldiers in New Jersey, United States in 1976 [28].

[k] Nine human cases could not be assigned: Six of them were infected with reassortants that did not group with current SIV lineages. Two of the six cases were from the Philippines and Thailand, infected with A(H1N1) and A(H1N2) bearing HA from the North American lineage from the 1990s and NA from European swine influenza lineages [85]. Three of the six cases were from Canada, infected with an A(H1N1) reassortant with HA and NA genes resembling those of A/Brisbane/59/2007(H1N1)-like viruses and internal genes (NS, NP, M, PA, PB1, and PB2) descending from a contemporary North American SIV A(H3N2) triple reassortant [91]. The last of the six cases was infected with triple-reassortant A(H1N1) with HA, PA, PB1, PB2, NP, M, NS from North American triple-reassortant SIV A(H1N1) lineage and NA from North American, classical swine A(H1N1) [92,123]. The remaining three cases infected with SIV A(H1N1) were described in Russian by Chuvakova et al. [27] for which no further isolate characterisation was given in the abstract of the paper.

not been included in this review due to missing case history and in order to avoid double counting of cases described in the published literature.

Human infections with swine influenza A H3 subtype viruses

North America: In our search we detected two cases of trSIV A(H3N2) from Canada [95,96] and one from Kansas, US [97] infected before 2011. In Canada, a six year-old boy who lived on a swine farm presented with parotitis, nasal congestion, cough and pharyngitis, but had no fever. The swine appeared clinically healthy [95]. No swine exposure was reported in the second Canadian patient, a seven month-old child, who lived on a community farm and showed ILI symptoms [96]. Similarly, the third case from Kansas presented with ILI and is likely to have contracted trSIV A(H3N2) from swine he was exposed to at a county fair [97]. It is assumed that swine harboured the virus; PCR results performed on swine samples were negative but sera showed raised titres against SIV A(H3N2) indicating prior infection.

Between July and August 2011, a SIV variant, which accounted for the majority of reported human SIV A(H3N2) cases, appeared in the US, possibly reflecting enhanced surveillance activities in the country. This SIV A(H3N2) variant, A(H3N2)v, was first found in two children presenting with fever and respiratory signs [98,99]. Sequencing showed that this variant contained seven genes derived from the contemporary trSIV A(H3N2), circulating in the US swine population since 1998, as well as the M,gene from the A(H1N1) pdm09 virus. Since its first occurrence in 2011, A(H3N2) v has been detected in 340 humans according to data as of 18 October 2013 [25]. Since July 2012, 17 patients have been hospitalised and one patient has died due to SIV A(H3N2)v infection. Most cases have reported prolonged exposure to swine before getting ill.

Human infections following exposure to other animals

We have identified three studies describing human susceptibility to equine influenza virus, demonstrated by experimental infection with equine subtype A(H3N8) [100-102]. The literature search did not reveal evidence of humans naturally infected with equine influenza virus.

Discussion

Here we present a review of the literature for studies presenting any evidence for human infection with animal influenza viruses. Virological techniques, e.g. virus culture, PCR and sequencing provide more solid evidence of infection, whereas serological methods can help reaching a diagnosis after the virus has been cleared from the body. Virus isolation is still the gold standard in detecting AIV infection. Human cases with virological evidence identified by PCR only should be interpreted with caution as detection of viral RNA without additional serological evidence (seroconversion, more than fourfold rise in the titre of paired samples) does not necessary imply infection, although current diagnostic methods heavily rely on case identification by PCR [103,104]. Serological results can be misleading because of the existence of cross–reactive antibodies and thus provide less solid evidence than direct detection of the infecting virus itself [105]. Therefore, we limited the current paper to studies providing virological evidence only.

Most evidence of human infection with AIV is associated with subtypes H5 and H7. Both subtypes can be linked to devastating outbreaks in poultry with high mortality, if transition from a low to a highly pathogenic state occurs [106]. Pathogenicity shown in poultry clearly does not reflect disease severity in humans: before the emergence in LPAI A(H7N9) as a cause of severe human illness, LPAI and HPAI viruses of subtype H7 had in the majority of cases been associated with mild eye infections or ILI [107]. The LPAI A(H7N9) infections diagnosed to date, however, have been unusually severe [23,64]. In addition to the severity of illness associated with these and also A(H5N1) viruses, the widespread circulation of different lineages, made possible by mutations and reassortments, justifies enhanced surveillance activities, given that few genetic changes may lead to a human-to-human transmissible virus [108,109].

Nevertheless, the evidence from experimental infections and anecdotal natural infections shows that other AIV may infect humans as well. There is insufficient systematic surveillance data to address the question whether the identified human cases reflect the level of virus circulation among wild or domestic birds, or whether certain subtypes infect humans preferentially.

Regarding SIV, there is ample evidence of human infection with A(H3N2), A(H1N1) and A(H1N2) subtypes, as well as reassortants derived from these endemic SIV lineages. Nevertheless, one has to be aware that the true number of human SIV cases is probably higher than reported since clinical symptoms of SIV are indistinguishable from seasonal influenza [86]. Whereas recent human cases in Europe were detected almost accidentally, the larger number of cases reported in the US since 2005, especially for influenza A(H3N2)v since 2011, may be the result of increased surveillance activities [86,110]. Swine were assumed to play an important role as intermediate hosts or 'mixing vessels' for strains of human, avian and swine origin, because they possess avian and human influenza-specific receptors in the tracheal epithelium [111]. However, recent research showed that the distribution of sialic acid receptors in the porcine respiratory tract is similar to that in humans, leading to the conclusion that humans are equally likely to constitute 'mixing vessels' [112,113]. The fact that influenza viruses can circulate unnoticed in swine populations [114] warrants close surveillance in this animal species as well. Co-circulation of different influenza virus strains in swine may facilitate the generation of new variants that could potentially

pose a threat for public health [115]. For instance, it is assumed that influenza A(H1N1)pdm09 was present in swine herds for months before it emerged as a pandemic strain in humans [116]. Conversely, Nelson et al. [117] reported at least 49 transmission events of influenza A(H1N1)pdm09 from humans to swine between 2009 and 2011, as well as at least 23 separate introductions of human seasonal influenza into swine since 1990.

Although there is some evidence for infection in swine with non-H1 and non-H3 subtype viruses (H9N2, H4N6) [115,118], we found no case reports describing human infection with these influenza A virus subtypes after swine exposure. Since most human infection events are associated with swine exposure, awareness of risk factors and personal protective equipment is paramount to limiting the chance of infection and preventing people working with or recreationally exposed to swine (including children) from becoming 'bridging links' between swine and community contacts and vice versa [92,119].

There are a few limitations to this review. The language restriction set to papers published in English only and the unsystematic search of the grey literature probably lead to the omission of additional documented human infections with animal influenza virus. Although this limitation may affect the total count of human cases, the aim of this review was to identify animal influenza subtypes, which crossed the species barrier to humans, and to our knowledge, all relevant subtypes were covered by this review.

Conclusions

There is evidence of infection of humans with animal influenza viruses belonging to various subtypes. All reported SIV cases have been exclusively associated with subtypes H1 and H3, and most AIV cases were caused by subtypes H5 and H7. Whether this reflects the prevalence of these viruses in birds kept or sold for consumption or a preferential ability to transmit to humans cannot be concluded from the available evidence. Given the often, mild illness associated with non-H5 and non-H7 animal influenza virus infections in humans, such cases likely are underreported [120]. Standardisation of diagnostic methods has significantly improved case ascertainment in recent years, but the monitoring of the evolution of these viruses is less advanced. Recent research pointed out that the majority of Asian and African countries have contributed only few sequences to surveillance networks and do not regularly sequence viruses as part of their surveillance programme [121]. Genetic sequencing is paramount to identifying changes with potential effect on the phenotype of circulating influenza viruses, and could thereby strengthen worldwide epidemic and pandemic preparedness [121]. To be prepared for a potentially emerging influenza virus of animal origin in humans, enhanced global surveillance in animal populations is therefore indicated to monitor evolution and circulation of viruses with yet unknown public health risks.

Note:

Numbers on influenza H5N1 and H7N9 are as of 31 January 2014.

Funding

This work was conducted within the framework of the FLURISK project (CFP/EFSA/AHAW/2011/01), supported by the European Food Safety Authority. The sole responsibility of this review lies with the authors and the European Food Safety Authority shall not be considered responsible for any use that may be made of the information contained herein.

Authors' contributions

GF and MK drafted the analysis plan. GF performed the study of the literature and drafted the manuscript. MK, AM and EdB contributed to the analysis of the data and critically reviewed the manuscript. AM performed the final edit of the manuscript before submission, including an update of counts and addition of most recent evidence. All authors were involved in discussion of parts of the analyses that were presented during consortium meetings and critically reviewed drafts of the manuscript.

Conflict of interest

None declared.

References

1. Fouchier RAM, Munster V, Wallensten A, Bestebroer TM, Herfst S, Smith D, et al. Characterization of a novel influenza A virus hemagglutinin subtype (H16) obtained from black-headed gulls. J Virol. 2005;79(5):2814-22. http://dx.doi.org/10.1128/JVI.79.5.2814-2822.2005
2. Tong S, Li Y, Rivailler P, Conrardy C, Castillo DAA, Chen L-M, et al. A distinct lineage of influenza A virus from bats. Proc Natl Acad Sci U S A. 2012;109(11):4269-74. http://dx.doi.org/10.1073/pnas.1116200109
3. Tong S, Zhu X, Li Y, Shi M, Zhang J, Bourgeois M, et al. New World bats harbor diverse influenza A viruses. PLoS Pathog. 2013;9(10):e1003657. http://dx.doi.org/10.1371/journal.ppat.1003657
4. Zhu X, Yang H, Guo Z, Yu W, Carney PJ, Li Y, et al. Crystal structures of two subtype N10 neuraminidase-like proteins from bat influenza A viruses reveal a diverged putative active site. Proc Natl Acad Sci USA. 2012;109(46):18903-8. http://dx.doi.org/10.1073/pnas.1212579109
5. Li Q, Sun X, Li Z, Liu Y, Vavricka CJ, Qi J, et al. Structural and functional characterization of neuraminidase-like molecule N10 derived from bat influenza A virus. Proc Natl Acad Sci USA. 2012;109(46):18897-902. http://dx.doi.org/10.1073/pnas.1211037109
6. Hale BG, Albrecht RA, Garcia-Sastre A. Innate immune evasion strategies of influenza viruses. Future Microbiol. 2010;5(1):23-41. http://dx.doi.org/10.2217/fmb.09.108
7. Bouvier NM, Palese P. The biology of influenza viruses. Vaccine. 2008;26(Supplement 4):D49–53. http://dx.doi.org/10.1016/j.vaccine.2008.07.039
8. Kelly H. The classical definition of a pandemic is not elusive. Bull World Health Organ. 2011;89(7):540-1. http://dx.doi.org/10.2471/BLT.11.088815
9. Smith GJD, Bahl J, Vijaykrishna D, Zhang J, Poon LLM, Chen H, et al. Dating the emergence of pandemic influenza viruses. PNAS, 2009;106(28):11709-12. http://dx.doi.org/10.1073/pnas.0904991106

10. Smith GJD, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature. 2009;459(7250):1122-5. http://dx.doi.org/10.1038/nature08182
11. Neumann G, Kawaoka Y. The first influenza pandemic of the new Millennium. Influenza Other Respi Viruses. 2011;5(3):157-66. http://dx.doi.org/10.1111/j.1750-2659.2011.00231.x
12. Munster VJ, Baas C, Lexmond P, Waldenström J, Wallensten A, Fransson T, et al. Spatial, temporal, and species variation in prevalence of influenza A viruses in wild migratory birds. PLoS Pathog. 2007;3(5):e61. http://dx.doi.org/10.1371/journal.ppat.0030061
13. Ma W, Vincent AL, Gramer MR, Brockwell CB, Lager KM, Janke BH, et al. Identification of H2N3 influenza A viruses from swine in the United States. Proc Natl Acad Sci U S A. 2007;104(52):20949-54. http://dx.doi.org/10.1073/pnas.0710286104
14. Morse SS, Mazet JA, Woolhouse M, Parrish CR, Carroll D, Karesh WB, et al. Prediction and prevention of the next pandemic zoonosis. Lancet. 2012;380(9857):1956-65. http://dx.doi.org/10.1016/S0140-6736(12)61684-5
15. Claas EC, Osterhaus AD, van Beek R, De Jong JC, Rimmelzwaan GF, Senne DA, et al. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. Lancet. 1998;351(9101):472-7. http://dx.doi.org/10.1016/S0140-6736(97)11212-0
16. Peiris M, Yuen K, Leung C, Chan K, Ip P, Lai R, et al. Human infection with influenza H9N2. Lancet. 1999;354(9182):916-7. http://dx.doi.org/10.1016/S0140-6736(99)03311-5
17. Koopmans M, Wilbrink B, Conyn M, Natrop G, van der Nat H, Vennema H, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet. 2004;363(9409):587-93. http://dx.doi.org/10.1016/S0140-6736(04)15589-X
18. Tweed SA, Skowronski DM, David ST, Larder A, Petric M, Lees W, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis. 2004;10(12):2196-9. http://dx.doi.org/10.3201/eid1012.040961
19. Skowronski DM, Tweed SA, Petric M, Booth T, Li Y, Tam T. Human illness and isolation of low-pathogenicity avian influenza virus of the H7N3 subtype in British Columbia, Canada. J Infect Dis. 2006;193(6):899-900. http://dx.doi.org/10.1086/500219
20. Arzey G, Kirkland P, Edla A, Frost M, Maywood P, Conaty S, et al. Influenza virus A (H10N7) in chickens and poultry abattoir workers, Australia. Emerg Infect Dis. 2012;18(5):814-6. http://dx.doi.org/10.3201/eid1805.111852
21. Gregory V, Bennett M, Thomas Y, Kaiser L, Wunderli W, Matter H, et al. Human infection by a swine influenza A (H1N1) virus in Switzerland. Arch Virol. 2003;148:793-802. http://dx.doi.org/10.1007/s00705-002-0953-9
22. Adiego Sancho B, Omenaca Teres M, Martinez Cuenca S, Rodrigo Val P, Sanchez Villanueva P, Casas I, et al. Human case of swine influenza A (H1N1), Aragon, Spain, November 2008. Euro Surveill. 2009;14(7):pii=19120.
23. Centre for Disease Prevention and Control (ECDC). Updated rapid risk assessment: Human infection with a novel avian influenza A(H7N9) virus, China. Third update. Stockholm: ECDC; 2014. Available from: http://www.ecdc.europa.eu/en/publications/Publications/influenza-AH7N9-China-rapid-risk-assessment-27-January-2014.pdf
24. World Health Organization (WHO). Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. Geneva: WHO; 2013. Available from: http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/
25. Centers for Disease Control and Prevention (CDC). Case count: detected U.S. human infections with H3N2v by state since August 2011. Atlanta: CDC; 2013. Available from: http://www.cdc.gov/flu/swineflu/h3n2v-case-count.htm
26. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. Clin Infect Dis. 2007;44(8):1084-8. http://dx.doi.org/10.1086/512813
27. Chuvakova ZK, Rovnova ZI, Isaeva EI, Kim EV, Ignat'eva TV. [3 cases of isolating the influenza A virus with human hemagglutinin Hsw1 in 1983 in Alma-Ata]. Vopr Virusol. 1985;30(5):530-6. Russian.
28. Gaydos JC, Hodder RA, Top FH Jr, Soden VJ, Allen RG, Bartley JD, et al. Swine influenza A at Fort Dix, New Jersey (January-February 1976). I. Case finding and clinical study of cases. J Infect Dis. 1977;136 Suppl:S356-62. http://dx.doi.org/10.1093/infdis/136.Supplement_3.S363 http://dx.doi.org/10.1093/infdis/136.Supplement_3.S356
29. Centers for Disease Control and Prevention (CDC). Influenza–Wisconsin and Washington, DC. MMWR Morb Mortal Wkly Rep. 1976;25:392.
30. Centers for Disease Control and Prevention (CDC). Influenza—Wisconsin. MMWR Morb Mortal Wkly Rep. 1976;25:402.
31. Dacso CC, Couch RB, Six HR, Young JF, Quarles JM, Kasel JA. Sporadic occurrence of zoonotic swine influenza virus infections. J Clin Microbiol. 1984;20(4):833-5.
32. Patriarca PA, Kendal AP, Zakowski PC, Cox NJ, Trautman MS, Cherry JD, et al. Lack of significant person-to-person spread of swine influenza-like virus following fatal infection in an immunocompromised child. Am J Epidemiol. 1984;119(2):152-8.
33. De Jong JC, Paccaud MF, de Ronde-Verloop FM, Huffels NH, Verwei C, Weijers TF, et al. Isolation of swine-like influenza A(H1N1) viruses from man in Switzerland and The Netherlands. Ann Inst Pasteur Virol. 1988;139(4):429-37. http://dx.doi.org/10.1016/S0769-2617(88)80078-9
34. McKinney WP, Volkert P, Kaufman J. Fatal swine influenza pneumonia during late pregnancy. Arch Intern Med. 1990;150(1):213-5. http://dx.doi.org/10.1001/archinte.1990.00390130173029 http://dx.doi.org/10.1001/archinte.150.1.213
35. Wentworth DE, Thompson BL, Xu X, Regnery HL, Cooley AJ, McGregor MW, et al. An influenza A (H1N1) virus, closely related to swine influenza virus, responsible for a fatal case of human influenza. J Virol. 1994;68(4):2051-8.
36. Rimmelzwaan GF, de Jong JC, Bestebroer TM, van Loon AM, Claas ECJ, Fouchier RAM, et al. Antigenic and genetic characterization of swine influenza A (H1N1) viruses isolated from pneumonia patients in The Netherlands. Virology. 2001;282(2):301-6. http://dx.doi.org/10.1006/viro.2000.0810
37. Wentworth DE, McGregor MW, Macklin MD, Neumann V, Hinshaw VS. Transmission of swine influenza virus to humans after exposure to experimentally infected pigs. J Infect Dis. 1997;175(1):7-15. http://dx.doi.org/10.1093/infdis/175.1.7
38. Kimura K, Adlakha A, Simon PM. Fatal case of swine influenza virus in an immunocompetent host. Mayo Clin Proc. 1998;73(3):243-5. http://dx.doi.org/10.4065/73.3.243
39. Gregory V, Lim W, Cameron K, Bennett M, Marozin S, Klimov A, et al. Infection of a child in Hong Kong by an influenza A H3N2 virus closely related to viruses circulating in European pigs. J Gen Virol. 2001;82(6):1397-406.
40. Olsen CW, Karasin AI, Carman S, Li Y, Bastien N, Ojkic D, et al. Triple reassortant H3N2 influenza A viruses, Canada, 2005. Emerg Infect Dis. 2006;12(7):1132-5. http://dx.doi.org/10.3201/eid1207.060268
41. Claas EC, Kawaoka Y, de Jong JC, Masurel N, Webster RG. Infection of children with avian-human reassortant influenza virus from pigs in Europe. Virology. 1994;204(1):453-7. http://dx.doi.org/10.1006/viro.1994.1553
42. Smith TF, Burgert EO Jr., Dowdle WR, Noble GR, Campbell RJ, Van Scoy RE. Isolation of swine influenza virus from autopsy lung tissue of man. N Engl J Med. 1976;294(13):708-10 http://dx.doi.org/10.1056/NEJM197603252941308
43. Cooper LV, Olsen C, Xu W, Klimov A, Cox N, Subbarao K. Molecular characterization of human influenza A viruses bearing swine-like hemagglutinin genes. In: Program and abstracts of the Virus Evolution Workshop (Ardmore, OK). Ardmore: Samuel Roberts Noble Foundation; 1999.
44. Gray G, McCarthy T, Capuano A. Population-based surveillance for zoonotic influenza A in agricultural workers. Program and abstracts of the Second North American Congress of Epidemiology. Seattle; 2006.
45. Beare AS, Schild GC, Hall TS, Kundin WD. Antigenic characteristics of swine influenza virus closely related to human Hong Kong strain and results of experimental infection in volunteers. Lancet. 1971;1(7694):305-7. http://dx.doi.org/10.1016/S0140-6736(71)91039-7
46. Peiris JS. Avian influenza viruses in humans. Rev Sci Tech. 2009;28(1):161-73.
47. To KF, Chan PK, Chan KF, Lee WK, Lam WY, Wong KF, et al. Pathology of fatal human infection associated with avian influenza A H5N1 virus. J Med Virol. 2001;63(3):242-6. http://dx.doi.org/10.1002/1096-9071(200103)63:3<242::AID-JMV1007>3.0.CO;2-N

48. De Jong JC, Claas EC, Osterhaus AD, Webster RG, Lim WL. A pandemic warning? Nature. 1997;389(6651):554. http://dx.doi.org/10.1038/39221 http://dx.doi.org/10.1038/39218
49. Gillim-Ross L, Subbarao K. Emerging respiratory viruses: challenges and vaccine strategies. Clin Microbiol Rev. 2006;19(4):614-36. http://dx.doi.org/10.1128/CMR.00005-06
50. Liu J, Xiao H, Lei F, Zhu Q, Qin K, Zhang XL, et al. Highly pathogenic H5N1 influenza virus infection in migratory birds. Science. 2005;309(5738):1206. http://dx.doi.org/10.1126/science.1115273
51. Food and Agriculture Organization (FAO). Stamping out H5N1 avian influenza could take decades. Rome: FAO; 2011. Available from: http://www.fao.org/news/story/en/item/66118/icode/
52. Campbell CH, Webster RG, Breese SS Jr. Fowl plague virus from man. J Infect Dis. 1970;122(6):513-6. http://dx.doi.org/10.1093/infdis/122.6.513
53. Taylor HR, Turner AJ. A case report of fowl plague keratoconjunctivitis. Br J Ophthalmol. 1977;61(2):86-8. http://dx.doi.org/10.1136/bjo.61.2.86
54. Webster RG, Geraci J, Petursson G, Skirnisson K. Conjunctivitis in human beings caused by influenza A virus of seals. N Engl J Med. 1981;304(15):911. http://dx.doi.org/10.1056/NEJM198104093041515
55. Kurtz J, Manvell RJ, Banks J. Avian influenza virus isolated from a woman with conjunctivitis. Lancet. 1996;348(9031):901-2. http://dx.doi.org/10.1016/S0140-6736(05)64783-6
56. Fouchier RAM, Schneeberger PM, Rozendaal FW, Broekman JM, Kemink SAG, Munster V, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. PNAS. 2004;101(5):1356-61. http://dx.doi.org/10.1073/pnas.0308352100
57. Nguyen-Van-Tam JS, Nair P, Acheson P, Baker A, Barker M, Bracebridge S, et al. Outbreak of low pathogenicity H7N3 avian influenza in UK, including associated case of human conjunctivitis. Euro Surveill. 2006;11(18):pii=2952.
58. Editorial team. Avian influenza A/(H7N2) outbreak in the United Kingdom Euro Surveill. 2007;12(22):pii=3206.
59. Centers for Disease Control and Prevention (CDC). Notes from the field: Highly pathogenic avian influenza A (H7N3) virus infection in two poultry workers-Jalisco, Mexico, July 2012. MMWR Morb Mortal Wkly Rep. 2012;61(36):726-7.
60. Webster RG, Hinshaw VS, Bean WJ, Van Wyke KL, Geraci JR, St Aubin DJ, et al. Characterization of an influenza A virus from seals. Virology. 1981;113(2):712-24. http://dx.doi.org/10.1016/0042-6822(81)90200-2
61. Jonges M, Bataille A, Enserink R, Meijer A, Fouchier RAM, Stegeman A, et al. Comparative analysis of avian influenza virus diversity in poultry and humans during a highly pathogenic avian influenza A (H7N7) virus outbreak. J Virol. 2011;85(20):10598-604. http://dx.doi.org/10.1128/JVI.05369-11
62. Pasick J, Handel K, Robinson J, Copps J, Ridd D, Hills K, et al. Intersegmental recombination between the haemagglutinin and matrix genes was responsible for the emergence of a highly pathogenic H7N3 avian influenza virus in British Columbia. J Gen Virol. 2005;86(3):727-31. http://dx.doi.org/10.1099/vir.0.80478-0
63. Hirst M, Astell CR, Griffith M, Coughlin SM, Moksa M, Zeng T, et al. Novel avian influenza H7N3 strain outbreak, British Columbia. Emerg Infect Dis. 2004;10(12):2192-5. http://dx.doi.org/10.3201/eid1012.040743
64. Gao R, Cao B, Hu Y, Feng Z, Wang D, Hu W, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. N Eng J Med. 2013;368(20):1888-97. http://dx.doi.org/10.1056/NEJMoa1304459
65. ProMED-mail. Avian influenza (41): (China) zoonotic LPAI H7N9, animal, RFI. Archive Number 20130420.1659952. 20 April 2013. Available from: http://www.promedmail.org
66. Butt KM, Smith GJ, Chen H, Zhang LJ, Leung YH, Xu KM, et al. Human infection with an avian H9N2 influenza A virus in Hong Kong in 2003. J Clin Microbiol. 2005;43(11):5760-7. http://dx.doi.org/10.1128/JCM.43.11.5760-5767.2005
67. Centers for Disease Control and Prevention (CDC). Avian influenza (flu). Avian influenza A virus infections of humans. Atlanta: CDC; 2008. Available from: http://www.cdc.gov/flu/avian/gen-info/avian-flu-humans.htm
68. Cheng VC, Chan JF, Wen X, Wu WL, Que TL, Chen H, et al. Infection of immunocompromised patients by avian H9N2 influenza A virus. J Infect. 2011;62(5):394-9. http://dx.doi.org/10.1016/j.jinf.2011.02.007
69. International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). Outbreak of mild respiratory disease caused by H5N1 and H9N2 infections among young children in Dhaka, Bangladesh, 2011. Health and Science Bulletin. 2011;9(2):5-12.
70. Guo Y, Li J, Cheng X. [Discovery of men infected by avian influenza A (H9N2) virus]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi. 1999;13(2):105-8. Chinese.
71. Guo Y, Xie J, Wang M. [A strain of influenza A H9N2 virus repeatedly isolated from human population in China]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi. 2000;14(3):209-12. Chinese.
72. ProMED-mail. Avian influenza, human (164): China (HK) H9N2. Archive Number 20131230.2143709. 30 Dec 2013. Available from: http://www.promedmail.org
73. ProMED-mail. Avian influenza, human (02): China (HK) H9N2 ex (HN). Archive Number 20140102.2148327. 2 Jan 2014. Available from: http://www.promedmail.org
74. Matrosovich MN, Krauss S, Webster RG. H9N2 Influenza A Viruses from Poultry in Asia Have Human Virus-like Receptor Specificity. Virology. 2001;281(2):156-62. http://dx.doi.org/10.1006/viro.2000.0799
75. Beare AS, Webster RG. Replication of avian influenza viruses in humans. Archives of Virology. 1991;119(1-2):37-42. http://dx.doi.org/10.1007/BF01314321
76. Pan American Health Organization (PAHO). Avian influenza virus A(H10N7) circulating among humans in Egypt. Washington: PAHO; 2004. Available from: http://new.paho.org/hq/dmdocuments/2010/Avian_Influenza_Egypt_070503.pdf
77. ProMED-mail. Avian influenza, human (157): China (ZJ) H10N8, fatal. Archive Number 20131217.2121718. 17 Dec 2013. Available from: http://www.promedmail.org
78. ProMED-mail. Avian influenza, human (36): China (JX) H10N8. Archive Number 20140126.2233164 . 26 Jan 2014. Available from: http://www.promedmail.org/
79. Centers for Disease Control (CDC). Laboratory-confirmed case of human infection with avian influenza A(H6N1) virus in Taiwan recovered; Taiwan CDC urges public to take precautions to stay healthy. Taipei City: CDC; 2013. Available from: http://www.cdc.gov.tw/english%5Cinfo.aspx?treeid=bc2d4e89b154059b&nowtreeid=ee0a2987cfba3222&tid=E36A5E9AB3D3A216
80. Wei S-H, Yang J-R, Wu H-S, Chang M-C, Lin J-S, Lin C-Y, et al. Human infection with avian influenza A H6N1 virus: an epidemiological analysis. Lancet Respir Med. 2013;1(10):771-8. http://dx.doi.org/10.1016/S2213-2600(13)70221-2
81. Vincent AL, Ma W, Lager KM, Janke BH, Richt JA. Swine influenza viruses a North American perspective. Adv Virus Res. 2008;72:127-54. http://dx.doi.org/10.1016/S0065-3527(08)00403-X
82. Brown IH. History and epidemiology of swine influenza in Europe. Curr Top Microbiol Immunol. 2013;370:133-46. http://dx.doi.org/10.1007/82_2011_194
83. Van Reeth K. Avian and swine influenza viruses: our current understanding of the zoonotic risk. Vet Res. 2007;38(2):243-60. http://dx.doi.org/10.1051/vetres:2006062
84. Choi YK, Pascua PN, Song MS. Swine influenza viruses: an Asian perspective. Curr Top Microbiol Immunol. 2013;370:147-72. http://dx.doi.org/10.1007/82_2011_195
85. Komadina N, Roque V, Thawatsupha P, Rimando-Magalong J, Waicharoen S, Bomasang E, et al. Genetic analysis of two influenza A (H1) swine viruses isolated from humans in Thailand and the Philippines. Virus Genes. 2007;35(2):161-5. http://dx.doi.org/10.1007/s11262-007-0097-9
86. European Center for Disease Prevention and Control (ECDC). Update–Swine-origin triple reassortant influenza A(H3N2) variant viruses in North America. Stockholm: ECDC; 2012. Available from: http://www.ecdc.europa.eu/en/publications/publications/1208-ter-rapid-risk-assessment-influenza-ah3n2-us.pdf
87. Vincent AL, Swenson SL, Lager KM, Gauger PC, Loiacono C, Zhang Y. Characterization of an influenza A virus isolated from pigs during an outbreak of respiratory disease in swine and people during a county fair in the United States. Vet Microbiol. 2009;137(1-2):51-9. http://dx.doi.org/10.1016/j.vetmic.2009.01.003
88. Yassine HM, Khatri M, Zhang YJ, Lee CW, Byrum BA, O'Quin J, et al. Characterization of triple reassortant H1N1 influenza A viruses from swine in Ohio. Vet Microbiol.

2009;139(1–2):132-9.
http://dx.doi.org/10.1016/j.vetmic.2009.04.028

89. Newman AP. Human case of swine influenza A (H1N1) triple reassortant virus infection, Wisconsin. Emerg Infect Dis. 2008;14(9):1470-2.
http://dx.doi.org/10.3201/eid1409.080305

90. Dawood FS, Dong L, Liu F, Blau DM, Peebles PJ, Lu X, et al. A pre-pandemic outbreak of triple-reassortant swine influenza virus infection among university students, South Dakota, 2008. J Infect Dis. 2011;204(8):1165-71.
http://dx.doi.org/10.1093/infdis/jir502

91. Bastien N, Antonishyn NA, Brandt K, Wong CE, Chokani K, Vegh N, et al. Human infection with a triple-reassortant swine influenza A(H1N1) virus containing the hemagglutinin and neuraminidase genes of seasonal influenza virus. J Infect Dis. 2010;201(8):1178-82.
http://dx.doi.org/10.1086/651507

92. Gray GC, McCarthy T, Capuano AW, Setterquist SF, Olsen CW, Alavanja MC, et al. Swine workers and swine influenza virus infections. Emerg Infect Dis. 2007;13(12):1871-8.
http://dx.doi.org/10.3201/eid1312.061323

93. Shinde V, Bridges CB, Uyeki TM, Shu B, Balish A, Xu X, et al. Triple-reassortant Swine influenza A (H1) in humans in the United States, 2005–2009. N Eng J Med. 2009;360(25):2616-25.
http://dx.doi.org/10.1056/NEJMoa0903812

94. Centers for Disease Control and Prevention (CDC). Reported infections with variant influenza viruses in the United States since 2005. Atlanta: CDC; 2013. Available from: http://www.cdc.gov/flu/swineflu/variant-cases-us.htm

95. Bastien N, Bowness D, Burton L, Bontovics E, Winter A-L, Tipples G, et al. Parotitis in a child infected with triple-reassortant influenza A virus in Canada in 2007. J Clin Microbiol. 2009;47(6):1896–8.
http://dx.doi.org/10.1128/JCM.01684-08

96. Robinson J, Lee B, Patel J, Bastien N, Grimsrud K, Seal R, et al. Swine influenza (H3N2) infection in a child and possible community transmission, Canada. Emerg Infect Dis. 2007;13(12):1865-70.
http://dx.doi.org/10.3201/eid1312.070615

97. Cox C. Swine Influenza Virus A (H3N2) Infection in human, Kansas, USA, 2009. Emerg Infect Dis. 2011;17(16):1143-4.
http://dx.doi.org/10.3201/eid1706.101488

98. Centers for Disease Control and Prevention (CDC). Swine-origin influenza A (H3N2) virus infection in two children -- Indiana and Pennsylvania, July-August 2011. MMWR Morb Mortal Wkly Rep. 2011;60(35):1213-5.

99. Centers for Disease Control and Prevention (CDC). Update: Influenza A (H3N2)v transmission and guidelines - five states, 2011. MMWR Morb Mortal Wkly Rep. 2012;60(51-52):1741-4.

100. Kasel JA, Alford RH, Knight V, Waddel GH, Sigel MM. Experimental infection of human volunteers with equine influenza virus. Nature. 1965 Apr 3;206:41-3.
http://dx.doi.org/10.1038/206041a0

101. Couch RB, Douglas RG, Kasel JA, Riggs S, Knight V. Production of the influenza syndrome in man with equine influenza virus. Nature. 1969;224(5218):512–4.
http://dx.doi.org/10.1038/224512a0

102. Alford RH, Kasel JA, Lehrich JR, Knight V. Human responses to experimental infection with influenza a/Equi 2 virus. Am J Epidemiol. 1967;86(1):185-92.

103. Wallace LA, Collins TC, Douglas JDM, McIntyre S, Millar J, Carman WF. Virological surveillance of influenza-like illness in the community using PCR and serology. J Clin Virol. 2004;31(1):40-5.
http://dx.doi.org/10.1016/j.jcv.2003.12.003

104. World Health Organization (WHO). WHO information for molecular diagnosis of influenza virus in humans - update. Geneva: WHO; 2012. Available from: http://www.who.int/influenza/gisrs_laboratory/molecular_diagnosis/en/

105. Allwinn, Preiser, Rabenau, Buxbaum, Stürmer, Doerr. Laboratory diagnosis of influenza - virology or serology? Med Microbiol Immunol. 2002;191(3):157-60.

106. Swayne DE, Suarez DL. Highly pathogenic avian influenza. Rev - Off Int Epizoot. 2000;19(2):463-82.

107. Olofsson S, Kumlin U, Dimock K, Arnberg N. Avian influenza and sialic acid receptors: more than meets the eye? Lancet Inf Dis. 2005;5(3):184-8.
http://dx.doi.org/10.1016/S1473-3099(05)01311-3
http://dx.doi.org/10.1016/S1473-3099(05)70026-8

108. Imai M, Herfst S, Sorrell EM, Schrauwen EJA, Linster M, De Graaf M, et al. Transmission of influenza A/H5N1 viruses in mammals. Virus Res. 2013;178(1):15-20.
http://dx.doi.org/10.1016/j.virusres.2013.07.017

109. Herfst S, Schrauwen EJA, Linster M, Chutinimitkul S, de Wit E, Munster VJ, et al. Airborne transmission of influenza A/H5N1 virus between ferrets. Science. 2012;336(6088):1534-41.
http://dx.doi.org/10.1126/science.1213362

110. Shu B, Garten R, Emery S, Balish A, Cooper L, Sessions W, et al. Genetic analysis and antigenic characterization of swine origin influenza viruses isolated from humans in the United States, 1990–2010. Virology. 2012;422(1):151–60.
http://dx.doi.org/10.1016/j.virol.2011.10.016

111. Subbarao K, Katz J. Avian influenza viruses infecting humans. Cell Mol Life Sci. 2000;57(12):1770-84.
http://dx.doi.org/10.1007/PL00000657

112. Van Poucke SG, Nicholls JM, Nauwynck HJ, Van Reeth K. Replication of avian, human and swine influenza viruses in porcine respiratory explants and association with sialic acid distribution. Virol J. 2010;7:38.
http://dx.doi.org/10.1186/1743-422X-7-38

113. Nelli RK, Kuchipudi SV, White GA, Perez B, Dunham SP, Chang K-C. Comparative distribution of human and avian type sialic acid influenza receptors in the pig. BMC Vet Res. 2010;6:4.
http://dx.doi.org/10.1186/1746-6148-6-4

114. Gray GC, Bender JB, Bridges CB, Daly RF, Krueger WS, Male MJ, et al. Influenza A(H1N1)pdm09 virus among healthy show pigs, United States. Emerg Inf Dis. 2012;18(9):1519-21.
http://dx.doi.org/10.3201/eid1809.120431

115. Peiris JSM, Guan Y, Markwell D, Ghose P, Webster RG, Shortridge KF. Cocirculation of avian H9N2 and contemporary' human' H3N2 influenza A viruses in pigs in southeastern China: potential for genetic reassortment? J Virol. 2001;75(20):9679-86.
http://dx.doi.org/10.1128/JVI.75.20.9679-9686.2001

116. Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science. 2009;325(5937):197-201.
http://dx.doi.org/10.1126/science.1176225

117. Nelson MI, Gramer MR, Vincent AL, Holmes EC. Global transmission of influenza viruses from humans to swine. J Gen Virol. 2012;93(Pt 10):2195-203.
http://dx.doi.org/10.1099/vir.0.044974-0

118. Karasin AI, Olsen CW, Brown IH, Carman S, Stalker M, Josephson G. H4N6 influenza virus isolated from pigs in Ontario. Can Vet J. 2000;41(12):938-9.

119. Gray GC, Kayali G. Facing pandemic influenza threats: the importance of including poultry and swine workers in preparedness plans. Poultry science. 2009;88(4):880-4.
http://dx.doi.org/10.3382/ps.2008-00335

120. Wang TT, Parides MK, Palese P. Seroevidence for H5N1 Influenza infections in humans: meta-analysis. Science. 2012;335(6075):1463.
http://dx.doi.org/10.1126/science.1218888

121. Escorcia M, Attene-Ramos M, Estrada M, Nava G. Improving global influenza surveillance: trends of A(H5N1) virus in Africa and Asia. BMC Res Notes. 2012;5:62.
http://dx.doi.org/10.1186/1756-0500-5-62

122. Lange J, Groth M, Kanrai P, Pleschka S, Scholtissek C, Dürrwald, et al. Circulation of classical swine influenza virus in Europe between the wars? Arch Virol. 2013; Dec 15 [Epub ahead of print]. DOI 10.1007/s00705-013-1950-x

123. Han L, Lu W, Han Y, Li S, Yin J, Xie J et al. Evolutionary characteristics of swine-origin H1N1 influenza virus that infected humans from sporadic to pandemic. J Public Health Epidemiol. 2011;3(6):254-70.

Enhanced epidemic intelligence using a web-based screening system during the 2010 FIFA World Cup in South Africa

J Mantero[1], E Szegedi (edit.szegedi@ecdc.europa.eu)[1], L Payne Hallström[2], A Lenglet[2], E Depoortere[2], B Kaic[3], L Blumberg[4], J P Linge[5], D Coulombier[2]

1. Epidemic Intelligence group, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
2. Surveillance and Response Support Unit, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
3. Croatian National Institute of Public Health, Zagreb, Croatia (deployed at ECDC during the 2010 FIFA World Cup)
4. Division of Public Health Surveillance and Response, National Institute for Communicable Diseases (NICD), Johannesburg, South Africa
5. Global Security & Crisis Management Unit, Joint Research Centre of the European Commission, Ispra, Italy

Citation style for this article:
Mantero J, Szegedi E, Payne Hallström L, Lenglet A, Depoortere E, Kaic B, Blumberg L, Linge JP, Coulombier D. Enhanced epidemic intelligence using a web-based screening system during the 2010 FIFA World Cup in South Africa. Euro Surveill. 2014;19(18):pii=20796. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20796

Article submitted on 13 March 2013 / published on 08 May 2014

The 2010 FIFA World Cup took place in South Africa between 11 June and 11 July 2010. The European Centre for Disease Prevention and Control (ECDC), in collaboration with the hosting authorities, carried out enhanced epidemic intelligence activities from 7 June to 16 July 2010 for timely detection and monitoring of signals of public health events with a potential to pose a risk to participants and visitors. We adapted ECDC's routine epidemic intelligence process to targeted event-based surveillance of official and unofficial online information sources. A set of three specifically adapted alerts in the web-based screening system MedISys were set up: potential public health events in South Africa, those occurring in the participating countries and those in the rest of the world. Results were shared with national and international public health partners through daily bulletins. According to pre-established ECDC criteria for the World Cup, 21 events of potential public health relevance were identified at local and international level. Although none of the events detected were evaluated as posing a serious risk for the World Cup, we consider that the investment in targeted event-based surveillance activities during the tournament was relevant as it facilitated real-time detection and assessment of potential threats. An additional benefit was early communication of relevant information to public health partners.

Introduction

The 2010 FIFA World Cup

The 2010 Fédération Internationale de Football Association (FIFA) World Cup took place in South Africa between 11 June and 11 July 2010 [1]. It was one of the largest mass gathering events (MGs) ever organised on the African continent, with the participation of 32 national football teams (Figure), including 11 teams from European Union (EU)/ European Economic Area (EEA) countries: Denmark, England, France, Germany, Greece, Italy, the Netherlands, Portugal, Slovakia, Slovenia, and Spain. More than 300,000 foreign football fans visited South Africa to attend the event (around 72,000 (24%) from Europe), in addition to the 10 million tourists who visit South Africa each year [2].

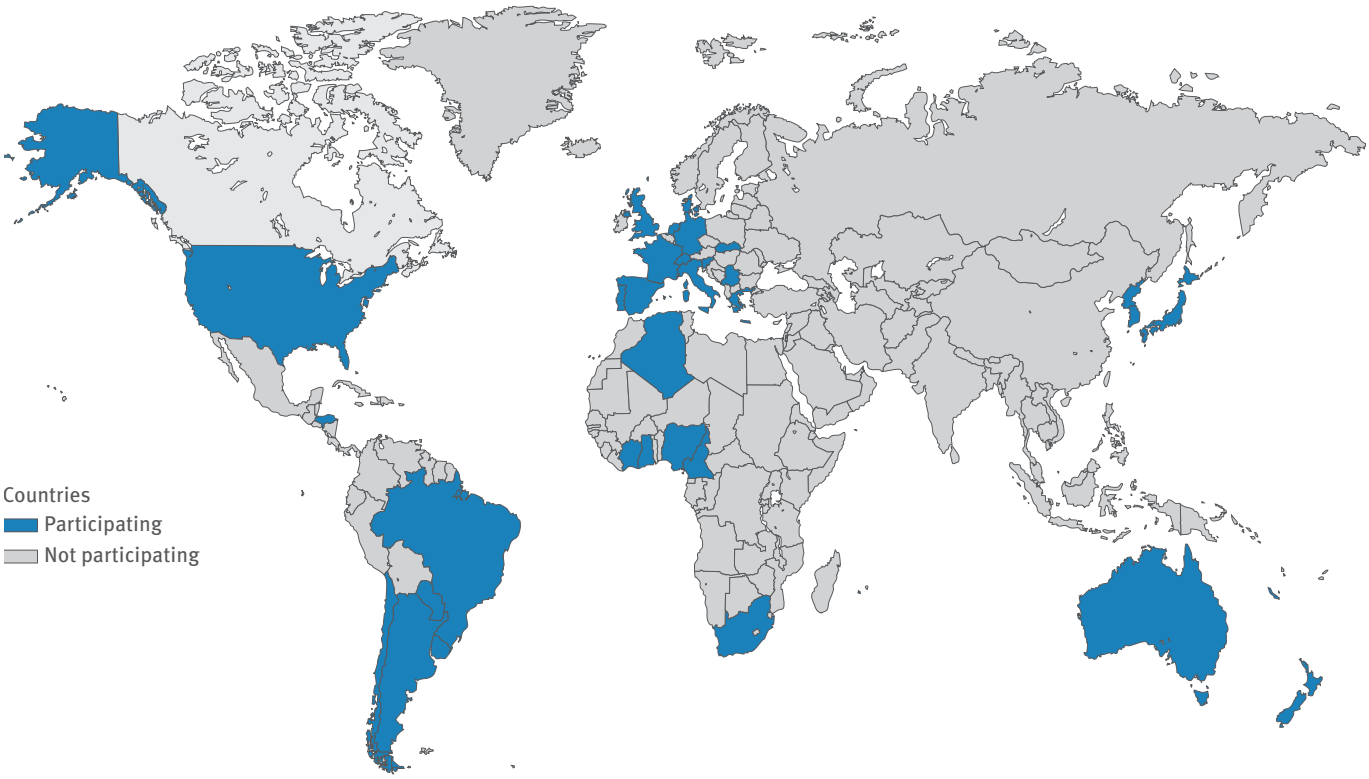
Mass gathering and risk of infectious diseases

The World Health Organization (WHO) defines a mass gathering event (MG) as an event attended by more than 1,000 individuals in a specific location for a specific purpose and for a defined period of time [3]. The term 'mass gathering' generally refers to major international public events, such as sporting events or religious gatherings as well as unplanned events with large number of attendees, which can put a strain on the planning and response resources of the hosting community.

Large numbers of visitors in the same area at the same time may increase the risk of communicable disease outbreaks. Several factors contribute to this theoretical increase, such as increased person-to-person transmission of pathogens due to the localised high population density, risk of importation of non- endemic diseases, exportation of endemic diseases, challenges in contact tracing due to visitor mobility and temporary structures such as mass catering and accommodation for visitors. Non-communicable health risks are also relevant, including heat stroke, crowd injury and drug- and alcohol-related conditions. Additionally, as MGs are often high-profile events, other risks such as security or bioterrorism threats also need to be taken into consideration. The increased risk of public health events during MGs poses special challenges for the hosting authorities in terms of public health preparedness and communication. Media attention might lead to the need for timely communication to the general public and to participants' home communities upon their return.

Figure

Countries participating in the 2010 FIFA World Cup, South Africa, 11 June–11 July 2010 (n=32)



FIFA: Fédération Internationale de Football Association.

ECDC epidemic intelligence activities

ECDC refers to epidemic intelligence (EI) as the systematic process of collection, validation and analysis of information about potential public health events from a virtually unlimited amount of sources [4,5]. Its purpose is to speed up the detection of possible public health events in order to allow the implementation of timely response actions after an adequate risk assessment. This includes real-time monitoring of the risk these events might pose. The EI process uses official data provided by national health authorities through indicator-based surveillance as well as the monitoring of additional information through event-based surveillance.

ECDC activities during a MG focus mostly on the event-based surveillance component, in particular on the processing of web-based information. To do so, we use advanced technologies, defined as event-based surveillance web systems, which are able to gather, filter and classify public health information online. MedISys is among the EBS web systems most frequently used for EI purposes at ECDC because of its extreme flexibility and possible customisation [6]. The system, developed in 2006 by the European Commission's Joint Research Centre, is capable of screening selected publicly available web sources, including online media and government websites, using multilingual categorisation based on alert definitions using keywords in over 40 languages [7,8]. Online items of potential public health interest are automatically classified in specific disease categories if they satisfy the corresponding alert definitions, which may contain Boolean operators, proximity operators, wildcard characters and the use of cumulative positive or negative weights with an adjustable threshold. All news items are classified and geo-located in a user interface accessible on the web.

ECDC epidemic intelligence activities during the 2010 World Cup

In line with ECDC's Founding Regulation, which states that the agency's role is to 'identify, assess and communicate current and emerging threats to human health from communicable diseases in order to strengthen Europe's defences against infectious diseases' [9], we undertook to inform EU national health authorities and the European Commission in real time about possible public health risks for EU citizens during the 2010 World Cup.

The aim of this article is to present the adapted ECDC EI strategy developed six months before and put in place specifically for 2010 World Cup, to present the web-technology used for performing event-based

Table 1

List of MedISys filters created for the 2010 FIFA World Cup, South Africa, 7 June–16 July 2010

MedISys filters	Description	Purpose
Filter 1	Selected communicable diseases occurring in South Africa	Identify web information about selected communicable diseases and syndromes considered to be more likely to occur in South Africa
Filter 2	Other public health events in South Africa	Identify web information about non-infectious disease events of possible public health interest at the game venues (e.g. crowd injuries, heat stroke and security issues)
Filter 3	Selected communicable diseases to South Africa from participating countries	Identify web information about selected communicable diseases considered to be at risk for importation to the host country from participating countries (excluding South Africa)[a]
Filter 4	Selected communicable diseases in countries neighbouring South Africa	Identify web information about selected communicable diseases considered to be at risk for importation to South Africa from bordering countries[b]

FIFA: Fédération Internationale de Football Association.

MedISys, developed at the Joint Research Centre of the European Commission, is an Internet-based system that continuously monitors specialist medical sites and news sites to rapidly identify potential threats to public health.

[a] Algeria, Argentina, Australia, Brazil, Cameroon, Chile, Côte d'Ivoire, Denmark, England, France, Germany, Ghana, Greece, Honduras, Italy, Japan, Mexico, Netherlands, New Zealand, Nigeria, North Korea, Paraguay, Portugal, Serbia, Slovakia, Slovenia, South Korea, Spain, Switzerland, Uruguay and the United States.

[b] Namibia, Botswana, Mozambique, Swaziland, Zimbabwe and Lesotho.

surveillance for this MG and report findings in terms of identified public health events communicated in real time with public health partners.

Methods

We adapted ECDC's routine EI process [4] for a defined period of time starting two weeks before the beginning of the 2010 World Cup (7 June 2010) and ending one week after the closing ceremony (16 July 2010). The objective was to allow early detection and monitoring of signals of public health events with a potential to pose a risk to participants and visitors.

Routine EI activities were enhanced by expanding the information sources, using a targeted and systematic screening approach using tailored tools (MediSys), determining validation sources, establishing a daily analysis and communication process with regular and specific public health partners and developing specific reports. Processes were then re-integrated into the structure of routine EI activities at ECDC with no additional allocated budget. We benefited from an additional full-time seconded expert (B. Kaic) for weekday additional screening and daily report production.

Screening of public health information potentially relevant to the 2010 World Cup through MedISys

Following a review of the existing list of online media sources screened by MedISys, we added, in collaboration with European Commission's Joint Research Centre, relevant publicly available media web sources and websites of health authorities of the host country, its neighbours and those of the participating countries.

New multilingual alert definitions were set up, which included languages of participating countries not yet covered by the system, geo-terms specific to South Africa in order to locate the information identified (names of regions, provinces, cities, neighbourhoods and game venues) as well as a limited set of communicable diseases and symptoms. The list of diseases and symptoms was based on an ECDC internal assessment of risk of infectious diseases considering official information from the National Institute for Communicable Diseases (NICD) in Johannesburg, public health reports and travel advice issued by national and international organisations worldwide before the event [10-13]. The list of diseases comprised the following: tick bite fever, Crimean Congo haemorrhagic fever, chikungunya, cholera, dengue, food-borne disease, hand, foot and mouth disease, human immunodeficiency virus (HIV) infection, influenza, legionellosis, malaria, measles, meningococcal meningitis, sexually transmitted infections, poliomyelitis, rabies, Rift Valley fever, respiratory syncytial virus infection, rubella, tuberculosis and yellow fever.

Customised pages were then created in MedISys dedicated to the 2010 World Cup, where selected disease alerts were combined with alerts for selected countries in order to create display filters for online information of potential interest (Table 1).

Filtering screened information for potential public health events

- We established criteria to evaluate the web information selected by MedISys regarding public health relevance for the tournament. These were:

Table 2

Detected or monitored public health events during the 2010 FIFA World Cup, South Africa, 7 June–16 July 2010 in the host country and their relevance for the event

Public health event	Source	Description	ECDC actions and assessment of relevance for the event
Influenza	NICD [10-12,29], WHO [31], media reports (MedISys alert)	Low activity with initially influenza B virus circulation, later moderate with the addition of A (H3N2) and pandemic A (H1N1) strains.	Several cases among participants/visitors reported by media but overall no relevant spread to the community for the 2010 World Cup.
Rift Valley fever	NICD [10-12], media reports (MedISys alert)	Ongoing nationwide outbreak, with first cases reported in February 2010 (228 confirmed cases including 26 deaths).	All confirmed cases had direct contact with infected animal tissue. No cases among visitors/ participants and no relevance for the 2010 World Cup.
Meningococcal meningitis	NICD [10-12,29], media reports (MedISys alert)	105 confirmed cases (n=85 due to *Neisseria meningitidis* B/W135).	No direct risk for visitors/participants and no cases reported among either group. It had no relevance for the 2010 World Cup.
Measles	NICD [10-12], media reports (MedISys alert)	An ongoing measles outbreak (B3 genotype) since 2009. A mass vaccination campaign took place before the event.	No cases reported among visitors/participants during the World Cup but cases potentially linked to the event afterwards in several countries.
Malaria	Media reports [22], (MedISys alert)	Two fatalities reported by media in a South Korean dance group were not considered to be linked to infection in South Africa.	Risk for malaria in visitors/participants was considered low.
Canine rabies	NICD [23,24], media reports (MedISys alert)	Ten canine cases were reported in domestic dogs in a suburb of Johannesburg.	No human exposure occurred during the surveillance period; however, a local case with symptom onset at end of August 2010 was confirmed later by the NICD. It had no relevance for the 2010 World Cup.
Food-borne illness	Media reports [26,27], (MedISys alert)	Two limited food-borne illness outbreaks at game venues.	Outbreaks confirmed by the NICD and assessed as local events with limited or no risk for visitors/ participants. It was of no relevance for the 2010 World Cup.

ECDC: European Centre for Disease Prevention and Control; FIFA: Fédération Internationale de Football Association; NCID: National Institute for Communicable Diseases, Johannesburg, South Africa; WHO: World Health Organization.

The enhanced surveillance period was from 7 June to 16 July 2010.

MedISys, developed at the Joint Research Centre of the European Commission, is an Internet-based system that continuously monitors specialist medical sites and news sites to rapidly identify potential threats to public health.

- suspected or confirmed cases of communicable diseases of public health relevance for the 2010 World Cup;
- suspected or confirmed cases of communicable diseases of public health relevance occurring in South Africa (risk to EU visitors/participants, risk of importation to the EU);
- incidents in South Africa related to international security, such as possible intentional release of biological agents, nuclear and chemical events;
- suspected or confirmed cases of communicable diseases of public health relevance for the World Cup occurring in countries with national teams participating in the World Cup and in countries bordering South Africa (risk of exportation to South Africa and local spread);
- incidents occurring in South Africa drawing media attention in the EU, such as outbreaks in tourist areas, crowd injuries, rumours about possible spread of communicable diseases among visitors or participants.

Validation and analysis of potential public health events

Information on public health events detected in EU/EEA countries was validated through routine channels with EU Member States, while those detected outside the EU/EEA (excluding South Africa) were validated through the WHO Regional Office for Europe and the ECDC EI international network.

Public health events identified in South Africa were validated and assessed through information available from the NICD. The NICD undertook daily laboratory surveillance at national level and was a core member of the Public Health Cluster at the National Operations Centre, which was responsible for the risk assessment of each incident/event. The NICD also posted regular official epidemiological updates on the web, providing real-time public information on current outbreaks or diseases of interest in the country, such as measles, influenza and Rift Valley fever.

We analysed all validated events at ECDC on a daily basis during regular EI meetings with the participation of ECDC disease-specific experts, taking into consideration the information provided by South Africa and WHO Regional Office for Europe.

Communicating the epidemic intelligence findings

During the entire period of the enhanced surveillance, ECDC produced a daily bulletin summarising the results of the daily EI activities (signal source, public health topic and summary, validation status, ECDC assessment of relevance).This bulletin was shared daily with the NICD, WHO Regional Office for Europe and interested EU Member States.

Results

Targeted ECDC EI activities during the 2010 World Cup were undertaken for six weeks: 21 incidents of potential public health relevance according to ECDC criteria were detected or monitored. Seven of them occurred in South Africa.

Potential public health incidents in South Africa

A short summary of all potential public health threats in South Africa identified or monitored by ECDC during the enhanced surveillance period is shown in Table 2.

Influenza

The football tournament occurred during the expected influenza season in South Africa. Thus, ECDC started to monitor the influenza activity in South Africa before the event, consulting the NICD and WHO reports supplemented with online media reports, which were verified when necessary. Overall, the influenza activity was low to moderate during the tournament. Initially, only influenza B virus was circulating; both A(H3N2) and A(H1N1)pdm09 virus strains were detected later during the surveillance period [10-12]. Despite some reported cases of influenza among participants and officials, no spread to other participants or officials was identified. We considered the risk of contracting influenza for EU visitors and/or participants as low during the enhanced surveillance period.

Rift Valley fever

There was an ongoing large nationwide outbreak of Rift Valley fever during 2010 in South Africa and there had been some concerns regarding the risk for EU tourists contracting the disease following reports of a German visitor who was thought to have been infected in the country before the start of the event [14]. ECDC monitored Rift Valley fever during the enhanced surveillance period using information regularly provided by the NICD and through media reports. However, all confirmed cases were reported in non-tourist areas and in individuals who had had direct contact with infected animal tissue (farm workers, as a result of occupational exposure). The German case was later discarded by the national authorities following a subsequent diagnosis of rickettsial infection [15].

Meningococcal disease

Meningococcal disease in South Africa occurs normally in sporadic outbreaks, mainly during droughts, dry and dusty conditions or winter seasons, with a predominance of *Neisseria meningitidis* serogroup B and W135. Media attention on this had been particularly intense shortly before the 2010 World Cup following the death due to meningococcal meningitis of a well-known local opera singer who was scheduled to perform during the opening ceremony [16]. Because of the risk of infection for unvaccinated visitors, vaccination against meningococcal disease was recommended for visitors and participants before the event by the NICD [13]. Updated information about new cases of meningitis was regularly published online by the NICD during the enhanced surveillance period and was included in the daily ECDC bulletin. No cases were reported among visitors and participants.

Measles

There was an ongoing measles outbreak in South Africa during the 2010 World Cup: it began in the second half of 2009, with more than 15,000 cases reported by July 2010 [10-12]. ECDC closely followed the situation in the country through regular updates provided by the NICD, taking into consideration the likelihood of unvaccinated visitors contracting the virus and the risk of exportation of cases to non-endemic countries. The NICD informed ECDC that there had been a mass vaccination campaign before the event. Measles updates were included in the daily ECDC bulletins in order to draw the attention of EU national health authorities to the importance of vaccination for EU citizens visiting South Africa. ECDC also informed the general public about the need for vaccination through the ECDC website, both before and during the MG. Sporadic cases were also reported in unvaccinated Australian visitors returning from the event [17,18]. In September 2010, health authorities in Argentina, a country that has been measles free since 2000, issued public health alerts after confirmed local transmission of measles virus suspected to be linked to measles cases in citizens who visited South Africa during the 2010 World Cup [19]. Other measles-free countries in South America including Brazil and Uruguay also issued public health alerts for measles in the following months [20,21].

Malaria

The risk of contracting malaria in South Africa was considered very low by the NICD and ECDC for participants and visitors, partly because the venues for the games were outside risk areas with high transmission and partly because the games took place during the low-transmission period. Two fatalities due to malaria were reported in South Korean members of an international dance group visiting South Africa before the World Cup [22]. This report led to increased media attention on the risk of malaria in South Africa. The NICD confirmed the

Table 3

Detected or monitored public health events during the 2010 FIFA World Cup, South Africa, 7 June–16 July 2010 in participating countries and their relevance for the event

Event, country	Source	Description	ECDC actions and assessment of relevance for the event
Hepatitis A, the Netherlands	Media reports (MedISys alert)	An increase in the number of cases was reported in Zeeland province	Validation through the national health authorities: two separate clusters confirmed among travellers abroad (not South Africa). No relevance for the 2010 World Cup.
Legionnaires' disease, Spain	Media reports (MedISys alert)	Outbreak reported in Alcoy	Validation through the national health authorities: confirmation of a local outbreak with no history of travelling. No relevance for the 2010 World Cup.
Measles, Italy	Media reports (MedISys alert)	Increased number of cases reported in Sicily	Validation through web-based information. At least three outbreaks identified, control measures taken (no travel history). No relevance for the 2010 World Cup.
Measles, Greece	Media reports [32]	A relevant increase in the number of cases was reported in Greece	Validation through national health authorities. Possible relation with cases in Bulgaria. No relevance for the 2010 World Cup.
Dengue, Italy	Media reports (MedISys alert), [33]	An imported case was reported in an area where the competent vector is present	Validation through local health authorities' website; the case travelled to South- East Asia. No relevance for the 2010 World Cup.
Anthrax, United Kingdom and Germany, in injecting drug users	Official reports [34], (MedISys alert)	Cases reported since December 2009. By the end of the World Cup, 47 cases had been identified, with 13 fatalities	Any update during the enhanced surveillance period for 2010 FIFA was validated through local authorities and shared with ECDC disease experts for analysis. No relevance for the 2010 World Cup.

ECDC: European Centre for Disease Prevention and Control; FIFA: Fédération Internationale de Football Association.

The enhanced surveillance period was from 7 June to 16 July 2010.

MedISys, developed at the Joint Research Centre of the European Commission, is an Internet-based system that continuously monitors specialist medical sites and news sites to rapidly identify potential threats to public health.

low level of risk as initially assessed and indicated that the two cases were thought not to have been infected in South Africa.

Canine rabies

Ten cases of canine rabies were reported in Metropolitan Johannesburg by the NICD [23]. However, the authorities considered the occurrence of rabies to be of limited public health concern, with post-exposure prophylaxis confirmed as being readily available [10-12,24]. Nonetheless, ECDC included the information about the canine cases in the daily ECDC bulletins to raise awareness among national health authorities about the potential risk of exposure for EU visitors. In September 2010, the NICD confirmed a human local case of rabies in Johannesburg in a child with onset of symptoms in August, which was linked to the animal cases reported during the previous weeks in the same city [25].

Food-borne illness

The NICD issued advice for travellers regarding food safety and recommending caution when purchasing food from street vendors or other food outlets. There were two isolated outbreaks of food-borne illness occurring at game venues during the enhanced surveillance period without serious effects, reported first by the media [26,27] and later confirmed by NICD: one with *Bacillus cereus* as the causative agent, the other with unknown aetiology [11-12].

Potential public health incidents in participating countries during the 2010 World Cup

We considered six events as being of potential public health risk at EU level during the enhanced surveillance period (hepatitis A, Legionnaires' disease, measles (in two countries), dengue and anthrax) but none were deemed relevant for the World Cup (see short description in Table 3).

Potential public health incidents in non-participating countries during the 2010 World Cup

ECDC detected or monitored six public health events of potential EU concern in non-participating countries, which were not deemed relevant the event (see short description in Table 4).

Discussion

ECDC seeks to protect EU/EEA citizens from infectious diseases through early detection, monitoring and assessment of public health signals in the EU/EEA and worldwide. In the case of large MGs attracting

Table 4

Public health events detected or monitored during the 2010 FIFA World Cup, 7 June–16 July 2010, in non-participating countries and their relevance for the event

Event, country	Source	Description	ECDC actions and assessment of relevance for the event
Measles, Bulgaria	National health authorities [35], media reports (MedISys alert)	This event was already being monitored by ECDC before the 2010 World Cup. From January 2010 to the end of the event, the cumulative number of cases was of 21,180 (with 20 deaths).	The outbreak started in 2009 and was monitored as part of ECDC routine activities. No relevance for the 2010 World Cup.
Poliomyelitis, worldwide	Official reports [36], media reports (MedISys alert)	At the end of the 2010 World Cup, 413 cases of WPV1 had been reported in 2010 in Tajikistan (76% of the cases worldwide). Local media reported cases in Russia.	The monitoring of poliomyelitis worldwide is part of ECDC routine epidemic intelligence activities. Considering the risk of appearance of the disease in the EU, special epidemic intelligence attention was dedicated to Tajikistan and Russia. No relevance for the 2010 World Cup.
Influenza, worldwide (excluding South Africa)	WHO [31], personal communication from national health authorities, media reports (MedISys alert)	Special emphasis was dedicated to southern hemisphere activity. During the period covered, most countries had sporadic to low activity. Circulation of influenza A(H3N2) and A(H1N1) viruses was described in several areas of Central and South America; limited activity was described in Africa; in Asia, the main circulation was reported in Malaysia, Singapore and south-west India.	In addition to ECDC routine monitoring, we selected three countries as sentinel sites (New Zealand, Singapore and Australia) with well-established surveillance systems in order to closely monitor the activity in the southern hemisphere. No relevance for the 2010 World Cup.
Dengue, worldwide	Personal communication from national health authorities, media reports (MedISys alert)	Central and South American countries were particularly affected, but no unusual situation was reported.	The monitoring of relevant dengue outbreaks worldwide is part of ECDC routine epidemic intelligence activities, considering the risk of locally acquired cases in Europe. No relevance for the 2010 World Cup.
Plague, Myanmar	Media reports (MedISys alert)	Several media reports about an outbreak in Rangoon (Myanmar).	ECDC validated the information through WHO. The event was considered very unusual but without implications for the 2010 World Cup.
Plague, Syria	ProMed [37], media reports (MedISys alert)	Several media reports about cases confirmed among military personnel in Syria, where no case has been described in the previous 40 years.	ECDC validated the information through its epidemic intelligence network. The source was found to be unreliable and no cases were confirmed by authorities. No relevance for the 2010 World Cup.

ECDC: European Centre for Disease Prevention and Control; EU: European Union; FIFA: Fédération Internationale de Football Association; WHO: World Health Organization; WPV1: wild poliovirus 1.

The enhanced surveillance period was from 7 June to 16 July 2010.

MedISys, developed at the Joint Research Centre of the European Commission, is an Internet-based system that continuously monitors specialist medical sites and news sites to rapidly identify potential threats to public health.

participants from all over the world, public health may benefit from specific surveillance activities directed at infectious diseases and other health risks during the event. ECDC carried out enhanced event-based surveillance for the 2010 World Cup to maximise timely detection and risk assessment communication to EU stakeholders concerning relevant infectious diseases circulating among participants at the tournament or occurring globally. Timeliness was achieved by using both official and non-official information sources. The gathering of information was made effective through a daily process making use of a tailored web-based screening tool (MedISys).

There are limitations on the use of public sources and web-screening tools for event-based surveillance. The detection of public health events from official sources is possible but is dependent on the information being made available regularly and in a timely manner in the public domain, e.g. as regional or national surveillance reports (as undertaken by the NICD during the World Cup). When information is gathered from non-official sources, such as the media, the reporting of isolated cases or outbreaks relies solely on what captures the interest of reporters/journalists, e.g. a disease that occurs in a high-profile individual or a public health rumour with political or economic implications. Thus it is important to take into consideration that reports of public health events detected through web-aggregators

using media sources can only be a complement to what is detected through mandatory event-based surveillance, such as the International Health Regulations (IHR) or the EU's Early Warning and Response System (EWRS) , together with traditional indicator-based surveillance used in national and international disease surveillance systems. Nonetheless, the advantage of reports from non-official sources, if corroborated after validation from official sources, is that they can provide a timely indication of a possible public health threat or can assist in directing corrective public health communication.

Our gathered and validated information was shared with all relevant decision-makers in EU Member States as well as the international community through our daily bulletins during the entire enhanced surveillance period. The enhanced surveillance by ECDC offered a rumour-control function as well, exemplified by a supposed plague outbreak in Syria (Table 4), which was reported by the media but quickly discarded after examination of information from the ECDC EI network.

There were no international or local events posing serious risk to the World Cup during the surveillance period apart from the ongoing local measles outbreak, which also affected visitors. The subsequent detection of measles cases in several countries after the World Cup, with secondary transmission in some places, clearly demonstrated the risk of exportation of vaccine-preventable diseases through visitors returning from a hosting country. This pattern was previously reported following a MG when measles occurred among residents of British Columbia, Canada, after the Winter Olympic Games in Vancouver in 2010, leading to the first major outbreak of the disease in the province since 1997 [28].

Regarding the other reported diseases, the majority of cases were community-based or local sporadic cases. Influenza activity was low to moderate and followed the seasonal trends in the country. There was an expected seasonal activity of meningococcal disease, with sporadic cases in the local population [29].

We also monitored media reports, later confirmed, about individuals in Pretoria being in possession of radioactive materials (caesium-137) and trying to sell it for the production of a dirty bomb during the tournament, but this was not considered a risk for the event [30].

Although no major relevant public health events related to the World Cup occurred, ECDC considers the investment of technical preparations and workforce time used in the enhanced surveillance during the World Cup to be justified. The targeted activities carried out by the ECDC EI team during the World Cup allowed the accurate and timely identification and analysis of public health risks during the event for the entire EU/EEA community, thus saving resources for the individual EU Member States. Additions to MedISys continue to be used beyond the specific filters of the 2010 World Cup and contacts and collaboration with public health partners are a long-term legacy for EI activities.

Furthermore, ECDC's enhanced surveillance activities provide an additional safety net to that of other EI actors at an international level, e.g. the Global Public Health Intelligence Network (GPHIN), HealthMap, PULS (an automated news media monitoring platform) and WHO. Redundancy among EI systems provides an added safety system for global public health security.

Conclusions

The enhanced EI activities by ECDC during the 2010 World Cup, together with the close collaboration of the NICD and WHO, allowed the detection, assessment and communication of relevant health threats potentially affecting EU Member States. Tailored EI surveillance for large international MGs should continue as a core function for ECDC. From each MG experience, ECDC learns how to improve its EI procedures, provide a sound basis for how to best support EU Member States and hosting countries worldwide and broaden the existing knowledge base for future MGs. The added value of the ECDC EI support for the national authorities in the hosting countries can vary considerably depending on existing surveillance systems and national surveillance capacities. It is important to define which tools to use for gathering information, to identify specific filtering criteria in collaboration with the authorities in the hosting countries and to clarify the information flow among the public health partners.

Acknowledgements

We thank the whole ECDC Epidemic Intelligence group for the work done during the event; the National Institute for Communicable Diseases, South Africa, for their strong participation in our epidemic intelligence process and for the availability for daily contacts and collaboration in risk assessment analysis.

Conflict of interest

None declared.

Authors' contributions

JM participated in the design, coordination and analysis of this study and drafted the manuscript. ES, LHP, AL, ED and DC helped in the draft of the manuscript and provided relevant feedback on discussion and conclusions; BK provided relevant input on results in particular, JL contributed to the methodology part; LB provided input and feedback on the manuscript, contributing mainly to the perspective from the host country authorities side.

References

1. FIFA. 2010 FIFA World Cup South Africa. Zurich: FIFA. [Accessed 2 Jun 2010]. Available from: http://www.fifa.com/worldcup/archive/southafrica2010/index.html

2. South African Tourism. Impact of 2010 FIFA World Cup. Johannesburg: South African Tourism; 2010. Available from: https://tkp.tourism.gov.za/documents/impact%20of%20 2010%20fifa%20world%20cup.pdf
3. World Health Organization (WHO). Communicable disease alert and response for mass gatherings: key considerations, June 2008. Geneva: WHO; 2008.
4. European Centre for Disease Prevention and Control (ECDC). Epidemic Intelligence tutorial. Stockholm: ECDC. [Accessed 2 May 2011]. Available from: http://external.ecdc.europa.eu/EI_Tutorial/course.htm
5. Paquet C, Coulombier D, Kaiser R, Ciotti M. Epidemic intelligence: a new framework for strengthening disease surveillance in Europe. Euro Surveill. 2006;11(12):pii=665.
6. Linge JP, Steinberger R, Weber TP, Yangarber R, van der Goot E, Al Khudhairy DH, et al. Internet surveillance systems for early alerting of health threats. Euro Surveill. 2009;14(13):pii=19162.
7. Mantero J, Belyaeva E, Linge JP. How to maximise event-based surveillance web-systems: the example of ECDC/JRC collaboration to improve the performance of MedISys. Luxembourg: Publications Office of the European Union; 2011. Available from: http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/16206/1/lb-na-24763-en-c.pdf
8. Barboza P, Vaillant L, Mawudeku A, Nelson NP, Hartley DM, Madoff LC, et al. Evaluation of epidemic intelligence systems integrated in the early alerting and reporting project for the detection of A/H5N1 influenza events. PLoS One. 2013;8(3):e57252. http://dx.doi.org/10.1371/journal.pone.0057252
9. Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 april 2004 establishing a European centre for disease prevention and control. Official Journal of the European Union. Luxembourg: Publications Office of the European Union. 30.4.2004: L 142. Available from: http://www.ecdc.europa.eu/en/aboutus/key%20documents/0404_kd_regulation_establishing_ecdc.pdf
10. National Institute for Communicable Diseases (NICD), South Africa. Communicable diseases communiqué. May 2010:9(5). Johannesburg: NCID; 2010. Available from: http://www.nicd.ac.za/assets/files/NICDCommMay10Vol09_05.pdf
11. National Institute for Communicable Diseases (NICD), South Africa. Communicable diseases communiqué. Jun 2010:9(6). Johannesburg: NCID; 2010. Available from: http://www.nicd.ac.za/assets/files/NICDCommJune10Vol09_06.pdf
12. National Institute for Communicable Diseases (NICD), South Africa. Communicable diseases communiqué. Jul 2010:9(7). Johannesburg: NCID; 2010. Available from: http://www.nicd.ac.za/assets/files/NICDCommJuly10Vol09_07.pdf
13. Blumberg L, de Frey A, Frean J, Mendelson M. The 2010 FIFA World Cup: communicable disease risks and advice for visitors to South Africa. J Travel Med. 2010;17(3):150-2. http://dx.doi.org/10.1111/j.1708-8305.2010.00413.x
14. Robert Koch Institute (RKI). Fallbericht. Aus Südafrika importierte Infektion mit Rifttal-Fieber-Virus. [Case report. Imported Rift Valley fever virus from South Africa]. Epidemiologisches Bulletin. 3 May 2010;17:158-9. Available from: http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2010/Ausgaben/17_10.pdf;jsessionid=044A188B78A877A25E2CE82B42D48711.2_cid298?__blob=publicationFile
15. Robert Koch Institute (RKI). Aktuelle Information zum Fallbericht: Fieberhafte Erkrankung nach Südafrikaaufenthal. [Update of case report: a case of febrile illness returning from South Africa]. Epidemiologisches Bulletin. 17 May 2010;19:176. Available from: http://edoc.rki.de/documents/rki_fv/reaN2E7gpPCX/PDF/24fprNAosjp6F2.pdf
16. Goal.com. World Cup opera singer Siphiwo Ntshebe dies from meningitis. Goal.com; 26 May 2010. Available from: http://www.goal.com/en/news/89/africa/2010/05/26/1944414/world-cup-opera-singer-siphiwo-ntshebe-dies-from-meningitis
17. ProMED-mail. Measles - Australia ex South Africa. Archive Number: 20100709.2299. 9 Jul 2010. Available from: http://www.promedmail.org/direct.php?id=20100709.2299
18. ProMED-mail. Measles - Australia (06): Queensland ex South Africa. Archive Number: 20100914.3329. 14 Aug 2010. Available from: http://www.promedmail.org/direct.php?id=20100914.3329
19. Ministry of Health, Argentina. Casos confirmados de sarampión. [Confirmed measles cases]. Alertas Epidemiológicos anteriores No. 8. [Latest epidemiological alerts No. 8]. Buenos Aires: Ministry of Health; 30 Sep 2010. [Accessed 2 May 2011]. Spanish. Available from: http://www.msal.gov.ar/images/stories/alertas_epidemiologia/2010/alerta_8_sarampion_30-9-2010.pdf
20. infobae. Casos de sarampión en Brasil y Argentina alertan a Uruguay. [Uruguy is on alert due to measles cases in Brazil and Argentina]. Buenos Aires: infobae; 23 Aug 2010. Spanish. Available from: http://www.infobae.com/2010/08/23/1007090-casos-sarampion-brasil-y-argentina-alertan-uruguay
21. La Nacion Digital. Sarampión: detectan dos casos en Brasil. [Measles: two cases detected in Brazil]. Buenos Aires: La Nacion; 21 Aug 2010. Spanish. Available from: http://www.lanacion.com.ar/1296559-sarampion-detectan-dos-casos-en-brasil
22. Yonhap News Agency. Korean dancer dies of malaria after trip to Africa. Seoul: Yonhap News Agency; 23 Jun 2010. Available from: http://english.yonhapnews.co.kr/news/2010/06/23/0200000000AEN20100623011100315.HTML?source=rss
23. ProMED-mail. Rabies - South Africa (02): (Gauteng) Canine, human suspected. Archive Number: 20100928.3519. 28 September 2010. Available from: http://www.promedmail.org/direct.php?id=540634
24. Malerczyk C, Nel LH, Gniel D, Blumberg L. Rabies in South Africa and the FIFA Soccer World Cup: travelers' awareness for an endemic but neglected disease. Hum Vaccin. 2010;6(5):385-9. http://dx.doi.org/10.4161/hv.6.5.11713
25. National Institute for Communicable Diseases (NICD), South Africa. Rabies confirmed In child In Johannesburg Metropolitan. Johannesburg: NCID: 27 Sep 2010. Available from: http://www.nicd.ac.za/?page=alerts&id=5&rid=41
26. IOL sport. Food poisoning hit Fifa workers. South Africa: IOL sport; 18 Jun 2010. Available from: http://www.iol.co.za/sport/food-poisoning-hit-fifa-workers-1.619038
27. dalje.com. 90 World Cup volunteers suffer food poisoning at stadium. Croatia: dalje.com; 18 Jun 2010. Available from: http://dalje.com/en-world/90-world-cup-volunteers-suffer-food-poisoning-at-stadium/310535
28. Naus M, Sahni V, Gustafson R, Brodkin E, Parker R, Fyfe M, et al. An outbreak of measles in British Columbia, Canada: an unwelcome consequence of the 2010 Winter Olympics. 48th annual meeting of the Infectious Diseases Society of America; 21-24 October 2010; Vancouver, British Columbia, Canada. Abstract available from: https://idsa.confex.com/idsa/2010/webprogram/Paper4104.html
29. Blumberg L. 2010 FIFA soccer World Cup, South Africa: communicable disease risks and surveillance. Communicable Diseases Surveillance Bulletin. November 2010;8(4):63-4. Available from: http://www.nicd.ac.za/assets/files/Bulletin%20November%202010(1).pdf
30. IOL news. Four bust in 'dirty bomb' sale sting. South Africa: IOL news; 10 Jul 2010. Available from: http://www.iol.co.za/news/south-africa/four-bust-in-dirty-bomb-sale-sting-1.489373#.UTYoaKKEoWk
31. World Health Organization (WHO). Situation updates - pandemic (H1N1) 2009. Geneva: WHO. [Accessed Jul 2010]. Available from: http://www.who.int/csr/disease/swineflu/updates/en/
32. Ethnos. [Measles ... introduction of the epidemic from Bulgaria]. Greece: Ethnos; 6 Jul 2010. Greek. Available from: http://www.ethnos.gr/article.asp?catid=22768&subid=2&pubid=19092956
33. Il Resto del Carlino. Carpigiano torna dal Brasile ammalato di dengue. Scatta la disinfestazione. [A returning visitor from Brazil falls ill with dengue in Carpi. Need for vector control]. Modena: Il Resto del Carlino. 15 Jun 2010. Italian. Available from: http://www.ilrestodelcarlino.it/modena/cronaca/2010/06/15/345592-carpi_caso_dengue.shtml
34. Health Protection Scotland (HPS). Anthrax outbreak information. Glasgow: HPS; 2010. [Accessed Jul 2010]. Available from: http://www.hps.scot.nhs.uk/giz/anthraxoutbreakdecember2009december2010.aspx
35. National Center of Infectious and Parasitic Diseases (NICPD), Bulgaria. [Measles in Bulgaria]. Sofia: NICPD; 2010. [Accessed Jul 2010]. Bulgarian. Available from: http://www.ncipd.org/?news=disease#28
36. Global Polio Eradication Initiative. Polio worldwide. Geneva: Global Polio Eradication Initiative; 2010. [Accessed Jul 2010]. Available from: http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
37. ProMED-mail. Plague - Syria: military, suspected, request for information. Archive Number: 20100704.2222. 4 July 2010. Available from: http://www.promedmail.org/direct.php?id=458779

Hepatitis A outbreak in British Columbia, Canada: the roles of established surveillance, consumer loyalty cards and collaboration, February to May 2012

H M Swinkels (helena.swinkels@fraserhealth.ca)[1,2], M Kuo[3], G Embree[4], Fraser Health Environmental Health Investigation Team[5], A Andonov[6], B Henry[2,3], J A Buxton[2,3]

1. Office of the Medical Health Officer, Public Health Fraser Health Authority, Surrey, Canada
2. School of Population and Public Health, University of British Columbia, Vancouver, Canada
3. Communicable Disease Prevention and Control Services, British Columbia Centre for Disease Control, Vancouver, Canada
4. Health Protection, Public Health, Fraser Health Authority, Surrey, Canada
5. The team members are listed at the end of the article
6. National Medical Laboratory, Canadian Science Centre for Human and Animal Health, Public Health Agency of Canada, Winnipeg, Canada

Citation style for this article:
Swinkels HM, Kuo M, Embree G, Fraser Health Environmental Health Investigation Team, Andonov A, Henry B, Buxton JA. Hepatitis A outbreak in British Columbia, Canada: the roles of established surveillance, consumer loyalty cards and collaboration, February to May 2012 . Euro Surveill. 2014;19(18):pii=20792. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20792

Article submitted on 02 July 2013 / published on 08 May 2014

Non-travel-related hepatitis A is rare in Canada. We describe a hepatitis A outbreak investigation in British Columbia in February to May 2012 in which exposure history was collected from nine confirmed non-travel-related cases. Suspected foods were tested for hepatitis A virus (HAV): a frozen fruit blend was identified as a common exposure for six of the nine cases using supermarket loyalty cards. Consumption of the product was confirmed in each case. Genetic analysis confirmed HAV genotype 1B in the six exposed cases. Of the three non-exposed cases, the virus could not be genotyped for two of them; the virus from the other case was found to be genotype 1A and this case was therefore not considered part of the outbreak. HAV was detected by PCR from pomegranate seeds, a component of the identified frozen fruit blend. Historically low levels of HAV infection in British Columbia triggered early recognition of the outbreak. Loyalty card histories facilitated product identification and a traceback investigation implicated imported pomegranate seeds.

Background

The annual number of reported cases of hepatitis A have consistently decreased in the past decade in British Columbia (BC), Canada, due to improved standards of hygiene and sanitation and provincially funded hepatitis A immunisation for high-risk groups, including people with chronic liver disease, chronic hepatitis B and C, people who inject drugs and men who have sex with men [1] and post-exposure prophylaxis [2]. in 2010-2011, 30 out of 45 cases reported in BC, were related to travel to countries where hepatitis A remains endemic [3].

Hepatitis A virus (HAV) is primarily spread by the faecal–oral route, either through direct contact or through ingestion of contaminated food or water. The incubation period is 15–50 days. Some infected persons have mild or no symptoms, while others may experience moderate to severe symptoms over weeks or months including fever, dark urine, loss of appetite, malaise, vomiting, pale stools, abdominal pain and/or jaundice [4].

Outbreaks may occur as a result of a food handler at a food establishment being infected; widespread foodborne outbreaks have been associated with uncooked or fresh food contaminated before distribution [5,6]. Epidemiological evidence (supported by identical molecular sequences among the cases) has implicated a variety of foods in outbreaks, for example, green onions, semi-dried tomatoes, blueberries and frozen strawberries [5,7-11]. Laboratory confirmation of HAV contamination of vegetables and fruit is rare, in part due to low viral loads in many foods [12,13]. Molecular subtyping has improved the ability to detect outbreaks caused by HAV [14].

In 2012, an investigation was launched following the identification of three non-travel-related hepatitis A cases within one week in one of BC's five geographically based health authorities, compared with 10 hepatitis A cases in the affected HA in the previous year, six of which were related to travel to endemic countries [3]. This paper describes the investigation of the outbreak which, despite its small size, was rapidly epidemiologically linked to a specific food product. Although genotypic matching to the cases was not possible, HAV was subsequently confirmed in a component of the implicated product.

Methods

Outbreak case definition

The initial outbreak case definition included residents of BC who had laboratory-confirmed acute HAV infection (IgM antibodies to HAV and acute illness with discrete onset of compatible symptoms and jaundice or elevated serum aminotransferase levels, in the absence of recent HAV vaccination) since 1 January 2012 AND no history of travel to an HAV-endemic country in the 50 days before onset of symptoms. The case definition was modified as additional laboratory and exposure data became available. The final case definition (used in this paper) was established in the seventh week of the outbreak and included a possible case (laboratory-confirmed non-travel-related HAV infection) and a confirmed case (HAV genotype 1B with matching sequencing results).

Sample collection and testing

Sera were screened for anti-HAV IgM by Siemens Advia Centaur HAV IgM (Siemens, Canada) and if positive, the result was confirmed on a second platform, Abbott Architect HAV IgM (Abbott, Canada). Dual enzyme immunoassay IgM samples were sent for HAV genotyping to the National Microbiological Laboratory in Winnipeg, Manitoba. HAV RNA was amplified by nested PCR using primers targeting the VP1-2A junction of the HAV genome (F1, 5- -GAC AGA TTC TAC ATT TGG ATT GGT-3', 2,870–2,894; R1 5- -CCA TTT CAA GAG TCC ACA CAC T-3- , 3,382–3,360; F2, 5- -CTA TTC AGA TTG CAA ATT ACA AT-3- ; 2,896–2,918; R2, 5- -AAC TTC ATT ATT TCA TGC TCC T-3- , 3,189–3,169). Primers were based on GenBank accession number M14707 HAV wild type. Amplicons were sequenced on an AB 373 XL genetic analyzer (Applied Biosystems) using BigDye v.3.1 Terminator chemistry. MEGA 5.2.1 software version was used to determine the best-fit nucleotide substitution model for the current HAV sequences. Maximum Likelihood analysis was done by the recommended Tamura-Nei distance model using the discrete gamma distribution with default rate category 5 (+G) and modeled for invariant sites (+I) [15]. Meaningful taxonomic relationships were obtained by bootstrap resampling analysis (200 replicates).

Investigation of possible source

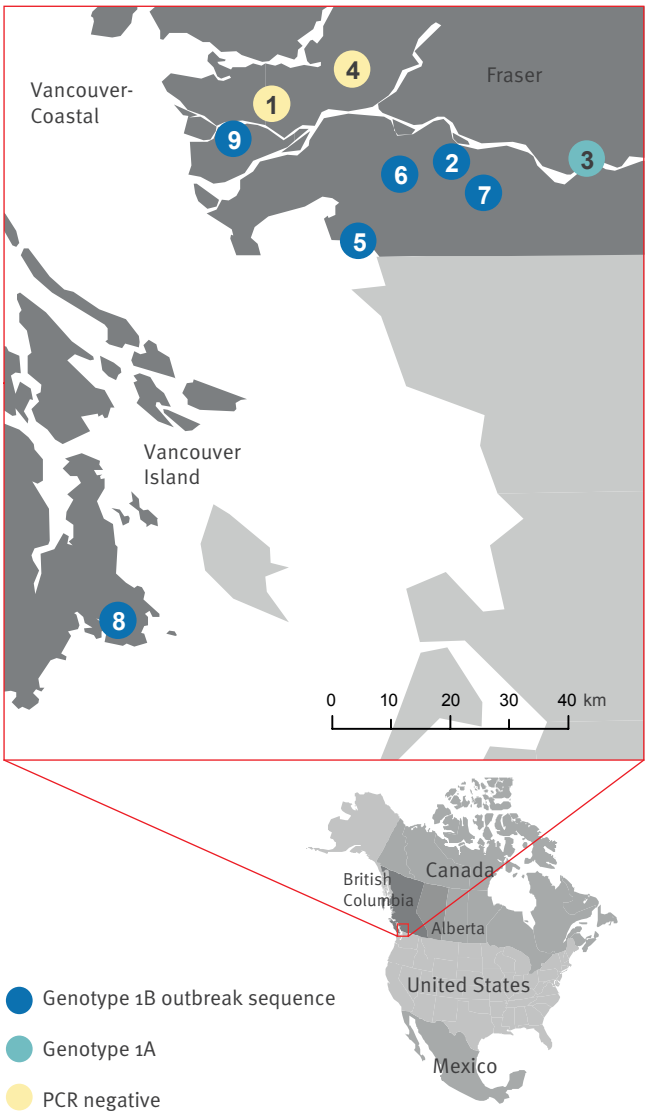
A provincially standardised questionnaire, focusing on common food shopping and dining experiences, was administered by telephone to cases. Case follow-up included evaluation of household and other contacts for symptoms and assessing the need for post-exposure prophylaxis. Based on an initial hypothesis that the common agent was a food product distributed only within the affected region, an enhanced questionnaire was then administered, again by telephone, further exploring locally produced and distributed food items.

In addition, authorisation was obtained from cases who shopped at major supermarket chains for those chains to release detailed shopping histories via the cases' store loyalty cards. Shopping histories going back three months were analysed to include products with an extended refrigerated or frozen storage life.

An investigation of the plant that produced the implicated food product included a review of shipping and purchase invoices, bills of lading (a legal document describing the merchandise in a shipment, confirming ownership and identifying the recipient), sources of ingredients and production records to determine

Figure 1

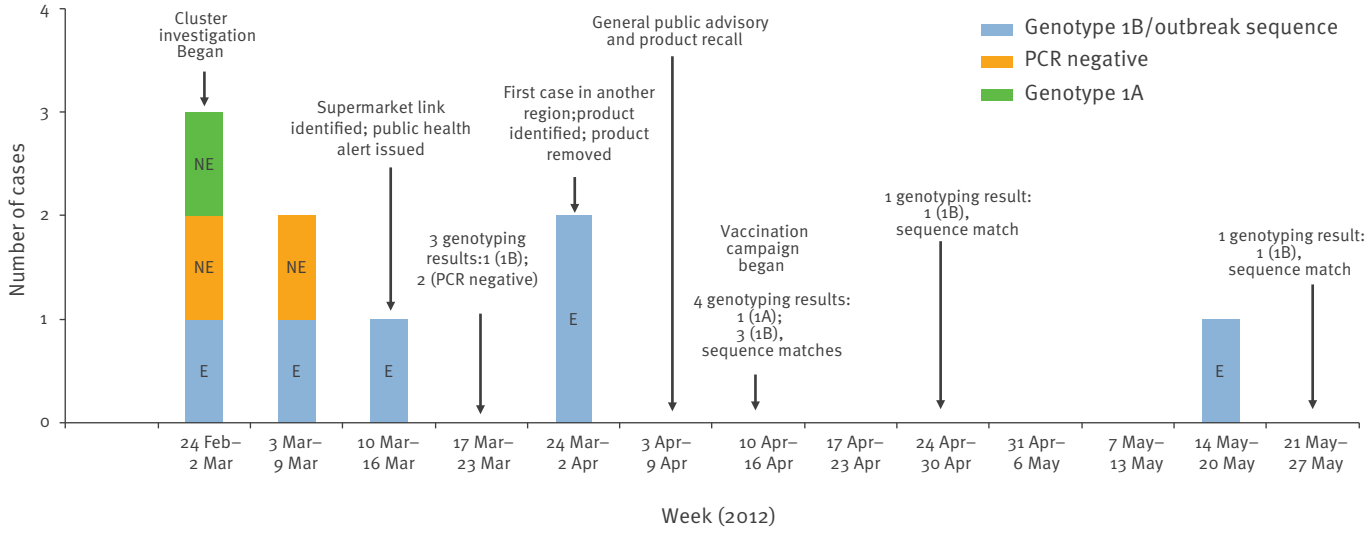
Location of non-travel-related hepatitis A cases reported to public health authorities, British Columbia, Canada, February–May 2012 (n=9)



The dots are oversized and represent the approximate place of residence of cases. They are offset by up to 500 m to avoid identification of the cases. The cases are numbered in order of the dates in which they were reported to the local public health authority. The first seven were reported in Fraser Health Authority, followed by one each in Vancouver Island (Case 8) [29] and Vancouver Coastal Health Authorities (Case 9).

Figure 2

Timeline of non-travel-related hepatitis A cases reported to public health authorities, British Columbia, Canada, February–May 2012



E: exposed; NE: not exposed.

production dates, worker travel and illness histories and distribution details of the product.

Several packages of the implicated product were tested: one open and one closed package from homes of two of the cases and a composite of five packaged units of the product obtained from the production facility. Samples of three of the four individual ingredients of the product from the manufacturer were available and tested for HAV by the Canadian Food Inspection Agency. Testing of implicated food products was conducted using magnetic cationic beads to capture and concentrate the viruses. Extracted viral RNA was subjected to a reverse-transcription PCR assay for HAV detection and quantification by real-time PCR.

Results

Detection of the outbreak

The investigation was triggered during the first week of March 2012, when three non-travel-related hepatitis A cases (Cases 1–3), residing in three different municipalities in BC located in one health authority, were identified within a week, based on laboratory reports to the local public health authority and subsequent public health follow-up (Figure 1). Three more cases (Cases 4–6) from three more municipalities in the same health authority were identified in the following two weeks (Figures 1 and 2). A further two cases (Cases 7 and 8) were identified later in March and a final case (Case 9) in May.

During this investigation, there were a total of nine possible outbreak cases (laboratory-confirmed HAV infection with no travel history). Symptoms included fever, nausea, abdominal pain, diarrhoea and jaundice; the onset dates ranged from the second week of February to the last week of April 2012. Dates of laboratory reports to the public health authorities ranged from the fourth week of February to the second week of May. Two cases were hospitalised.

Of the nine possible cases, six reported consumption of a frozen fruit blend; three did not. Analysis of the initial standard and enhanced questionnaire from these cases did not reveal any common activities, food purchases or consumption history above what would be expected for the general public.

Identifying the implicated food product

Food purchase histories obtained from the initial six possible cases showed that the majority (n=5) had shopped for groceries at a major chain of affiliated supermarkets. Analysis of loyalty card use indicated that three of the six cases had purchased the same frozen fruit blend at that retail chain. Consumption or not of the product was confirmed by interview for all six cases.

The outbreak team asked the chain to provide further details on production and distribution of this product in the third week of March 2012. It was a blend of raw frozen fruit (blueberries, strawberries, dark cherries and pomegranate seeds) in a 600 g package produced under a private house label for the supermarket chain and distributed to their stores in BC and the neighbouring province of Alberta. Multiple lot codes had been purchased by the cases. The chain

described the product as relatively uncommon, with sales of approximately 56,000 units of the product to 31,000 households throughout the two provinces during the four months before the query. With an average household size of 2.5 [16] and a total population of 8 million [17], approximately 1% of the population in the two provinces would have lived in households that had purchased the product.

Detection of further cases

By the end of March, a further two cases of hepatitis A who had consumed the frozen fruit blend were reported (Figure 1): one in the same health authority as the previous cases (Case 7) and the other, a food service worker, in another health authority (Case 8). Although only one genotype result was available at this time, based on the epidemiological information from cases and a product risk assessment conducted by the BC Centre for Disease Control in collaboration with the health authority in which the majority of cases occurred, a general public health advisory was issued on 5 April 2012 by the BC Centre for Disease Control [18]. This advisory included information that the product was available for sale or could be in the consumers' homes. Later the same day, the Canadian Food Inspection Agency also issued a Class I (high risk) Health Hazard Alert recalling the product [19,20]. This indicates a high risk that eating or drinking the product can lead to serious health problems [19,21]. This was triggered by a health risk assessment conducted by Health Canada consistent with weight of evidence standards [21] and based on the epidemiological information provided and collated by the health authorities and the BC Centre for Disease Control [20].

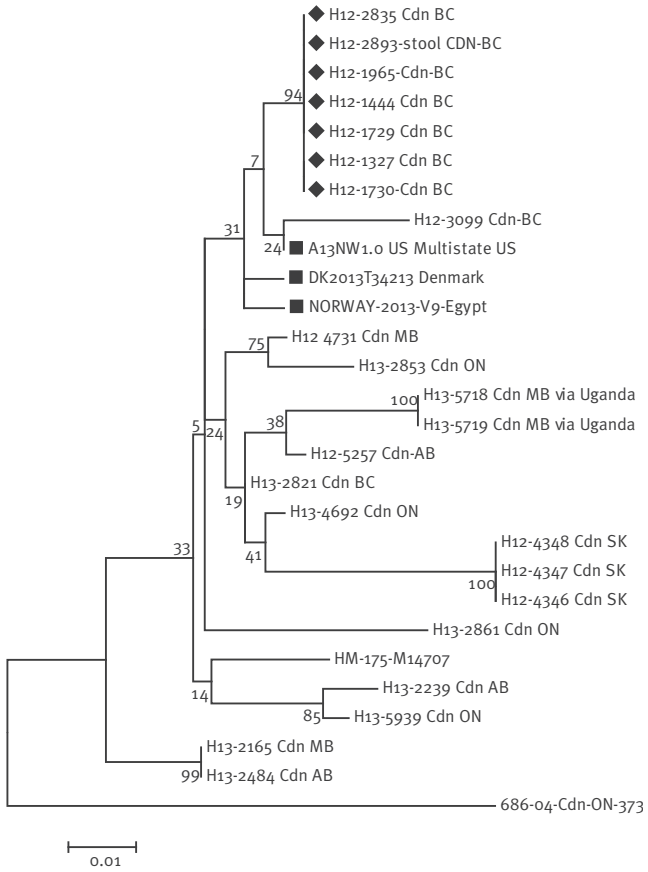
A final non-travel-related hepatitis A case (Case 9), who confirmed consumption of the implicated product, was identified in another health authority six weeks after the product recall, bringing the total number of possible outbreak cases to nine, six with the exposure and three without the exposure.

The six exposed cases were classed as confirmed outbreak cases, as they were found to be infected with HAV genotype 1B with matching genetic sequences. The sequence of the first identified case (H12-1327) used as a reference sequence for the outbreak has the GenBank accession number KF947077. Three of the six confirmed cases were male and three female. The median age was 32 years (range: 19–49).

Of the three non-exposed cases, the virus could not be genotyped for two of them; the virus from the third case was found to be genotype 1A and was therefore excluded as an outbreak case. There were no secondary cases. The outbreak strain was compared with available HAV strains from the United States (US) as well as some European strains in GenBank available at that time and was found to be unique (Figure 3).

Figure 3

Phylogenetic tree derived from sequences of the VP1-P2A junction of the hepatitis A virus genome of the 2012 British Columbia, Canada, outbreak strain and reference strains



HAV: hepatitis A virus.

Neighbour-joining phylogenetic tree showing the relationship between the British Columbia HAV outbreak strain with reference HAV strains (recent European and US HAV 1B sequences from GenBank and all Canadian genotype 1B samples from 2012 to 2013). Note that the stool sample H12-2893 and serum sample H12-2835 are from the same patient. HAV genotype 1A sequence (686-04-CDN-ON-373) located at the bottom of the tree is included as an outlier.

◆ British Columbia, Canada, HAV outbreak strain

■ Reference HAV strains

Public health measures

A general post-exposure immunisation campaign was initiated in April 2012 for individuals who had consumed the frozen fruit blend within two weeks, with a targeted campaign directed to customers potentially exposed to the virus through the case who worked at a food establishment (Case 8). These vaccinations were offered through the local public health authorities and communicated through news releases to media channels.

The plant that produced the frozen fruit blend was a federally registered facility located in the same region of BC as the majority of possible cases and subject to

regular inspection. Incoming products at the plant were routinely screened for bacterial contamination but not for viral pathogens. Investigation revealed the blueberries and strawberries in the implicated product were also used in a variety of other frozen products sold by several retailers under multiple brand names. The frozen fruit blend was the only one produced at the facility that contained cherries or pomegranate seeds. The cherries were imported from a supplier in Washington State in the US and the country of origin was not identified. The last shipment was received about four months before symptom onset of the first case. A shipment of pomegranate seeds used in the product was received 11 months before the outbreak from a supplier in Egypt. Records indicated that the Egyptian supplier had made only this single shipment to Canada in the previous year. These pomegranate seeds were used briefly upon arrival and then a switch was made to a US product. Use of the Egyptian product resumed when the US product ran out six months before the outbreak.

The investigation confirmed that the plant had a written staff illness policy requiring all ill staff to be off work (in context of food safety, illness was defined as gastrointestinal illness or any other illness that impedes the maintenance of good personal hygiene, such as respiratory illness). No staff illness relevant to food safety was reported in the 50 days before a site visit to investigate the outbreak in the first week of April. However, some of the workers at the manufacturing facility had a history of recent travel to HAV-endemic areas. Use of gloves, hairnets and gowns was mandated for production area staff and hand hygiene stations were readily available. Direct hand-to-product contact during packaging occurred only to remove unacceptable or poor-quality products from the packaging line. There was no HAV vaccination programme for workers but the hygiene conditions, procedures and processes observed during investigation were assessed as adequate to minimise the risk of HAV transmission from a potentially infected worker to food products.

Workers typically packaged multiple products for various clients on any given day. The suspect frozen fruit blend was produced to order for the supermarket chain. Each product order, estimated to be about two weeks apart, would take about two hours to package. The product was then sent to the chain's distribution warehouse, from where in turn it was distributed to their stores. The retailer voluntarily removed remaining stock of the product from sale, without public notification, the day before it was recalled, when they became aware from investigators that the product was under increased scrutiny as a possible source of this outbreak.

HAV was not identified in any packaged samples but was confirmed by PCR in one lot of pomegranate seeds obtained from the manufacturer of the frozen fruit blend; however, genotype analysis was not successful.

Discussion

Some of the largest food-borne outbreaks of hepatitis A in industrialised countries have been traced to produce [5]. As frozen fruit has a long shelf life (up to a year) and HAV has a long incubation period (up to 50 days), outbreaks may be identified only after large numbers of people have been exposed [4]. Outbreaks due to HAV-contaminated frozen fruit have recently been the cause of considerable morbidity: in April 2013, frozen strawberries were implicated in more than 70 cases of HAV infection in four Nordic countries [22,23] and as of 21 June 2013, an outbreak investigation in the US associated with a frozen berry and pomegranate mix confirmed 120 cases of HAV infection in eight states, of whom 54 (45%) were hospitalised [24].

HAV infection is a reportable communicable disease in BC and cases are routinely reported to the public health authorities. Low background rates of HAV infection, timely identification and reporting and well-communicated follow-up protocols that are used routinely in investigating cases of HAV infection in BC allowed early identification of this outbreak. In the previous year, there were 10 hepatitis A cases in the health authority mostly affected, six of whom were related to travel to HAV-endemic countries. Suspicion was raised in BC when three non-travel-related cases were noted in one health authority in one week; in the end, only one of the initial three cases was linked to the outbreak.

Case–control studies are the classical analytical study for food-borne outbreaks. In this outbreak, the weight of epidemiological evidence was deemed sufficient to implicate the frozen fruit as the cause of the outbreak and to trigger a product recall without resorting to an analytical study [21]. The two confirmed cases identified after the recall reported consumption of the frozen fruit blend. Of the three possible outbreak cases in which consumption of the product was not confirmed, one was identified to be infected with HAV genotype 1A and the other two remained possible cases as the HAV sequences could not be genotyped.

Published outbreaks of hepatitis A that have identified the virus in a specific product are generally much larger than this outbreak [22,24]. Identification of a specific food source can be difficult in outbreaks because of poor food history recall by cases following the long incubation period and the difficulty identifying HAV in food products. Use of loyalty card data from cases allows a more accurate food purchase history to be obtained than is possible through interviews [25]. Although these data cannot provide information on actual consumption, they can be used to supplement the interviews, to improve recall. Cooperation with the supermarkets was facilitated by well-established local processes [25] for obtaining food purchase histories and good working relationships between the provincial and regional health authorities as well as with the retailers.

Blends that contain a variety of fruits from a variety of sources are a challenge in terms of identifying a particular component that may be the source. In this outbreak in BC, identification of a specific cause was further complicated by the fact that some of the workers at the manufacturing facility had a history of recent travel to HAV-endemic areas. However, although several different products were manufactured each day at the facility and all the workers worked on multiple production lines, only the frozen fruit blend was implicated in the outbreak. Follow-up by the Canadian Food Inspection Agency determined that the contamination was unlikely to be linked to activities at the federally registered facility where the product was assembled. The investigation then focused on the cherries and pomegranate seeds, which were exclusive to the implicated product: HAV was detected in a sample of the source pomegranate seeds used in the product.

Genotypic confirmation of the virus in the food product could not be obtained, but this is consistent with other outbreaks where HAV sequencing has only occasionally been successful [10,26]. Very low viral load in the product may explain our inability to obtain genotypic confirmation and the very low number of cases in the approximately 31,000 potentially exposed households. Although the genotype was not ascertained, we consider that this outbreak was probably due to contamination of the pomegranate seeds. This is consistent with the suggestion of Hida et al. that water quality and handling procedures after harvest may play a role in disease transmission [13]. The geographical distribution of the cases was not consistent with the much broader geographical distribution of the implicated product. This delayed source attribution as the investigation initially considered only locally distributed products. Ultimately, no pattern of production or distribution could explain why most of the outbreak cases were restricted to one health authority within BC.

In Canada, over 90% of hepatitis A cases from whom the virus is typed are genotype 1A, with HAV genotype 1B making up less than 10% [27]. Recent outbreaks of hepatitis A associated with frozen fruits in Nordic countries and the US have likewise been 1B. Genetic similarity between these and the BC HAV 1B strain was high: 98.7% with the Danish, 98.6% with the Norwegian and 99.2% with the US strains. Although based on 373 nucleotides from the VP1-2A region, there was no bootstrap support for phylogenetic relatedness (Figure 3).

The very low number of cases in this outbreak, despite widespread purchase and probable consumption of the product, led to challenges in determining the appropriate response, both in terms of public messaging and offering vaccination. Approximately 3,000 vaccines were given in response to exposure to the food service worker and between 300 and 340 vaccines across the province in response to the alert for the implicated product. One confirmed case consumed the product after the recall had been issued, suggesting incomplete penetration of public health messaging. While the number of annual reported cases of hepatitis A is low in BC, seroprevalence of anti-HAV antibodies is also low [28], leading to the ongoing potential for outbreaks.

Fraser Health Environmental Health Investigation Team
Jason Stone, Steven Trerise, Shendra Brisdon, Ken Louie, Rod Asplin, Andrea Stiller, Tara Abraham, Inderjeet Singh Gill and George Rice.

Acknowledgments

Thanks to Elsie Grudeski (Public Health Agency of Canada), Eliza Yue (Canadian Food Inspection Agency), Marsha Taylor (BC Centre for Disease Control), Fraser Health Authority, Vancouver Coastal Health Authority and Vancouver Island Health Authority.

The authors would also like to acknowledge the work of Sunny Mak, BC Centre for Disease Control Medical Geographer, in creating the map in Figure 1.
Conflict of interest
None declared.

Authors' contributions

HS, BH and JAB led the epidemiological investigations at the local and provincial level. GE and the Fraser Health Environmental Health Investigation Team interviewed the initial cases and performed an environmental investigation. MK drafted the manuscript. AA was in charge of the laboratory genotyping. HS, AA, BH, JAB and GE critically reviewed the draft manuscript and provided substantive input. All authors contributed to the epidemiological investigation and writing of the manuscript and approved the final version.

References

1. British Columbia Centre for Disease Control (BCCDC). Communicable disease control. Hepatitis A. August 2008. Vancouver: BCCDC. [Accessed 5 May 2014]. Available from: http://www.bccdc.ca/NR/rdonlyres/92CF634C-23D6-4B49-B6BA-98B83C77FF00/0/HepA_August_2008.pdf
2. British Columbia Centre for Disease Control (BCCDC). 2011 Annual summary of reportable diseases. Vancouver: BCCDC. [Accessed 15 Apr 2014]. Available at: http://www.bccdc.ca/util/about/annreport/default.htm
3. British Columbia Centre for Disease Control (BCCDC). Hepatitis A in British Columbia, 2010 – 2011. Vancouver: BCCDC. [Accessed 15 Apr 2014]. Available from: http://www.bccdc.ca/NR/rdonlyres/BAFDED8C-77EA-4493-A3A9-6AD7483A65D6/0/HepatitisAUpdateBC20102011.pdf
4. Heymann DL. Hepatitis, viral. In: Control of communicable diseases manual. 19th ed. Washington, DC: American Public Health Association; 2008. p. 278-84.
5. Hutin YJ, Pool V, Cramer EH, Nainan OV, Weth J, Williams IT, et al. A multistate outbreak of hepatitis A. National hepatitis A investigation team. N Engl J Med. 1999;340(8):595-602. http://dx.doi.org/10.1056/NEJM199902253400802
6. Tricco AC, Pham B, Duval B, De Serres G, Gilca V, Vrbova L, et al. A review of interventions triggered by hepatitis A infected food-handlers in Canada. BMC Health Serv Res. 2006;6:157. http://dx.doi.org/10.1186/1472-6963-6-157
7. Wheeler C, Vogt TM, Armstrong GL, Vaughan G, Weltman A, Nainan OV, et al. An outbreak of hepatitis A associated with green onions. N Engl J Med. 2005;353(9):890-7. http://dx.doi.org/10.1056/NEJMoa050855
8. Amon JJ, Devasia R, Xia G, Nainan OV, Hall S, Lawson B, et al. Molecular epidemiology of foodborne hepatitis A outbreaks in the United States , 2003. J Infect Dis. 2005;192(8):1323-30. http://dx.doi.org/10.1086/462425
9. Calder L, Simmons G, Thornley C, Taylor P, Pritchard K, Greening G, Bishop J, et al. An outbreak of hepatitis A

associated with consumption of raw blueberries. Epidemiol Infect. 2003;131(1):745-51. http://dx.doi.org/10.1017/S0950268803008586

10. Niu MT, Polish LB, Robertson BH, Khanna BK, Woodruff BA, Shapiro CN, et al. Multistate outbreak of hepatitis A associated with frozen strawberries. J Infect Dis. 1992;166(3):518-24. http://dx.doi.org/10.1093/infdis/166.3.518
11. Carvalho C, Thomas HL, Balogun K, et al. A possible outbreak of hepatitis A associated with semi-dried tomatoes, England, July–November 2011. Euro Surveill. 2012;17(6):pii=20083.
12. Coudray C, Merle G, Martin-Latil S, Guillier L, , Perelle S. Comparison of two extraction methods for the detection of hepatitis A virus in lettuces using the murine norovirus as a process control. J Virol Methods. 2013;193(1):96-102. http://dx.doi.org/10.1016/j.jviromet.2013.05.003
13. Hida K, Kulka M, Papafragkou E. Development of a rapid total nucleic acid extraction method for the isolation of hepatitis A virus from fresh produce. Int J Food Microbiol. 2013;161(3):143-50. http://dx.doi.org/10.1016/j.ijfoodmicro.2012.12.007
14. Chironna M, Lopalco P, Prato R, Germinario C, Barbuti S, Quarto M. J Clin Microbiol. 2004;42(6):2825-8. http://dx.doi.org/10.1128/JCM.42.6.2825-2828.2004
15. Tamura K, Stecher G, Peterson D, Filipski A, Kumar S. MEGA6: Molecular Evolutionary Genetics Analysis version 6.0. Mol Biol Evol. 2013:30(12):2725-9. http://dx.doi.org/10.1093/molbev/mst197
16. Statistics Canada. Household size, by province and territory (2011 census) (Manitoba, Saskatchewan, Alberta, British Columbia). Ottawa: Statistics Canada. [Accessed 9 Dec 2013]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/lo1/cst01/famil53c-eng.htm
17. Statistics Canada. Population and dwelling counts, for Canada, provinces and territories, 2011 and 2006 censuses. Ottawa: Statistics Canada. [Accessed 9 Dec 2013]. Available from: http://www12.statcan.gc.ca/census-recensement/2011/dp-pd/hlt-fst/pd-pl/Table-Tableau.cfm?LANG=Eng&T=101&S=50&O=A
18. British Columbia Centre for Disease Control (BCCDC). Pomeberry frozen berries may contain hepatitis A. Vancouver: BCCDC; 5 April 2012. Available from: http://www.bccdc.ca/resourcematerials/newsandalerts/healthalerts/2012HealthAlerts/Pomeberry+frozen+berries+may+contain+hepatitis+A.htm
19. Canadian Food Inspection Agency (CIFA). The Canadian food safety system: food recalls. Ottawa: CIFA. [Accessed 222 Apr 2014]. Available from: http://www.inspection.gc.ca/about-the-cfia/newsroom/food-safety-system/food-recalls/eng/1332206599275/1332207914673
20. Canadian Food Inspection Agency (CIFA). Health Hazard Alert - Certain Western Family brand Pomeberry Blend berries may contain hepatitis A virus. 5 April 2012. Ottawa: CIFA. [Accessed 15 Apr 2013]. Available from: http://www.inspection.gc.ca/english/corpaffr/recarapp/2012/20120405de.shtml
21. Health Canada. Weight of evidence: factors to consider for appropriate and timely action in a foodborne illness outbreak investigation. Ottawa: Health Canada; Jan 2011. Available from: http://www.hc-sc.gc.ca/fn-an/pubs/securit/2011-food-illness-outbreak-eclosion-malad-ailments/index-eng.php
22. Gillesberg Lassen S, Soborg B, Midgley SE, Steens A, Vold L, Stene-Johansen K, et al. Ongoing multi-strain food-borne hepatitis A outbreak with frozen berries as suspected vehicle: four Nordic countries affected, October 2012 to April 2013. Euro Surveill. 2013;18(17):pii=20467.
23. Nordic outbreak investigation team. Joint analysis by the Nordic countries of a hepatitis A outbreak, October 2012 to June 2013: frozen strawberries suspected. Euro Surveill. 2013;18(27):pii=20520.
24. Centers for Disease Control and Prevention (CDC). Multistate outbreak of Hepatitis A infections linked to pomegranate seeds from Turkey (final update). Atlanta, GA: CDC; 28 Oct 2013. Available from: http://www.cdc.gov/hepatitis/Outbreaks/2013/A1b-03-31/
25. Shah L, MacDougall L, Ellis A, Ong C, Shyng S, LeBlanc L, et al. Challenges of investigating community outbreaks of cyclosporiasis, British Columbia, Canada. Emerg Infect Dis. 2009;15(8):1286-8. http://dx.doi.org/10.3201/eid1508.081585
26. Petrignani M, Verhoef L, van Hunen R, van Steenbergen J, Boxman I, Ober HJ, et al. A possible foodborne outbreak of hepatitis A in the Netherlands, January-February 2010. Euro Surveill. 2010;15(11):pii=19512.
27. Andonov A, Grudeski E, Morbey M. Molecular epidemiology of hepatitis A virus (HAV) in Canada. Proceedings of the Canadian Association for Clinical Microbiology and Infectious Diseases (CACMID) 72nd Conjoint Meeting on Infectious Diseases; 2004 Nov 7-10; Regina, Saskatchewan. Abstract, p. 44.
28. Pham B, Duval B, De Serres G, Gilca V, Tricco AC, Ochnio J, et al. Seroprevalence of hepatitis A infection in a low endemicity country: a systematic review. BMC Infect Dis. 2005;5:56. http://dx.doi.org/10.1186/1471-2334-5-56
29. Island Health. Hepatitis A immunizations available To Fairway Markets Quadra location employees and members of the public. Victoria: Island Health; 31 Mar 2012. Available from: http://www.viha.ca/about_viha/news/news_releases/hep_a_nr_march12.htm

Note from the editors: WHO declares international spread of wild poliovirus a public health emergency of international concern

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. Note from the editors: WHO declares international spread of wild poliovirus a public health emergency of international concern. Euro Surveill. 2014;19(18):pii=20798. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20798

Article published on 08 May 2014

On 5 May 2013, based on the advice of the International Health Regulations Emergency Committee and its expert advisors, the World Health Organization (WHO) declared that the situation related to the international spread of wild poliovirus constitutes a Public Health Emergency of International Concern (PHEIC) [1].

The declaration followed an assessment of the poliovirus situation in 2014 as of 26 April and included updates from countries affected, namely Afghanistan, Cameroon, Equatorial Guinea, Ethiopia, Israel, Nigeria, Pakistan, Somalia and the Syrian Arab Republic. It concluded that the current situation required coordinated international response because this situation could result in failure to eradicate polio globally.

Currently 10 countries worldwide are affected by active transmission of polio: Afghanistan, Equatorial Guinea, Ethiopia, Iraq, Israel, Somalia and Nigeria, with three of them Cameroon, Pakistan and Syria and Cameroon, having exported polio cases in 2014.

Based on advice from the Emergency Committee, the WHO issued temporary recommendations under the International Health Regulations (IHR 2005) to reduce the international spread of wild poliovirus, effective from 5 May 2014, for 'States infected with wild poliovirus but not currently exporting' and 'States currently exporting wild polioviruses'.

For the exporting countries WHO's temporary recommendation is to ensure that residents and long-term visitors receive a dose of oral poliovirus vaccine (OPV) or inactivated poliovirus vaccine (IPV) four weeks to 12 months before international travel.

The European Centre for Disease Prevention and Control has assessed the risk of polio importation for Europe and published regularly updated risk assessments on its website [2].

References

1. World Health Organization (WHO). WHO statement on the meeting of the International Health Regulations Emergency Committee concerning the international spread of wild poliovirus. Geneva: WHO; 2014. Available from: http://www.who.int/mediacentre/news/statements/2014/polio-20140505/en/
2. European Centre for Disease Prevention and Control (ECDC). Available from: http://ecdc.europa.eu/en/publications/Publications/polio-international-spread-rapid-risk-assessment.pdf

European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) 2014 - call for abstracts

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 Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) 2014 - call for abstracts. Euro Surveill. 2014;19(18):pii=20794. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20794

Article published on 08 May 2014

The eighth European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) will take place in Stockholm, Sweden from 5 to 7 November 2014.

As every year, ESCAIDE 2014 will bring together public health professionals from Europe and the rest of the world to present and discuss developments in infectious disease prevention and control.

The call for abstracts for the conference is now open, and abstracts can be submitted via the dedicated 'call for abstracts' portal on the ESCAIDE website (http://www.escaide.eu/). The closing date for submissions is 25 May 2014.

Abstracts are welcomed in all areas related to infectious disease intervention, including epidemiology, public health microbiology, surveillance, vaccinology and the application of tools and methods to prevent and control communicable diseases.

The final programme details and conference registration instructions will be posted soon on the ESCAIDE website.

For further information, contact:
escaide.conference@ecdc.europa.eu