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Surveillance of avian influenza A(H7N9) virus infection in humans and detection of the first imported human case in Taiwan, 3 April to 10 May 2013

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On 3 April 2013, suspected and confirmed cases of influenza A(H7N9) virus infection became notifiable in the primary care sector in Taiwan, and detection of the virus became part of the surveillance of severe community-acquired pneumonia. On 24 April, the first imported case, reported through both surveillance systems, was confirmed in a man returning from China by sequencing from endotracheal aspirates after two negative throat swabs. Three of 139 contacts were ill and tested influenza A(H7N9)-negative.

The Taiwan Centers for Disease Control (TCDC) listed avian influenza A(H7N9) virus infection in humans as a nationally notifiable disease on 3 April 2013 [1], after the Chinese authorities had on 31 March 2013 announced the identification of two male influenza cases in Shanghai and one female case in Anhui with severe respiratory disease caused by an avian influenza A(H7N9) virus that had not previously been detected in humans or animals [2]. The viruses had genetic markers known to be associated with adaptation to mammalian hosts and respiratory transmission of avian influenza viruses, raising concerns about their pandemic potential [2]. The probability of introduction of this virus into Taiwan is considered high because of geographic proximity and more than 90,000 personal or business travels from Shanghai and Anhui to Taiwan per month. This report summarises Taiwan's surveillance for avian influenza A(H7N9) virus infection in humans in the period from 3 April to 10 May 2013.

Influenza surveillance in Taiwan

The National Influenza Surveillance System (NISS) in Taiwan consists of virological surveillance by sentinel primary care physicians, syndromic surveillance of influenza-like illness in emergency and outpatient departments, and surveillance of influenza with complications reported through the National Notifiable Disease Surveillance System. These surveillance activities have been described [3,4]. On 3 April 2013, the TCDC added human infection with avian influenza A(H7N9) virus into the National Notifiable Disease Surveillance System to detect suspected and confirmed cases in the primary care sector. Before 3 April 2013, specimens positive for untypeable influenza A submitted through NISS were routinely tested for influenza A(H5) by realtime RT-PCR. Since 3 April 2013, such specimens have in addition been routinely tested by RT-PCR for influenza A(H7). The TCDC has also conducted surveillance of severe community-acquired pneumonia (CAP) of unknown aetiology since 2010. We focused on these two surveillance activities in this report.

Surveillance of influenza A(H7N9) virus infection in the primary care sector

The maximal incubation period of influenza A(H7N9) was defined as seven days in the period from 3 to 25 April and was revised as 10 days on 26 April based on a recent study [5]. Contacts were defined as those who had provided care to, had been in the same place with, or had directly exposed to respiratory secretions or body fluids of a case since the day before illness onset of the case.

A suspected influenza A(H7N9) case was defined as a person with onset of pneumonia or fever (≥38 oC) with cough within the maximal incubation period of at least one the following exposures: (i) contact with a confirmed case; (ii) travel to provinces or cities in China where human infections with the avian influenza A(H7N9) virus have been reported; (iii) exposure to human, animal or environmental specimens or laboratory samples that are suspected or confirmed to contain the influenza A(H7N9) virus. A case was confirmed if tested positive for the influenza A(H7N9) virus by RT-PCR and/or culture at TCDC.

Physicians were required to report suspected cases to their local health departments within 24 h of identification and to submit nasopharyngeal or oropharyngeal swabs of all suspected cases to TCDC for influenza

testing. Local public health professionals verified case characteristics including presenting symptoms, dates of illness onset, underlying medical conditions, and exposure to poultry based on the physicians' reports and interviews with the patients or their parents.

Contact persons were identified through interviews with patients and their family and through hospital records. All contacts were interviewed for dates and mode of the exposure as well as and protective measures, and followed up daily for fever and respiratory symptoms during the maximal incubation period after last exposure.

Surveillance of influenza A(H7N9) virus in severe pneumonia of unknown aetiology

Surveillance of severe CAP of unknown aetiology has been established in Taiwan since 2010. Physicians from 29 hospitals (including 13 tertiary referral hospitals) were requested to submit respiratory specimens from CAP patients with respiratory failure for whom no aetiologic pathogen had been identified through general clinical investigations. Submitted specimens were tested for viruses using a specifically designed multiplex PCR panel targeting influenza A(H1N1), A(H3N2) and B viruses, parainfluenza viruses 1–3, adenovirus, respiratory syncytial virus (A and B), human bocavirus, human coronavirus (229E, NL63, OC43, and HKU1), enterovirus, rhinovirus, human metapneumovirus, parvovirus B19, and viruses of the human Herpesviridae. Since 3 April, influenza A(H7) virus has been incorporated into the multiplex PCR panel as a supplementary target for all cases of severe CAP of unknown aetiology. Retrospective testing of influenza A(H7) virus was also conducted on stored samples from cases of severe CAP of unknown aetiology reported from 1 January to 2 April 2013.

Laboratory testing of influenza A(H7N9) virus

Viral culture was performed on respiratory specimens using Madin Darby canine kidney cells. The RT-PCR for influenza A and B viruses and subtyping of human influenza A(H1N1) and A(H3N2) have been described before [6]. Subtyping of influenza A(H7N9) viruses was conducted with the protocol provided by the World Health Organization Collaborating Center for Reference and Research on Influenza [7].

Case description

In the period from 3 April to 10 May, TCDC was notified of 358 suspected human cases of avian influenza A(H7N9) virus infection and 41 cases of severe CAP of unknown aetiology, including one confirmed case reported through both of the surveillance systems. Of the 357 suspected cases that tested negative for influenza A(H7), 49 tested positive for influenza A(H1N1), 29 tested positive for influenza A(H3N2), and five tested positive for influenza B. Of the 88 cases of severe CAP of unknown aetiology reported in the period from 1 January to 10 May, 47 cases were negative in all tests, 16 were positive for influenza virus (13A(H1N1) , two A(H3N2), and one A(H7N9)), and 25 were positive for other viruses (details not presented because the review of the medical records is still outstanding). None of the specimens submitted through other NISS surveillance activities from 3 April to 10 May tested positive for influenza A(H7) viruses.

The confirmed case occurred in a man in his 50s who returned from Jiangsu Province, China on 9 April. The clinical course has been described in details elsewhere [8]. The patient experienced fever and general malaise without respiratory symptoms on 12 April, first sought medical attention on 16 April because of high fever (40 oC) and mild sore throat, and was reported as a suspected influenza A(H7N9) case on 16 April. A throat swab collected on 16 April tested negative for influenza A(H7N9) virus by RT-PCR. Right lower lobe interstitial pneumonia developed on 18 April and progressed to bilateral lower lung consolidation and respiratory failure on 20 April. The patient was reported to TCDC on 21 April as severe pneumonia of unknown aetiology and a throat swab was collected and submitted to TCDC on the same day for testing by RT-PCR; this sample was negative for influenza A(H7N9) virus. Endotracheal aspirates collected on 20 April tested positive for influenza A on 22 April and were subtyped as influenza A(H7N9) in the evening of 23 April at a university research laboratory. On 24 April, influenza A(H7N9) virus infection was confirmed by positive influenza A(H7N9) RT-PCR and sequencing at the TCDC National Influenza Center on endotracheal aspirates collected in the late evening of 23 April. As of 10 May, the patient had made a good recovery; mechanical ventilation had been removed.

All of 139 contact persons of this case, including three family contacts, 26 casual contacts (colleagues and friends), and 110 healthcare workers, were followed up for 10 days after last exposure. Three healthcare workers at the intensive care unit experienced respiratory symptoms within two to three days after providing routine nursing care to the patient, using N95 respirators, goggles, gloves and protective clothing. Throat swabs collected from all three symptomatic contacts on April 24 tested negative for influenza A(H7N9) virus by RT-PCR. Further epidemiological and laboratory investigations of this confirmed case and close contacts are ongoing.

Discussion

This first human influenza A(H7N9) case outside China provided important lessons on public health surveillance and detection of human influenza A(H7N9) cases. Firstly, influenza A(H7N9) RT-PCR was negative on two throat swabs collected on Day 4 and Day 9 after illness onset, but was positive on endotracheal aspirates collected on Day 8 after onset. The findings are consistent with a recent study based on four cases, that indicated sputum specimens were more likely to test influenza A(H7N9)-positive than throat swabs [9]. As a result, TCDC revised the sampling guidance on 26

April to include sputum, endotracheal aspirates and other lower airway specimens, in addition to pharyngeal swabs, as recommended specimens for collection in suspected reported influenza A(H7N9) cases with productive cough, pneumonia or other complications. TCDC also recommended that physicians submit follow-up respiratory specimens in suspected influenza A(H7N9) cases with progressive disease after initially negative test results.

Secondly, the patient presented with fever but no cough. Although the presenting symptoms did not meet our case definitions, his clinician decided to report the case based on recent travel in eastern China and fever with sore throat, and the reporting was accepted by our surveillance system. The case presentation was different from that of the first three influenza A(H7N9) cases reported in China, all of whom presented with fever and cough [2]. However, adult and paediatric influenza A(H7N9) cases that presented without cough have been reported [10,11]. This illustrates possible limitations of current case definitions using fever and cough as one of the clinical criteria. Although inclusion of respiratory symptoms other than cough might improve sensitivity of the case definitions, broader clinical criteria might not necessarily lead to strengthened case confirmation, if testing on pharyngeal specimens at an early stage is not sensitive for influenza A(H7N9) virus detection. Alternatively, as exemplified by this case, physicians should be allowed to report suspected cases that do not fully meet the case definitions.

Further studies that characterise influenza A(H7N9) virus infection in humans will provide evidence for public health practices of case detection. For example, because a recent study showed maximal intervals of 10 days between poultry exposure and illness onset in influenza A(H7N9) cases [5], T CDC revised case definitions on 26 April to extend the maximal incubation period to 10 days. Studies that examine viral positivity at different anatomic sites and shedding over the disease course in comparison with seasonal influenza, such as previous studies on pandemic influenza A(H1N1)pdm09, could provide guidance for laboratory testing and monitoring of influenza A(H7N9) cases [12-14].

Conclusions

This first imported human influenza A(H7N9) case in Taiwan was reported through both the National Notifiable Disease Surveillance and severe CAP surveillance systems. Laboratory confirmation was achieved through astute pursuit of laboratory diagnoses by physicians, testing a deep endotracheal sample despite two earlier negative throat swabs and absence of cough as the initial presentation. A flexible surveillance system allows for timely revision of case definitions and sampling guidance. Sensitivity in case detection is likely to improve with collection of sputum, endotracheal aspirates, or other lower airway specimens in addition to pharyngeal swabs. Retrospective testing of severe CAP cases since January 2013 did not demonstrate any earlier influenza A(H7N9) cases. Preliminary results of contact investigations indicated no evidence of person-to-person transmission. We recommend rapid communication and dissemination of results of epidemiological and virological studies to ensure evidence-based surveillance and detection of influenza A(H7N9) virus infection.

Authors' contributions

Yi-Chun Lo, Wan-Chin Chen, Wan-Ting Huang, Yung-Ching Lin, and Ming-Chih Liu prepared the first draft of this manuscript. Hung-Wei Kuo, and Jen-Hsiang Chuang provided the surveillance data. Ji-Rong Yang, Ming-Tsan Liu, and Ho-Sheng Wu provided the virological data. Chin-Hui Yang, Jih-Haw Chou, Feng-Yee Chang interpreted the surveillance and virological data. All authors reviewed and revised the first and final drafts of this manuscript.

Conflict of interest

None declared.

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Epidemiological link between exposure to poultry and all influenza A(H7N9) confirmed cases in Huzhou city, China, March to May 2013

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We analysed the association between influenza A(H7N9) confirmed cases and exposure to poultry in Huzhou city, China. All cases (n=12) had a history of direct exposure to poultry or live poultry markets. We detected A(H7N9)-positive poultry samples from each site that was epidemiologically associated with cases. None of the cases' close contacts tested positive. After closure of the markets, no new cases were identified, suggesting an epidemiological link between poultry exposure and A(H7N9) virus infection.

Background

Since February 2013, a novel avian influenza A(H7N9) virus has led to an outbreak in the Yangtze River Delta Region and elsewhere in China [1,2]. As of 10 May 2013, it has resulted in 129 cases, including 31 deaths. Sporadic human infections by several H7 subtypes of influenza A viruses (e.g. H7N2, H7N3 and H7N7) had been reported previously in several countries in Europe and North America [3]. Apart from an influenza A(H7N7) outbreak in the Netherlands in 2003, infections with these H7 subtypes usually result in a mild, self-limiting illness [3]. In contrast, in the current influenza A (H7N9) outbreak, infection with the virus has resulted in severe and fatal respiratory disease [2,4] – the first time human infections have been seen for this virus [1]. The origin of the virus has been demonstrated to be associated with a reassortant event between three earlier avian influenza viruses [1,5]. Its genome comprises a haemagglutinin (HA) fragment from A(H7N3), a neuraminidase (NA) fragment from an earlier A(H7N9) virus and six internal genomic fragments from A(H9N2).

Two recent studies have provided compelling evidence that the novel A(H7N9) viruses from patients have a close genetic relationship with isolates from poultry [6,7], suggesting that the A(H7N9) virus may have spread to humans from poultry. However, preliminary epidemiological data showed that 18 of 77 confirmed cases did not have a history of contact with poultry [2]. Therefore, it remains to be determined whether there is a direct epidemiological link between exposure to poultry and human A(H7N9) virus infection.

Huzhou city, located in northern Zhejiang Province, China, is the geographical centre of the Yangtze River Delta (Figure 1). As of 10 May, 12 confirmed A(H7N9) cases have been reported in Huzhou city, accounting for about 9% (12/129) of all cases in China. There are two natural wetlands that provide habitats for over a 160 kinds of wild birds and, until the markets were closed, there had been an active live poultry business in Huzhou city. Therefore, we performed a detailed epidemiological study of the links between the confirmed cases and prior exposure to poultry.

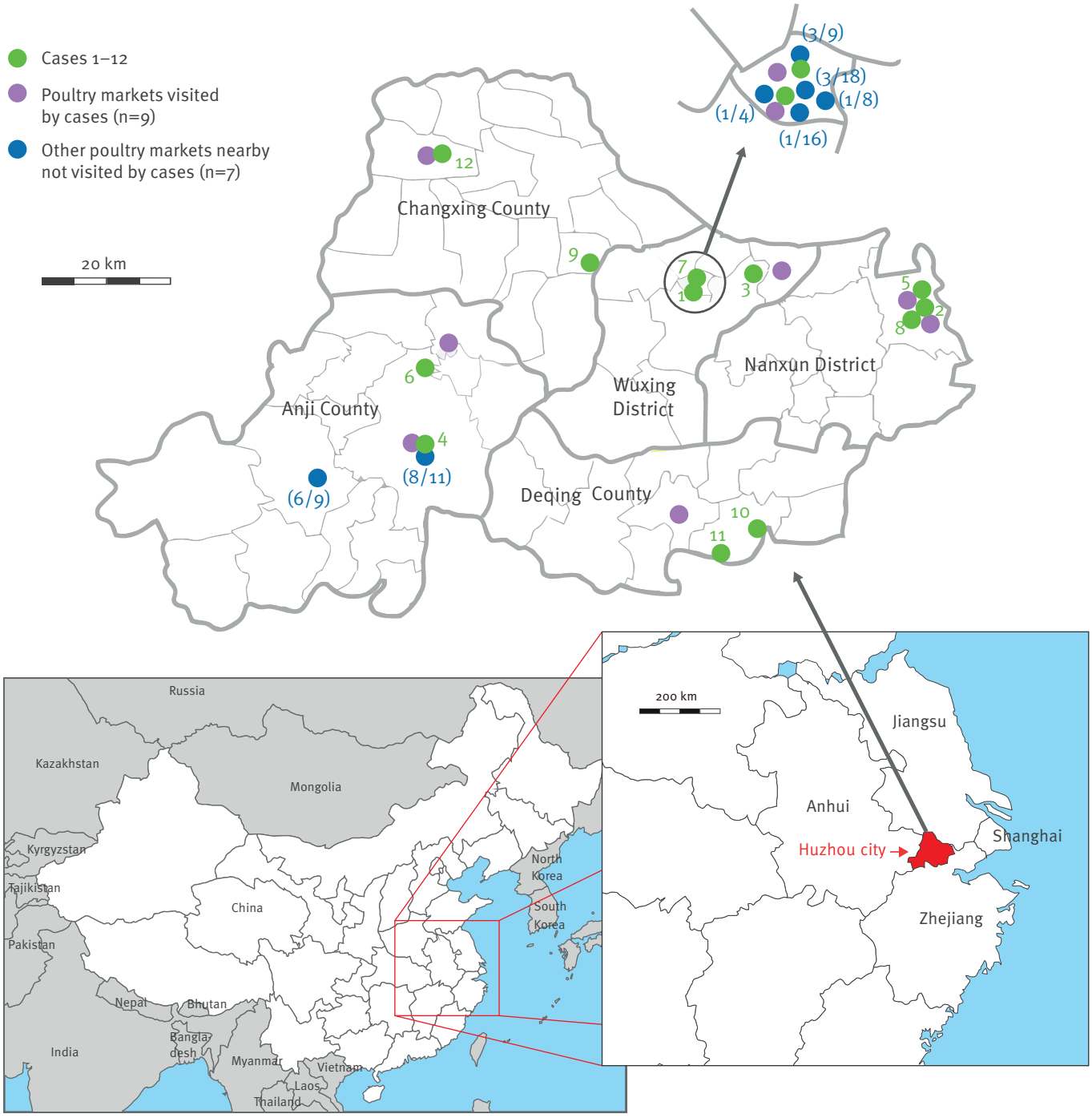
Data collection

A total of 12 persons were identified as influenza A(H7N9) confirmed cases, according to the definition in the national guidelines [8]. The infection was laboratory confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis [9].

A close contact was defined as a person who came within two metres of a confirmed case without the use of effective personal protective equipment (e.g. masks and gloves) during the presumed infectious period. The close contacts included, among others, the cases' families and clinical staff (doctors and nurses) who had been in contact with the cases. All close contacts were traced and quarantined for seven days after their most recent exposure to a confirmed case.

Figure 1

Distribution of the influenza A(H7N9) confirmed cases and live poultry markets in Huzhou city, China, March–May 2013



For markets that the cases did not visit, the numbers of the samples positive for influenza A(H7N9) virus are shown (number of positive/number of total samples). The results for the markets that the cases visited are shown in Table 1.

In our investigation, a 'visit' included only occasions in which a case either bought poultry, or had been close to (within a distance of two metres) or touched live poultry booths at the market.

Information on cases' demographic characteristics, dates of symptom onset, exposure to poultry and/or other animals and/or visits to a live poultry market during the 10 days before symptom onset, as well as clinical signs and symptoms were collected using a standardised questionnaire and an open interview with the cases or their relatives when the cases were admitted to hospital. In our investigation, a 'visit' included only occasions in which a case either bought poultry, or had been close to or touched live poultry booths at a market.

To determine the source of the influenza A(H7N9) virus, we collected poultry faeces, waste (swab samples from culling benches) and sewage from the nine live poultry markets visited by the cases, for detection of A(H7N9) viral RNA by real-time RT-PCR.

In addition, samples from several surrounding live poultry markets (n=7) not visited by cases were also collected.

Data analysis

Demographic and clinical characteristics of influenza A(H7N9) cases in Huzhou city

As of 10 May 2013, 12 influenza A(H7N9) cases (four were male and eight female) were confirmed in Huzhou city (Table 1). As of 30 April, two had died, four had recovered fully, two were recovering and the other four remained critically ill (Figure 2). The median age was 60 years (range: 32–81) and most (n=9) were aged over 50 years.

The first case developed symptoms on 29 March 2013; the infection was laboratory confirmed on 4 April [6]. In fact, another patient (Case 2) became ill earlier, on 12 March, but the infection was not laboratory confirmed until 8 April. The last two patients (Cases 11 and 12) both became ill on 17 April and were laboratory confirmed on 25 and 26 April, respectively. The initial symptoms were fever (axillary temperature greater than 37.5 °C) (n=7), cough (n=4), myalgia (n=4), chills

Table 1

Demographic and exposure information of influenza A(H7N9) confirmed cases in Huzhou city, China, March–May 2013 (n=12)

Case number	Sex	Age (years)	Visits to live poultry markets[a] during 10 days before symptom onset		Testing for A(H7N9) viral RNA by real-time RT-PCR in markets visited by cases			Testing for A(H7N9) viral RNA by real-time RT-PCR in close contacts of cases	
			Date of last visit (2013)	Number of visits	Number of markets	Number of samples	Number of positive samples	Number of close contacts	Number who were positive
1	Male	64	NA	10	1	21	6	55	0
2	Female	50	NA	4	1	2	2	68	0
3	Female	54	NA	1	1	12	2	26	0
4	Female	61	31 March	1	1	17	5	26	0
5	Female	64	4 Apr	4	1[b]	19	7	57	0
6	Female	66	30 March	4	1	18	3	35	0
7	Male	41	8 April	0[c]	1	18	5	6	0
8	Female	66	3 April	1	1[b]	19	7	4	0
9	Female	81	None	0	NA[d]	10	2	53	0
10	Male	32	NA	6	1	6[e]	2	9	0
11	Female	60	None	0	NA[f]	6	2	8	0
12	Male	38	NA	2	1	6	2	22	0
Total	–	–	–	**33**	**9**	**135**	**38**	**339**	**0**

NA: not available; RT-PCR: reverse transcription-polymerase chain reaction.

[a] In our investigation, a 'visit' included only occasions in which a case either bought poultry, or had been close to (within a distance of two metres) or touched live poultry booths at a market.

[b] Cases 5 and 8 visited, on separate occasions, the same live poultry market.

[c] Although this case did not purchase poultry, he took part in a government campaign of culling poultry at a live poultry market to limit the transmission of the novel influenza A(H7N9) virus, for about three hours on 8 April 2013.

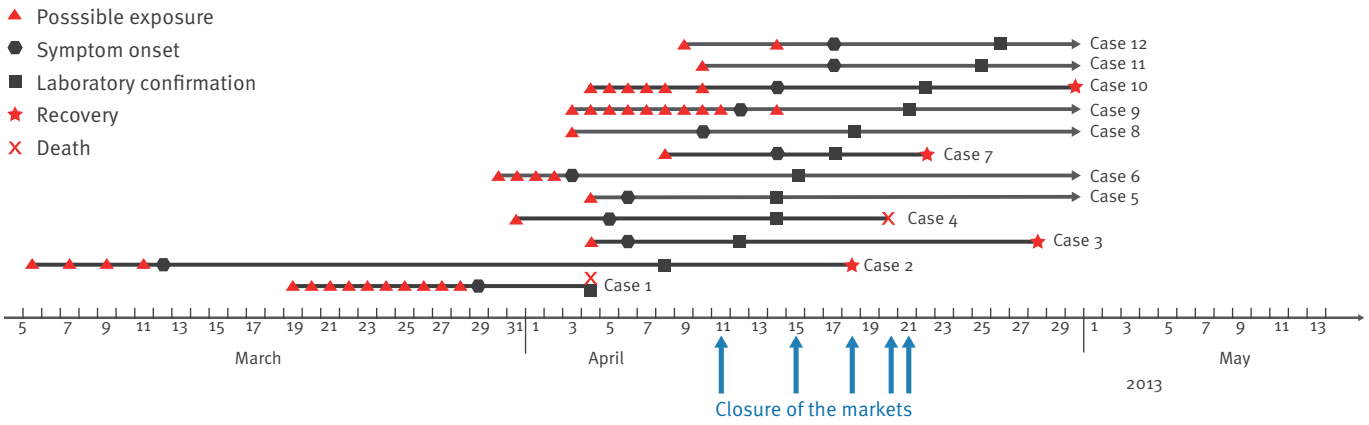
[d] This case did not visit a live poultry market. She raised chickens in a courtyard with her neighbour. Because the case slaughtered all her chickens, we collected 10 samples from five chickens raised by her neighbour.

[e] Pigeon-related samples. All other samples in the study were chicken-related samples.

[f] The case's husband purchased four live chickens from a market on 8 April 2013 and raised them at home. On 10 April, because the chickens developed an acute illness, the case gave them antibiotics. We collected chicken faeces from her house.

Figure 2

Timeline of laboratory-confirmed influenza A(H7N9) cases in Huzhou city, China, March–May 2013 (n=12)



(n=2), weakness (n=2), nasal obstruction and runny nose (n=1), expectoration (n=1), pruritic body rash (n=1), chest tightness (n=1) and nausea (n=1). Of the 12 cases, nine developed severe pneumonia and pulmonary dysfunction 2–10 days after symptom onset.

Of the 12 cases, 10 had chronic underlying conditions such as hypertension, bronchitis or heart disease, before infection. Three cases had low counts of white blood cells (between 1.7 x 10^9/L and 3.5 x 10^9/L); in another two, the count was high (12.7 x 10^9/L and 13.4 x 10^9/L), while the others were within the normal reference range (4–10 x 10^9/L). All but one case (with 3.4 mg/L) had high levels of high-sensitivity C-reactive protein (between 18.4 mg/L and >200 mg/L (i.e. exceeding the detection range); normal reference range: 0–10 mg/L).

All cases had a history of exposure to poultry before symptom onset

Nine of the 12 cases had visited nearby live poultry markets at least once (range: 1–10 times) during the 10 days before symptom onset (Table 1). Of these nine cases, four (Cases 4, 5, 6, and 8) had had direct contact with live poultry during this time. Although three patients had not visited poultry markets, they all had a history of direct contact with live poultry during the 10 days before symptom onset. Case 7 was exposed to live poultry as part of a government campaign to cull poultry at live poultry markets. Case 9 and her neighbour had purchased 12 chickens from a chicken vendor and had raised them in the same courtyard for about 20 days. Case 9 killed her seven chickens when she found that one of them had become ill. For Case 11, her husband purchased four live chickens from a market on 8 April and raised them at home. On 10 April, because the chickens developed an acute illness, the patient gave them antibiotics.

Influenza A(H7N9) viral RNA was detected in all poultry markets visited by cases

In total, nine live poultry markets were epidemiologically associated with the patients (Table 1, Figure 1). Therefore, we collected poultry faeces, waste and sewage from these markets, to test for the presence of A(H7N9) viral RNA. We also collected throat and anal swabs and faeces from the chickens raised by the neighbour of Case 9 and chicken faeces from the house of Case 11. Of the 135 samples obtained, 38 samples were positive. Of particular note, A(H7N9) viral RNA was detected in samples from all nine markets, as well as those from the courtyard of Case 9 and the house of Case 11.

In addition, we expanded our surveillance to seven other nearby live poultry markets that the cases had not visited. Of 75 samples tested, 23 were positive for A(H7N9) viral RNA.

We also collected throat swabs from the close contacts (n=339) of the 12 patients. Among 339 samples, none tested positive for A(H7N9) viral RNA, indicating no human-to-human transmission of the virus.

Discussion

Previous studies have suggested that several mutations in the HA might be involved in the acquisition of the ability of the A(H7N9) virus to infect humans [5-7,10], and genetic evidence indicates that poultry is the reservoir of the virus [6,7]. However, preliminary observations that not all patients have had a history of exposure to poultry raise the controversial issue of the source and transmission route of the A(H7N9) virus [2].

Our results provide epidemiological evidence to support the hypothesis that A(H7N9) virus-infected poultry are a transmission source. A total of 139 live poultry

Table 2

Effect of closure of live poultry markets in the five regions of Huzhou city, China, March–May 2013

Region	Date of symptom onset (2013)		Date of market closure (2013)	Number of markets closed	Number of confirmed influenza A(H7N9) cases[a]	
	First case	Last case			Before market closure	After market closure
Wuxing District	29 March	14 April	11 April	32	3	0
Nanxun District	12 March	10 April	15 April	30	3	0
Deqing County	14 April	17 April	21 April	19	2	0
Changxing County	12 April	17 April	20 April	38	2	0
Anji County	3 April	15 April	18 April	20	2	0
Total	–	–	–	**139**	**12**	**0**

[a] In order to exclude people who were infected by the virus but did not develop symptoms before market closure, case numbers were counted seven days after closure of the corresponding market.

markets (including those tested) in the five districts or counties in Huzhou city were closed sequentially, from 11 April to 21 April (Table 2). As of 15 May, no new cases have been identified in Huzhou city ($p<0.01$). Although based on small case numbers, our findings support the view that poultry are a crucial transmission source and also indicate that closing live poultry markets in affected areas is an effective strategy to stop the outbreak.

With respect to the absence of reported poultry exposures in some patients (n=18) in a previous study [2], we can suggest two possible explanations, arising from our findings: (i) some patients may have forgotten some details of their exposure history by the time the epidemiological investigation was carried out; or (ii) some patients may have been unable to provide timely and reliable information due to their serious clinical conditions. It may therefore be possible that patients with no documented exposure may have in fact been exposed to poultry.

We tested 339 throat swabs from the cases' close contacts, but none tested positive for the A(H7N9) viral RNA, suggesting that these patients did not spread the virus to their close contacts. Although throat swabs may not be as often positive as deep sputum samples [7,11], we did not collect sputum samples from these close contacts because they had no obvious symptoms. Most patients (n=9) were aged 50 years or older, consistent with the nationwide data (78/107) [4]. Distinct from the nationwide data, however, two thirds (8/12) of the cases in Huzhou city were female (nationwide data: 32/106). This could possibly be due to the fact that in Huzhou city, housewives are mainly responsible for buying food, such as meat or vegetables, in local markets. It should also be borne in mind that most of the cases (n=10) had chronic underlying conditions. Whether an individual's health status is associated with susceptibility to A(H7N9) virus infection remains to be proved.

Although an earlier study found that some live poultry markets tested positive, only a few poultry vendors (n=4) were found to be infected with the virus [2]. Why most vendors remained infection-free despite extremely frequent exposure to infected poultry is also unclear. Whether there is some pre-existing cross-reactive immunity, which enhances the susceptibility of patients to A(H7N9) virus infection [4] or prevents poultry vendors from infection needs to be determined.

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Authors' contributions

KL, CZ, JH and MJ designed and supervised the study. JH, PZ, MJ, JL, LW, DW, GL, XL, YZ, XD, BS, and SG performed the epidemiological investigation, sample collection, and laboratory confirmation of H7N9 infection. KL, CZ, JH, QL and MJ analysed and discussed the results. CZ wrote the paper, and KL and QL revised the paper. All authors have seen and approved the final version.

Conflict of interest

None declared.

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Outbreak with a novel avian influenza A(H7N9) virus in China - scenarios and triggers for assessing risks and planning responses in the European Union, May 2013

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As part of the risk assessment and strategic planning related to the emergence of avian influenza A(H7N9) in China the European Centre for Disease Prevention and Control (ECDC) has considered two major scenarios. The current situation is the one of a zoonotic epidemic (Scenario A) in which the virus might be transmitted sporadically to humans in close contact with an animal reservoir. The second scenario is the movement towards efficient human to human transmission (a pandemic Scenario B). We identified epidemiological events within the different scenarios that would trigger a new risk assessment and a review of the response activities to implement in the European Union (EU). Further, we identified the surveillance activities needed to detect these events. The EU should prepare for importation of isolated human cases infected in the affected area, though this event would not change the level of public health risk. Awareness among clinicians and local public health authorities, combined with nationally available testing, will be crucial. A 'one health' surveillance strategy is needed to detect extension of the infection towards Europe. The emergence of a novel reassortant influenza A(H7N9) underlines that pandemic preparedness remains important for Europe.

Introduction

On 31 March 2013, human cases of infection with a novel avian influenza A(H7N9) were reported in eastern China [1,2]. The first two cases in Shanghai had been detected through astute clinicians alerting the public health authorities. The isolated viruses were of an un-subtypeable influenza A strain that was determined to be a novel reassortant strain by the World Health Organization (WHO) Collaborating Centre in the Chinese Center for Disease Control and Prevention in Beijing. A similar virus was identified in a third human case in Anhui province and subsequently in poultry in live bird markets in Shanghai [1,3,4]. The emergence of a novel reassortant avian influenza virus causing disease among humans is a significant threat for public health. Molecular analysis of this avian origin virus genome identified markers associated with mammalian adaptation. However, there are difficulties in interpreting the significance of molecular data from the limited number of virus sequences posted to date and without linked information on the clinical and epidemiological behaviour of the viruses in humans [2]. There is also a particular lack of data on both the geographic spread and the distribution of the viruses among avian species in China [5].

The European Centre for Disease Prevention and Control (ECDC) systematically gathers, analyses and interprets epidemic intelligence data to fulfil its mandate for risk assessment and developing guidance for Europe. For the emergence of influenza A(H7N9) virus, we used scenario analysis as a tool for assessing risks, anticipating possible developments and prioritising preparedness activities. The aim of this paper is to identify the critical events that should inform preparedness, define surveillance priorities and be the basis for risk management options at the European level and in the European Union (EU) Member States.

Scenario analysis

The scenario analysis method was first developed after the Second World War as part of game analysis. In public health, scenario analysis is a tool for strategic planning and for preparing for future events [6]. Subsequently, the significance of a given event can be estimated based on a set of assumptions and premises [7,8].

One important lesson from the influenza A(H1N1)pdm09 pandemic in 2009 was the need for flexible planning based on a range of scenarios, which are refined as more data becomes available [9-11]. Determining the behaviour of a novel reassortant strain of an influenza virus at the early stages of its appearance is challenging. Predicting its future behaviour is impossible. The objective of the analysis in this context is to consider the most likely scenarios for how the underlying patterns of infection and transmission could evolve, and

to identify the key events (triggers) that would prompt a re-assessment of the situation and the strategic planning.

The underlying epidemiological patterns were estimated based on the documented behaviours of avian influenza viruses, their genetic propensity to adapt to a variety of hosts and their ability to cause a broad spectrum of clinical disease in humans [12,13]. Some avian influenza virus subtypes cause sporadic human infections of variable severity. Efficient person-to-person transmission as a result of genetic evolution of the virus would result in a pandemic. Between these two situations, there is a theoretical phase with viruses in transition [14]. However, that phase has never been observed before a pandemic. In this theoretical transition phase, variable epidemiological patterns might be observed with different animal sources, different groups of affected humans, variable clinical severity and variety of cluster size and geographical expansion. In this situation, risk assessments have to be speculative, but can draw upon tools like the international Influenza Risk Assessment Tool (IRAT) [15,16].

Based on the above spectrum of possible human influenza infections, two scenarios were elaborated. Results from the genetic analysis of the isolated strains, the current epidemiology of the influenza A(H7N9) viruses in humans and the very limited knowledge of its epidemiology and behaviour in animals were taken into account [17]. Subsequently, we examined various possible developments from the current epidemiological situation (Table). We categorised the events in human versus animal health related, starting with the current situation and ordered them within each category according to significance. For this, a simple scale was used to estimate the significance of each possible development, based on the likely impact on public health in the EU as perceived by the authors. For each event we described the applicable scenario and the method to detect the event.

Scenarios and triggers

As of 16 May 2013, there are 131 laboratory-confirmed cases, including 32 deaths, with influenza A(H7N9) infection. Cases have been reported from eight provinces (Anhui, Fujian, Henan, Hunan, Jiangsu, Jiangxi, Shandong, and Zhejiang) and two municipalities (Shanghai and Beijing) in mainland China. In addition, one travel-related case is reported by Taiwan [18,19].

Scenario A, the zoonotic scenario, is consistent with the current situation, as of May 2013, in which the novel influenza A(H7N9) virus is distributed in poultry populations in an unknown area of eastern China [5]. The virus has a low pathogenicity for domestic poultry, though there is a possibility of change to high pathogenicity for poultry [5].Whether it circulates in other animal reservoirs is yet to be determined, for example whether the virus is being transmitted from a wild bird reservoir to poultry in multiple locations or if the virus has spread to the affected areas through poultry-to-poultry transmission. The transmissibility from poultry to humans is overall low, but higher than for influenza A(H5N1) and therefore resulting in occasional human infections [20]. Epidemiological and virological investigations are expected to accrue evidence over time for the exposure of cases to an animal source. Human-to-human transmissibility seems to be very low [21]. Small clusters occur, but are uncommon in this scenario where most human infections are sporadic and the clinical spectrum of disease is still unclear [20,22]. In some ways influenza A(H7N9) resembles the influenza A(H5N1) zoonotic epidemic, but critical differences from influenza A(H5N1) include the occurrence of some mild or asymptomatic influenza A(H7N9) cases, the absence of pathogenicity for birds at present, the somewhat higher transmissibility of influenza A(H7N9) to human and age and sex distributions among humans which are older and more male-orientated than for influenza A(H5N1). From a European perspective, travellers from the affected area might be infected and diagnosed after arriving in Europe without any change in scenario [23]. Spread of the virus to European poultry might eventually take place either through (illegal) imported birds or migratory birds and failure of biosecurity arrangements in Europe [24]. In that case, human infections might occur mainly in an occupational setting. In Europe, this is the basis for statutory surveillance for low pathogenic avian influenza viruses in poultry and wild bird surveillance [25].

Scenario B, the pandemic scenario entails the emergence of sustained human-to-human transmission resulting in a pandemic [26]. The case-fatality could be low like that of swine-origin influenza A(H1N1)pdm09 in 2009 or of higher magnitude akin to that of influenza A(H1N1) in 1918 [27,28]. Should this scenario occur, the influenza A(H7N9) viruses were detected early in the course of adaptation and would have become increasingly transmissible between humans. An exponential increase in the number of cases and clusters as well as in cluster size would then result [29]. In this scenario, if a substantial proportion of infections were to be mild or asymptomatic, this would also facilitate the spread of the virus. Because spread would occur through human-to-human transmission rather than selective common exposure, all age groups would be exposed. Due to possible pre-existing population immunity, certain risk groups might emerge and be predominantly affected as occurred with influenza A(H1N1)pdm09 [30].

Between these two scenarios, in the theoretical transition phase, multiple variants could be observed based on the dimensions of transmissibility, susceptibility and severity.

The critical events or triggers that we have identified and their likely significance or impact for Europe are listed in the Table. For each event is indicated to which scenario it could apply and which surveillance activity could detect the event.

Table

Critical epidemiological events (triggers) for Europe in the context of the emergence of influenza A(H7N9) in China

Event		Public health significance/ impact for Europe	Scenario	How to detect event by public health authorities in Europe
Human health				
1.	Clusters of <4 cases, isolated in time and place[a]	Low: no or limited human to human transmission, as seen with influenza A(H5N1)	Zoonotic	- Epidemic intelligence[b] [38]
2.	Locally acquired human infections taking place within neighbouring provinces to affected area in China[a]	Low: indicator of increased testing or spread in bird populations	Zoonotic	- Epidemic intelligence
3.	Imported case in person returning from affected area to Europe	Low, but with high communication impact	Zoonotic	- Awareness among clinicians and public health authorities in Europe - Human surveillance[c] (case finding algorithm, laboratory capacity and case definition)
4.	Locally acquired human infections in Chinese provinces not next to affected area, or in neighbouring countries of China	Medium, indicating either:		- Epidemic intelligence
		- increased testing or spread in bird populations	Zoonotic	
		- or increasing human-to-human transmission	Transition	
5.	Locally acquired human infections in countries distant from China (excluding Europe)	High, indicating either:		- Epidemic intelligence
		- wide spread in bird populations	Zoonotic	
		- or increasing human-to-human transmission	Transition	
6.	Locally acquired human infections in Europe	High, indicating either:		- Awareness among clinicians and public health authorities in Europe - Human surveillance[c] (case finding algorithm, laboratory capacity and case definition) - European veterinary surveillance and link to human occupational surveillance - Case investigation
		- spread of virus in bird population in Europe	Zoonotic	
		- or increasing human-to-human transmission	Transition	
7.	Multiple or larger clusters of human infections	High: increasing risk of efficient human-to-human transmission	Transition	- Epidemic intelligence/human surveillance[c] (EU/EEA) - Case investigations (EU/EEA) - Cluster investigations (EU/EEA)
8.	Continuous chains of human transmission	High: sustained human-to-human transmission	Pandemic	- Epidemic intelligence/human surveillance[c] (EU/EEA) - Case investigations (EU/EEA) - Cluster investigations (EU/EEA)
9.	Apparently decreased severity/case-fatality ratio	High: compromises detection of cases, resulting in increased risk of spread	Any scenario	- Epidemiological evaluation
10.	Primary resistance to neuraminidase inhibitors	High: compromises antiviral treatment	Any scenario	- Monitoring through EU and global (WHO) reference laboratory networks [39,40]
Animal health				
11.	Isolation of virus from other animals than poultry in affected areas (e.g. migratory birds, swine)	Medium: change in exposure risk	Zoonotic	- Veterinary surveillance by national authorities, OIE and FAO
12.	Isolation of virus from wild birds in Europe	Medium: indicating risk for spread to domestic birds in the EU	Zoonotic	- Wild bird surveillance by national authorities, OIE and FAO
13.	Isolation of virus from domestic birds in Europe	High: indicating risk for occupational exposure	Zoonotic	- European veterinary surveillance and link to human occupational surveillance

EEA: European Economic Area; EU: European Union; FAO: Food and Agriculture Organization of the United Nations; OIE: World Organisation for Animal Health; WHO: World Health Organization.

[a] Currently only the first two events have been observed in China.

[b] Epidemic intelligence activities, including monitoring of notifications through International Health Regulations (IHR) and Early Warning and Response System (EWRS).

[c] Human surveillance: severe acute respiratory illness and/or influenza-like-illness and/or seroepidemiology (consortium for the standardization of influenza seroepidemiology (CONSISE) surveys), depending on the epidemiological situation and clinical picture.

Discussion

The emergence of a novel influenza virus infection in humans in China triggered the production of a rapid risk assessment by ECDC, which has subsequently been updated in the light of further developments. The risk of exposure may be limited to a few provinces in eastern China, but the virus may also be more widespread in poultry [5]. Recommendations for European citizens living in or visiting the affected areas have appeared in the rapid risk assessment [17]. An important consideration is that the zoonotic scenario (A) may develop slowly, not progressing towards transition scenarios. ECDC will closely monitor the epidemiological and veterinary situation and report this through updates of its risk assessment and epidemiological updates on its website. In this analysis, thirteen critical epidemiologic events within the different scenarios, summarised in a table, have been identified of which a number would have a high impact for EU. Therefore it is essential to remain alert and capable of timely detecting the occurrence of these critical events, by monitoring of the clinical spectrum of disease and the epidemiological, virological and animal health situation, internationally and in the EU. Currently only the first two events in the table, both with low significance and applicable to scenario A, have been observed in China. Two triggers with a high impact on public health in Europe (increasing resistance to treatment and an apparent decrease in severity) can appear independently of any scenario.

The final column in the table indicates particular priorities for surveillance. It stresses the importance of awareness among hospital clinicians and of surveillance among local public health authorities in Europe. Epidemic intelligence, which also serves for the detection of other threats, plays a key role in detecting events outside Europe. It shows how crucial veterinary and human surveillance is in countries outside Europe, along with transparency and adherence to the International Health Regulations and the procedures of the World Organisation for Animal Health (OIE) [31]. From the activities needed to detect the events, one can deduct the institutional partners with whom to collaborate on national and international level.

The importation into Europe of a human case is likely, given the high volume of international travel between Europe and China and the higher potential for animal to human transmission of influenza A(H7N9) than that of influenza A(H5N1). The likelihood for importation of cases into Europe might increase if the affected area expands. However, if influenza A(H7N9) behaves similar to influenza A(H5N1), transmission to humans is expected to decline during the summer in China and the first European imported cases may not occur in the near future. Even though the significance of the event is ranked as low, EU Member States need to be prepared to manage such cases. Some Member States have already started with this. Following consultation with Member States, ECDC has now published an interim case-finding strategy and a case definition [32]. Local accurate testing is crucial for this and together with the WHO Regional Office for Europe and the Community Network Reference Laboratory (CNRL), ECDC is facilitating the availability of accurate testing in National Influenza Centres or their equivalents in all EU and European Economic Area (EEA) countries [33]. It is important that physicians and clinical laboratories receive all relevant guidance. Also, guidance on managing contacts (prophylaxis) needs to be established and distributed prior to the event and guidance for case management and use of antivirals will be especially important given the severity of influenza A(H7N9) disease in the majority of the cases.

The probability of the appearance of influenza A(H7N9) in wild birds in Europe is difficult to comment upon as the distribution of the virus in the wild bird population in China has not been determined [5]. In this context, it will be essential to sustain the current EU wild bird surveillance for avian influenza after validating the serological and virological tests for influenza A(H7N9) [25]. The risk of spread of infection to domestic birds in the EU is also difficult to comment upon. Importation of live birds from the Far East is prohibited, but cannot be ruled-out. A more likely scenario is that the virus spreads via the mixing of migratory birds, which might allow for westward extension of the virus. This may be a long term event, as it took influenza A(H5N1) nearly a decade to spread in wild birds from China to the EU [34]. Although some flocks of poultry were infected with influenza A(H5N1), rapid detection, stringent action and high levels of biosafety stamped out the infection and the influenza A(H5N1) has never become established in EU poultry the way it has in domestic birds in countries with more informal poultry sectors [25]. An important distinction is that influenza A(H7N9) is currently a low pathogenic avian influenza virus for birds and will not produce the characteristic 'die-offs' signal which trigger testing of poultry flocks. Hence, the statutory low pathogenicity surveillance will become more important for human health. The mandate of public health agencies will not cover animal surveillance and the current collaboration with animal health agencies will need to be intensified under the one health surveillance strategy with greater emphasis on occupational surveillance. In the event of influenza A(H7N9) being detected in domestic animals in the EU, it will be especially important for national public health and animal health authorities to collaborate intensively to ensure timely exchange of surveillance data and early recognition of potential human cases. Occupational guidance to prevent human infections from poultry should build on that for influenza A(H5N1).

Though the risk of person-to-person transmission of influenza A(H7N9) resulting in disease seems to be low at present, the infection of a human with influenza A(H7N9) by transmission within Europe will be a critical event with high significance. Agreed guidance for the assessment of human-to-human transmission will be necessary using the consortium for the standardization

of influenza seroepidemiology (CONSISE) protocols and their national counterparts established for other respiratory infections [35,36]. In addition, epidemiological studies need to be prepared and agreed between countries to identify risk factors among hospitalised cases in the EU. This should again build on routine severe disease surveillance and the CONSISE protocols [37]. The appearance of expanding clusters or chains of transmission, and eventually sustained human-to-human transmission would be another highly significant critical event. Finally, the appearance of influenza A(H7N9) indicates that revising pandemic plans and preparedness in light of the 2009 experience and the anticipated new guidance from WHO should remain a priority for Europe.

In Scenario A, a zoonotic epidemic, the production of a manufactured human vaccine is not of highest priority, though candidate viruses and reagents are being developed by the WHO guided strain selection system as they were previously for other zoonotic viruses of pandemic potential, A(H7) and A(H9) viruses. Decisions on whether to progress to the development of clinical lots to allow early clinical trials, for example for determining dosage and efficacy, will be a matter of judgment informed by tools like the IRAT [15,16]. Relevant CONSISE studies will again be essential in order to determine background protection in the European population [35,36].

Conclusions

The confirmation of novel avian influenza virus infections in humans is a significant threat for public health because of the potential for the virus to develop into a pandemic strain [26] and demonstrates the importance of pandemic preparedness. Developing and examining possible outbreak scenarios and identifying critical events are essential exercises to assess risks. The currently most probable scenario is one of sporadic human infections caused by exposure to birds but with a yet undetermined animal reservoir. Neither importation of human cases into the EU nor limited person-to-person transmission in the currently affected areas [29] would be of significance or change the scenario. Events of medium significance include increasing geographical spread of human infections within China and neighbouring countries, isolation of viruses in animals other than domestic birds or detection of virus in wild birds in Europe. Highly significant events include: transmission in countries distant from China, isolation of viruses from domestic birds in Europe, locally acquired infections in Europe and sustained human-to-human transmission. Epidemic intelligence is crucial for detecting trigger events. Public health authorities and clinicians need to be aware of surveillance guidance and laboratory testing needs to be made available. A comprehensive human and veterinary surveillance strategy is needed to detect extension of the infection towards Europe.

Authors' contributions

All authors were involved in the development of the scenarios and identification of the critical events. Cindy Schenk, Diamantis Plachouras, Niklas Danielsson, Emmanuel Robesyn drafted the manuscript, which was critically reviewed by Angus Nicoll and Denis Coulombier.

Conflict of interest

None declared.

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Analysis of national measles surveillance data in Italy from October 2010 to December 2011 and priorities for reaching the 2015 measles elimination goal

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From 1 October 2010 to 31 December 2011, Italy experienced high measles burden with 5,568 measles cases (37.4% laboratory-confirmed) reported to the enhanced measles surveillance system (cumulative incidence in the 15-month reference period: 9.2/100,000 population). Adolescents and young adults were especially affected, and the median age of cases was 18 years. Most cases (95.8%) were either unvaccinated or incompletely vaccinated. Complications were reported for 20.3% of cases, including 135 cases of pneumonia, seven of encephalitis and one case of Guillain–Barré syndrome. One death occurred in an immunocompromised adult. Over 1,300 cases were hospitalised. Identified priorities for reaching the measles elimination goal include evidence-based interventions such as reminder/recall for both doses of measles vaccine, supplementary immunisation activities aimed at susceptible age cohorts, and vaccinating healthcare workers.

Introduction

Measles is an acute viral illness with the potential for severe and life-threatening complications. The disease can be prevented by a safe and effective vaccine and globally, measles control activities have been very successful in reducing measles incidence and mortality. Since measles virus infects only humans, elimination is possible, and all regions of the World Health Organization (WHO) except the South-East Asia Region have set an elimination goal to be achieved by 2020 or sooner [1,2]. In the European Region the target date for elimination has recently been moved from 2010 to 2015. As most other European countries, Italy failed to reach measles elimination by 2010 and in accordance with European goals, also revised its target date for elimination to 2015 [3]. Thanks to intensive vaccination and surveillance efforts, elimination was achieved in the WHO Region of the Americas in 2002 and in many other countries such as Finland (in 1994) and South Korea (in 2006) [1, 4-5].

The very high transmissibility of measles infection, as evidenced by a basic reproduction number (Ro) between 11 and18, poses a great challenge to elimination and requires very low susceptibility levels in the population [6]. This can be achieved by reaching and maintaining very high coverage levels of over 95% for two doses of measles vaccine. Besides introducing a routine two-dose schedule for measles vaccine, most countries that have interrupted endemic measles transmission have also undertaken supplementary mass immunisation activities (SIAs) to rapidly immunise a high proportion of susceptible persons in the population [5,7-8].

Measles vaccination strategy and uptake in Italy

In Italy, monovalent measles vaccine was first introduced in 1976. This was replaced in the early 1990s by the combined measles–mumps–rubella (MMR) vaccine, but only since 1999 has vaccination with MMR been included in the national immunisation programme. Only one dose of MMR was offered until 2003 when Italy approved the first national measles elimination plan and a two-dose schedule was adopted in all regions starting with the 2002 birth cohort [9]. Currently, a first dose of MMR vaccine is recommended at the age of 12 to15 months and a second dose at five to six years.

The Italian national health system is decentralised, but state authorities determine the minimum level of healthcare services that regional authorities must provide to citizens free of charge. With regards to vaccination, the National Vaccine Plan outlines the objectives of the national immunisation programme, agreed upon by regional authorities who are responsible for the implementation of vaccination programmes in their respective regions [10]. In all regions, vaccinations included in the national immunisation programme (including MMR) must be provided free of charge by local vaccination

Figure 1

Vaccine coverage for the first dose of measles-containing vaccine in children aged two years (administrative method), by region. Italy, 2011

centres. Family paediatricians and general practitioners generally do not provide vaccinations.

Vaccination coverage for all childhood vaccines included in the national immunisation schedule is measured annually in two year-old children in all regions, by the administrative method (dividing the number of vaccine doses administered in the target population by the number of persons in the target population). In addition, epi-cluster surveys were conducted in 1998, 2003 and 2008, to validate administrative coverage data and to collect information regarding reasons for non-vaccination [11]. The 2008 epi-cluster survey also aimed at collecting information on vaccination coverage in 16 year-old adolescents (1992 birth cohort), including data on second-dose MMR coverage which is not routinely measured in Italy.

Uptake of measles vaccine remained very low in Italy for years after its introduction and was not uniform across regions. The percentage of two year-old children vaccinated against measles was consistently below 21% before 1988, increased to 50% in the 1990s, reaching 74% in the year 2000. Since the implementation of the first national measles elimination plan in 2003, coverage with measles-containing vaccine increased to 90.1% in 2011 (Figure 1) [12]. According to the 2008 epi-cluster survey, conducted in 18 of 21 Italian regions, measles vaccine coverage in 16 year-old adolescents was 78.1 % for the first dose and only 53.9% for the second dose [11].

A supplementary catch-up immunisation campaign was conducted in the years 2003 to 2005, targeting 2,544,386 children born in the years 1991 to 1997. Overall MMR vaccination coverage in this group, measured at the start of the campaign, was 71% for the first dose and only 15% for the second dose. Following the campaign, first-dose coverage increased to 81% and second-dose coverage to 39%.

Measles incidence

The Italian measles surveillance system has been previously described [13]. The overall incidence of measles has decreased in Italy since the measles vaccine was introduced, from a mean incidence of 150 cases per 100,000 population in the 1970s to 81 cases per 100,000 in the 1980s and 41 cases per 100,000 in the 90s. In the past decade, large epidemics occurred in the years 2002 to 2003 and in 2008, with 18,020 reported cases (incidence 32/100,000 population) in 2002 and 5,312 cases in 2008 (8.9/100,000 population). The latter outbreak affected mainly northern Italian regions, especially the Piedmont region (46% of cases). A new resurgence of cases was then observed in December 2009 [13]. Outbreaks in recent years have mainly affected adolescents and young adults [13-14].

In this article we describe measles cases reported to the Italian national measles surveillance system with dates of rash onset between 1 October 2010 and 31 December 2011, and discuss some of the priorities for reaching measles elimination. Since measles is targeted for elimination in the European Region, it is worthwhile to share information with other public health actors in Europe and direct attention to the severity of measles even in industrialised countries.

Methods

Reported cases were classified according to the 2008 European Commission (EC) case definition for measles [15]. Recent vaccination was defined as having received a measles-containing vaccine six to 45 days before onset of rash [16]. Recently vaccinated cases with a positive IgM response were classified as possible or probable cases according to clinical and epidemiological criteria. Suspected cases not meeting the EC measles case definition were discarded. Cases vaccinated up to and including four days before rash onset were probably incubating the disease at the time of vaccination and were classified either as not vaccinated (if they had received only one dose) or as vaccinated with one dose (if the recent vaccination was the second dose). Imported cases were defined as cases exposed outside the country during a period seven to18 days before rash onset as supported by epidemiological and/or virological evidence [17]. Healthcare worker was defined as any hospital staff or other healthcare staff

having regular contact with patients, including clinical physicians, nurses, students in these disciplines, paramedical professionals, social workers, ambulance workers, porters, other hospital support staff, and healthcare staff in primary care medical facilities and nursing homes.

Incidence was calculated by using age-specific population data for 2011, by region and geographical area, obtained from the National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT) [18]. Three geographical areas are described in Italy: northern, central and southern Italy. Northern Italy includes the following nine regions: Piedmont, Valle d'Aosta, Liguria, Lombardy, South Tyrol, Autonomous Province of Trento, Veneto, Friuli-Venezia Giulia, and Emilia-Romagna. Central Italy includes Marche, Tuscany, Umbria and Lazio. Southern regions include Campania, Abruzzo, Molise, Apulia, Basilicata, Calabria, Sicily and Sardinia.

Biological samples for genotyping were analysed by the national reference laboratory at the National Institute of Health in Rome. Data were analysed using Excel and Epi Info software.

Results

A total of 5,568 possible, probable or confirmed cases were reported, giving a national cumulative incidence in the 15-month reference period of 9.2 per 100,000 population (population of 60,626,442 as of 1 Jan 2011). An additional 1,103 suspected cases were reported and discarded because they did not meet the measles case definition for a possible, probable or confirmed case. Overall, 2,085 cases (37.4%) were laboratory-confirmed, 1,902 (34.2%) were probable cases and 1,581 (28.4%) were possible cases. The epidemic curve (Figure 2) shows that the peak number of reported cases was reached in May 2011 (n=1,195).

Twenty of 21 regions and autonomous provinces (AP) reported cases, with incidences varying from 0.2 per 100,000 population to 246.6 per 100,000 population (Figure 3). The highest incidence rates were reported from two very small regions in northern Italy which accounted for 31.8% of cases (n=1,772): South Tyrol (population 507,657; incidence 246.6/100,000) and the neighbouring AP of Trento (population 529,457; incidence 98.2/100,000). The Lazio region, in central Italy, also reported a high incidence (population 5,728,688; incidence 27.5/100,000). Two regions in northern

Figure 2

Epidemic curve showing reported measles cases by month of rash onset and case classification, Italy, October 2010–December 2011 (n=5,568)

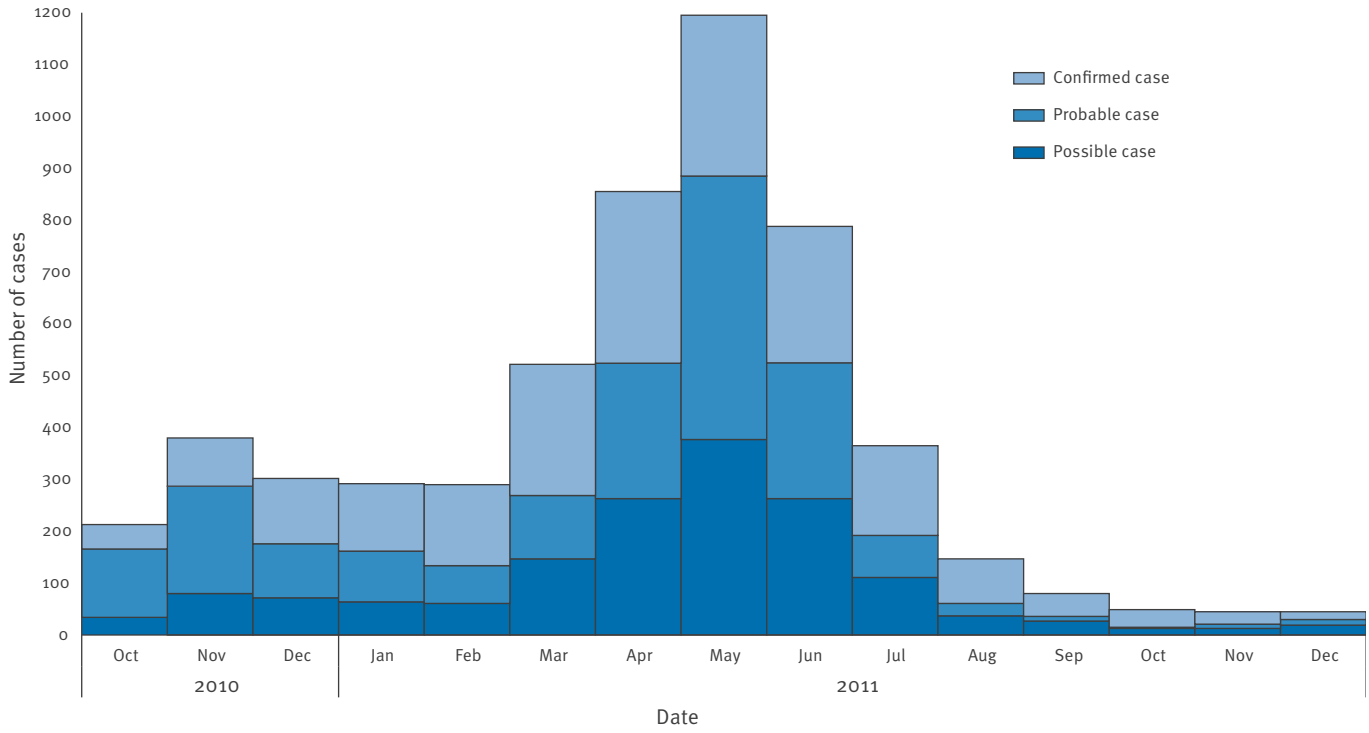
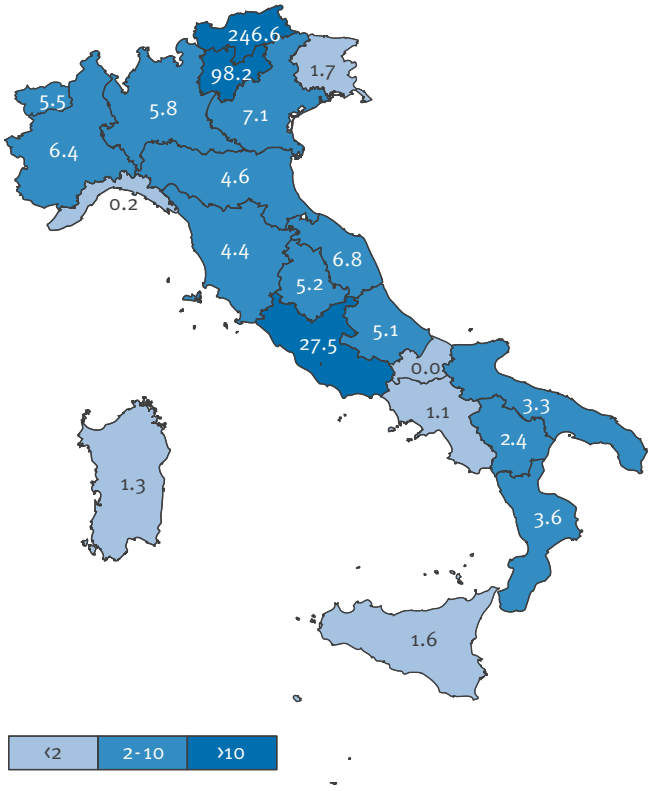


Figure 3

Reported measles incidence per 100,000 population, by region, Italy, October 2010– December 2011 (n=5,568)



Italy (Valle d'Aosta and Liguria) reported less than 10 cases each. Incidences by geographical area were 11.6/100,000 in northern Italy, 15.8/100,000 in central Italy, 2.2/100,000 in southern Italy.

Age and sex of cases

Information on sex was available for 5,565 cases (99.9%): 2,955 (53.1%) were male. Age was reported for 5,345 cases (96.0%). The age distribution and incidence per age group are shown in Table 1.

The highest incidence was seen in the age group 15–19 years followed by the age group under one year. Sixty-two per cent of cases were aged 15–44 years. The median age was 18 years (range: two months–78 years) and varied by region from four years in the Valle d'Aosta region (northern Italy), where only seven cases were reported, to 28.5 years in the Marche region in central Italy (n=107). In 13 regions the median age of reported cases was above the national figure (range: 21–28.5 years).

Vaccination status

Vaccination status was available for 4,938 cases (88.7%). Overall, 4,458 cases (90.3%) were unvaccinated, 272 (5.5%) had received only one dose of measles-containing vaccine, 36 (0.7%) were vaccinated with two doses, and 172 cases (3.5%) had received at least one dose but the number of doses was unspecified. Among unvaccinated cases, 164 were too young to be vaccinated routinely (aged under one year).

Complications and hospitalisations

Overall, 1,130 cases (20.3%) reported at least one complication, and a total of 1,544 complications were reported (Table 2). The median age of complicated cases was 19 years (range: 0–68 years) and the highest frequency of complications (28.6%) was seen in the age group 25–44 years. Information regarding hospital admissions for measles was available for 5,034 patients (90.4%), of whom 1,317 (26.2%) were hospitalised.

Diarrhoea was the most frequently reported complication but more severe complications such as pneumonia, thrombocytopenia, and encephalitis were also reported. The category 'Other complications' included respiratory complications, vomiting and dehydration, hepatitis, arthralgias, and complications in pregnancy. A case of Guillain–Barré syndrome was also reported. Three cases developed respiratory failure.

The seven reported cases of encephalitis ranged in age from 13 to 62 years (median: 29 years). Five of seven cases were laboratory-confirmed, one had an epidemiological link to a confirmed case and one was a clinical case. None had been vaccinated against measles. One case of encephalitis occurred in a healthcare worker (HCW).

A young adult patient who developed measles in late 2011, subsequently died 64 days after rash onset. The patient was affected by hypogammaglobulinaemia and developed laboratory-confirmed measles following contact with an infected co-worker. The cause of death was pneumonia with respiratory failure.

Table 1

Age distribution of measles cases and incidence by age group, Italy, October 2010–December 2011 (n=5,345[a])

Age group (years)	Number of cases	Incidence per 100,000 population
<1	181	32.6
1–4	450	19.6
5–9	452	15.9
10–14	812	28.7
15–19	1,130	38.5
20–24	773	24.7
25–44	1,387	8.0
≥45	160	0.6

[a] Information on age was not available for 223 of 5,568 cases.

Table 2

Reported measles complications, Italy, October 2010–December 2011

Diagnosis	Number of reports	Incidence per 1,000 measles cases[a]
Diarrhoea	634	113.9
Otitis	195	35.0
Pneumonia	135	24.2
Keratoconjunctivitis	104	18.7
Laryngotracheobronchitis	167	30.0
Thrombocytopenia	9	1.6
Encephalitis	7	1.3
Convulsions	10	1.8
Other complication	283	50.8
Total[b]	1,544	27.7

[a] Calculated using as the denominator the total number of measles cases reported, n= 5,568.

[b] A total of 1,130 cases reported at least one complication; some reported more than one complication.

Transmission settings and occupation of cases

Transmission occurred in various settings including families, schools (nursery schools, elementary and middle schools, universities), healthcare facilities, vacation camps and other community settings. Healthcare settings in which transmission occurred included hospital wards and emergency rooms.

Since the type of occupation cannot be reported for students and pre-school children, this information is available only for 1,595 cases (28.6%), 185 of whom were HCWs. Some 164 of 185 (88.7%) HCWs were unvaccinated, 14 (7.6%) were not aware of their measles vaccination status, five (2.7%) had received one dose of measles vaccine, one (0.5%) had received two doses, and one (0.5%) had been vaccinated but could not recall the number of doses received. Forty-four cases with known occupation were school workers, of whom 38 were unvaccinated, five were not aware of their measles vaccination status, and one had received two doses.

Four regions in northern Italy (Lombardy, Friuli Venezia Giulia, AP Trento and Emilia Romagna) reported measles cases among Roma/Sinti populations, for a total of 40 cases: in Lombardy, 10 clusters were reported for a total of 28 cases; Emilia Romagna reported nine cases, eight of whom were part of a single cluster; Friuli Venezia Giulia and AP Trento reported one and two cases, respectively.

A total of 32 cases were likely to have acquired measles abroad, mainly from other European countries such as France, Germany and the United Kingdom, but four cases were imported from North Africa, India, and China.

Phylogenetic analysis of measles virus

Measles viruses, from specimens collected from 257 cases in 15 of the 20 affected regions, were genotyped and three main genotypes were detected: D4 (isolated from 161 cases in 14 regions), D8 (isolated from 69 cases in 11 regions), and B3 (23 cases in eight regions). Genotypes D9 (two cases in one region), H1 (single case) and A genotypes (single case) were isolated from the remaining four specimens.

Discussion

From October 2010 and throughout 2011, Italy experienced a severe measles burden with a cumulative incidence that was 2.5 times higher than that reported in the previous 15-month period [13]. Factors contributing to this upsurge include suboptimal routine vaccination coverage (‹95%) and especially the presence of large numbers of susceptible adolescents and young adults born in the 1980s and 1990s when uptake of measles vaccine was very low and the second dose had not yet been introduced. Adolescents and young adults have been frequently affected in outbreaks in recent years, but there continue to be high levels of susceptibility in these age groups.

Incidence varied greatly among geographical regions, and factors such as local epidemiology and accumulation of susceptible groups, but also underreporting, may account for these differences. The degree of underreporting to the enhanced measles surveillance system is unknown. However, a study performed in the year 2000 indicated that the national measles incidence in Italy, as estimated through data from a network of sentinel paediatricians that existed at the time, was 3.6 times higher than that estimated from statutory notification data [19]. Underreporting was found to be significantly higher in southern Italy than in northern and central Italy: the ratio between measles incidence estimated through the sentinel system and that estimated through statutory notification data was 1:1 in northern Italy, 3:1 in central Italy and 22:1 in southern Italy. Although patterns of measles reporting may since have changed, our data seem to indicate a continuing greater degree of underreporting in southern Italy.

The frequency of complications is within the range of frequencies reported in other European countries (11.4–38.6%) [20-24]. The wide range of frequencies reported in the literature may be partly due to different degrees of underreporting in the various settings but also to differences in the types of complications being reported and in different age distributions of cases. Measles complications can affect almost any organ system, but the types included in published studies

are not always specified and may differ from one setting to the next.

One measles-related death occurred in an immunocompromised patient in 2012 and was reported here because the patient had developed measles rash during the study period. Death occurred 64 days after rash onset and was due to respiratory complications of measles. The WHO defines a measles-associated death as one occurring within 30 days of rash onset and not obviously due to another cause. However, a broad range of death definitions are used in case fatality studies [25]. This death serves as a reminder that immunocompromised persons are at particular risk of severe measles complications and depend on high vaccination coverage among their contacts to protect them from infection.

In 2011, Italy renewed its commitment to eliminate measles by approving a new national elimination plan [3]. The plan, which addresses once again all components of the WHO elimination strategy, was approved by the State-Regions collegial body (Conferenza Stato Regioni), which means that all 21 regions have committed to the objectives and strategies included in the plan. Following approval of the elimination plan, a national task force of representatives of the Ministry of Health, the National Health Institute and five regional health authorities, has been established to define priorities, coordinate activities, prepare technical documents, promote sharing of information and best practice between the different regions, and implement elimination strategies in all regions. A monitoring and evaluation framework has been developed based on the recently published document by the WHO Regional Office for Europe [17].

One of the priorities identified by the task force is to improve the delivery of MMR vaccine by implementing a standard protocol for systematic reminder/recall interventions by telephone or post, to be adopted in all local health authorities for both doses of MMR vaccine. Reminder/recall is an evidence-based strategy that has been shown to be effective in increasing vaccination uptake in young children and adults, and a recent study has shown its effectiveness in adolescents as well [26-27]. A survey conducted in Italy in 2009 to evaluate the degree of implementation of strategies included in the first national measles elimination plan revealed that reminder/recall activities for the first dose of MMR vaccine at 12–15 months of age were being conducted in 93% of 143 local health authorities while 90% conducted reminder/recall for the second MMR dose at five to six years [28]. However, the types and combinations of reminder/recall activities used in the various vaccination centres may vary, and there are no data documenting whether the implemented interventions have successfully increased MMR coverage rates locally.

A second priority identified by the task force is conducting a national MMR catch-up campaign. A mathematical modelling study is being conducted to identify the age cohorts to be targeted in each region. The model will take into consideration historical and current MMR coverage levels, case notifications and the median age of reported cases in the each region.

Additional immunisation efforts should be targeted at susceptible groups such as HCWs who accounted for a non-negligible proportion (11.6%) of cases for whom the information on occupation was recorded. It is well known that HCWs are at higher risk of exposure to measles than the general population and a HCW with measles will inevitably result in large numbers of exposed high-risk patients [29]. In Italy, measles vaccination is recommended for all susceptible HCWs [30] and individual regions have developed specific guidelines; however, documentation of measles immunity is not required for employment as a doctor or nurse or for medical or nursing students in training and no coverage data among HCWs is available. Seroprevalence studies performed in HCWs in Italy indicate varying levels of seropositivity but always higher than 90% [31]. A study conducted in France showed that knowledge of recommended occupational vaccinations is insufficient in HCWs [32]. Italian HCWs' attitudes towards measles vaccination and barriers to immunisation should be investigated.

Conclusion

The experience of 2011 demonstrates that there are still major challenges to the country's 2015 elimination goals in Italy, as in the rest of Europe. In Italy, several priorities have been identified by the national task force, but all regions need to be fully committed to eliminating measles by taking action to reach high population immunity in children, identify susceptible groups and conduct supplementary immunisation activities.

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