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

Vol. 17 | Weekly issue 13 | 29 March 2012

Rapid communications

Research articles

Surveillance and outbreak reports

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Ongoing outbreak of *Shigella flexneri* serotype 3a in men who have sex with men in England and Wales, data from 2009–2011

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Citation style for this article:
Borg ML, Modi A, Tostmann A, Gobin M, Cartwright J, Quigley C, Crook P, Boxall N, Paul J, Cheasty T, Gill N, Hughes G, Simms I, Oliver I. Ongoing outbreak of Shigella flexneri serotype 3a in men who have sex with men in England and Wales, data from 2009–2011.
Euro Surveill. 2012;17(13):pii=20137. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20137

Article published on 29 March 2012

Diagnoses of *Shigella flexneri* in the United Kingdom (UK) are usually travel-related. However, since 2009, there has been an overall increase in UK-acquired cases. The Health Protection Agency has been investigating a national outbreak of *S. flexneri* detected in 2011 and which is still ongoing. Cases occurred mostly in men who have sex with men and were of serotype 3a. The investigation aimed at obtaining epidemiological data to inform targeted outbreak management and control.

Cases of *Shigella flexneri* in the United Kingdom (UK) usually originate from travel or contact with travellers from higher incidence regions such as Indian subcontinent, North and East Africa and South America [1]. Following analyses of laboratory data, an increase in UK-acquired *S. flexneri* cases was detected in London in November 2010. A subsequent rise in UK-acquired cases was also noted in Manchester in May 2011. The initial cases reported were predominantly of serotype 3a and mostly among men who have sex with men (MSM) aged between 30 and 50 years, some of whom were HIV positive. Pulsed field gel electrophoresis (PGFE) performed on initial stool specimen showed that some of the isolates were indistinguishable, however preliminary investigation failed to identify a common venue or point source [2,3].
In response, a national outbreak control team was formally established in September 2011 to investigate and manage the outbreak of *S. flexneri*. Enhanced surveillance was initiated in order to:

- describe the epidemiology of *S. flexneri* infection in individuals who had no travel history or who had travelled to countries with low risk for infection;
- estimate the proportion of UK-acquired cases or cases associated with travel in low-risk countries that are explained by transmission in MSM;
- identify risk factors for transmission of *S. flexneri* between MSM.

Sexual transmission of *Shigella* was first described in the United States during the 1970s [4]. Since then, several outbreaks of sexually transmitted *Shigella*, predominantly in MSM, have been reported [5-8]. In 2006, an outbreak of *Shigella* among MSM in London coincided with a similar outbreak in Berlin suggesting that travel plays a role in introducing *Shigella* species to populations at risk [9,10].

Outbreak investigation

National enhanced surveillance of *S. flexneri* was conducted from September to December 2011 inclusive, in order to describe and monitor the epidemiology of the outbreak. The population under surveillance consisted of UK-acquired *S. flexneri* infection cases and reported cases associated with travel in low-risk countries.

Low-risk travel-associated individuals were defined as individuals who returned to the UK in the four days before onset of illness after travel to countries with low risk for *Shigella* infection (Europe, North America and Australia). High-risk travel-associated diagnoses were defined as individuals who returned to the UK in the four days before onset of illness after travel to countries with high risk for *Shigella* infection (South America, Asia and Africa) [1].

A confirmed case was defined as a laboratory-confirmed case of *S. flexneri* with a specimen date

between 1 September and 31 December 2011 with no recent travel or who reported recent travel to low-risk countries.

A probable case was defined as a laboratory-confirmed case of *S. flexneri* with an unknown travel history.

Cases of *S. flexneri* among people who had travelled to high-risk countries or secondary cases of *S. flexneri* who were contacts of high risk travel-associated cases were excluded.

All laboratories were asked to notify *Shigella* isolations and to send stool specimens to the national reference laboratory (Gastrointestinal Infections Reference Unit, Health Protection Agency - Colindale, London) for serotyping, PFGE analysis and sensitivity testing. Weekly updates on laboratory-confirmed *S. flexneri* diagnoses were forwarded to the respective regions for further follow-up.

Local health protection units confirmed the travel history for every reported *S. flexneri* diagnosis and conducted an interview using a surveillance questionnaire for UK-acquired or low-risk travel-associated diagnoses of *S. flexneri*. The questionnaire contained additional questions on exposures such as travel, food history, contact with symptomatic individuals and sexual contact to assist with case management. In-depth interviews with confirmed MSM cases were also conducted to identify potential risk factors for infection.
S. flexneri reports from the national laboratory databases, regions and local units were collected and analysed and feedback was disseminated to the regional units and identified leads through epidemiological update reports.

Increased awareness and guidance for health professionals and people at risk of infection was issued through HPA briefings, information leaflets and press releases [11].

S. flexneri diagnoses reported by the national laboratories between 2001 and 2011 were also analysed to provide context to the current outbreak and to produce historical time trends.

Results

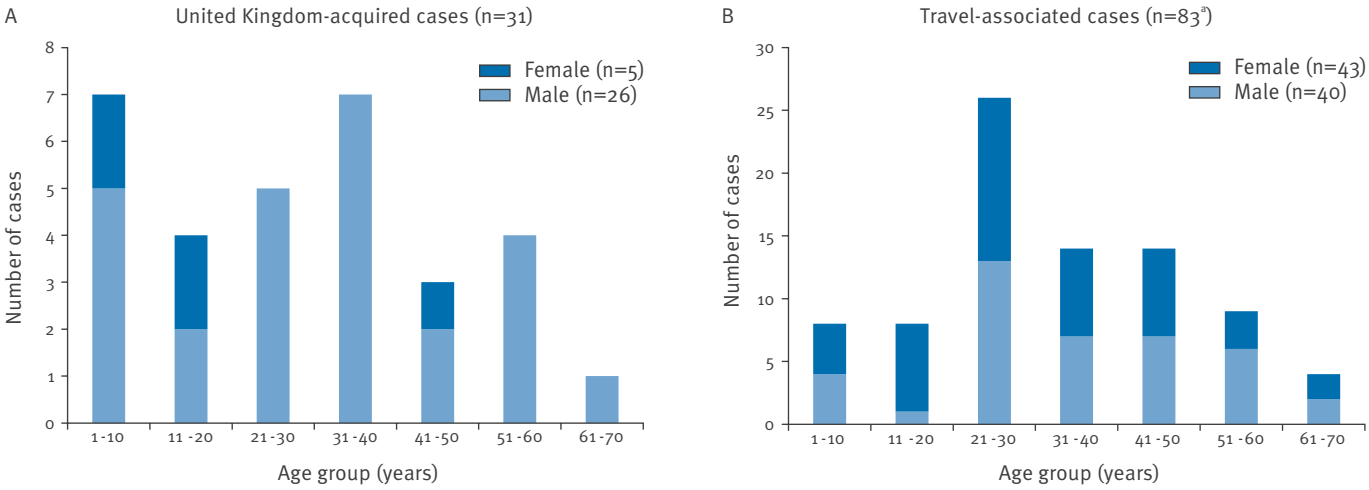
During the enhanced surveillance period between September and December 2011, 145 *S. flexneri* diagnoses were reported of which 37 (25.5%) were non-travel related. Thirty-one cases were confirmed as being UK-acquired whereas six reported diagnoses were likely to be secondary cases linked to a symptomatic contact with recent travel to a high-risk country.

Eighty-six cases (59.3%) were associated with travel to high-risk countries and the travel history was unknown for 22 individuals (15.2%). No low-risk travel-associated cases of *S. flexneri* were reported during the enhanced surveillance period.

The UK-acquired cases were predominantly male (n=26) whereas travel-associated *S. flexneri* diagnoses were equally distributed between both sexes: 48% male (n=40) and 52% female (n=43) as shown in Figure 1. The sex and age of three travel-associated cases was not known.

Figure 1

Cases of *Shigella flexneri* reported during the enhanced surveillance period by age group and sex, England and Wales, September – December 2011



[a] The gender and age of three travel-associated cases was not known.

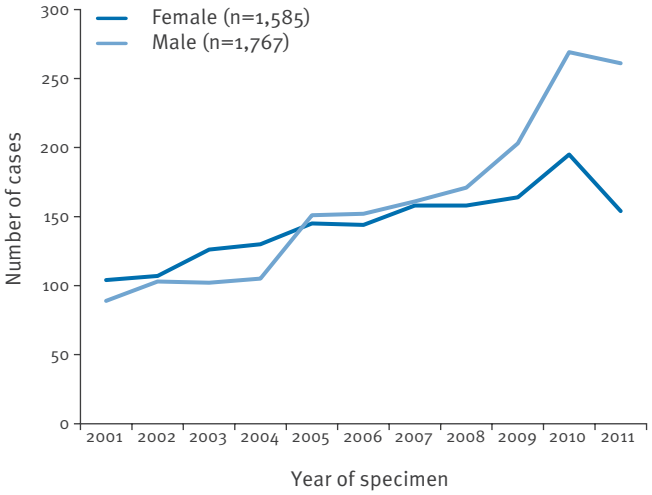
Source: National reference laboratory database (GDW- Gastro Data Warehouse), Health Protection Agency, Colindale, United Kingdom.
National laboratory reporting database (LabBase 2), Health Protection Agency, Colindale, United Kingdom.

Eleven male cases with UK-acquired *S. flexneri* reported MSM activity in the week before developing gastroenteritis. Three individuals refused to disclose their sexual orientation.

Ten of the 31 reported UK-acquired *S. flexneri* cases were serotype 3a, seven were serotype 1b, five were serotype 2a, three were serotype 6 and one case was reported for serotypes 1a, 1c, 2b and 3b. The serotype was unknown for two reported *S. flexneri* diagnoses. More than half (n=5) of the infections in MSM were caused by serotype 3a, four by serotype 1b, one by serotype 2a and one by serotype 6.

Figure 2

Shigella flexneri cases with no or unknown travel history stratified by year and sex, England and Wales, 2001–2011 (n=3,352)



Source: National laboratory reporting database (LabBase 2), Health Protection Agency, Colindale, United Kingdom.

In depth interviews with seven MSM cases showed that they all had one long term partner and attended regular medical examinations. However, all cases reported having a casual sexual partner in the week preceding illness. These interviews revealed lack of awareness about *Shigella* and of the risks associated with unprotected oral and oral-anal sex.

Trends in *S. flexneri* diagnoses reported between 2001 and 2011 showed a gradual increase in the number of cases with no or unknown history of travel since 2001, with a similar trend in both sexes until 2008 (Figure 2). However, from 2009 onwards, numbers of diagnoses rose far more rapidly in men (Figure 2).

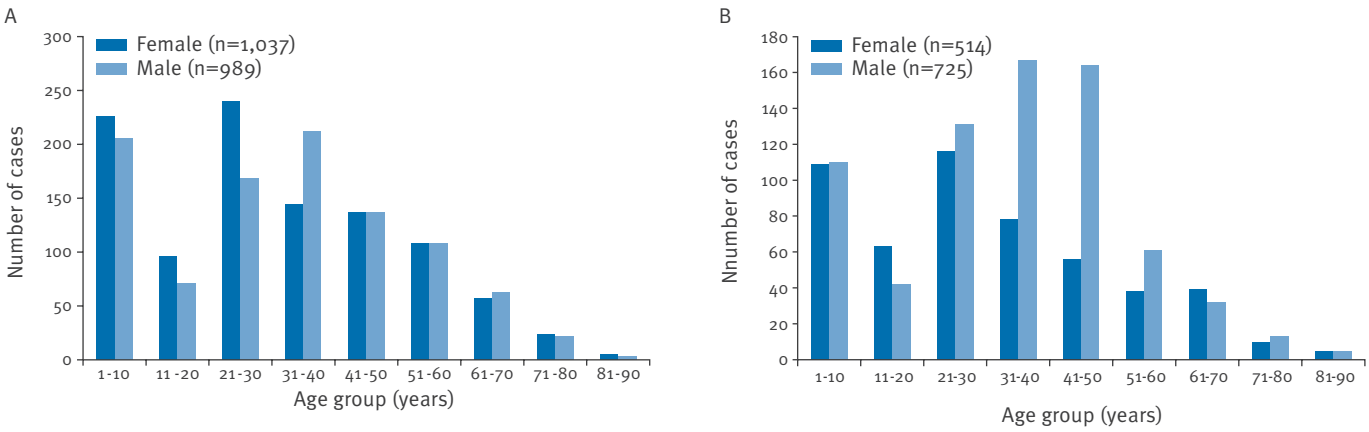
Data analysis revealed similar trends in cases between sexes and within the same age group, however, since 2009 the increase in the number of *S. flexneri* cases reported was attributable to an overrepresentation of men aged between 31 and 50 years (Figure 3).

Figure 4 shows the number of *S. flexneri* diagnoses by serotype from 2004 to 2011. The number of cases infected with serotype 3a has increased considerably and as from 2009 it has become as predominant as the 2a serotype and accounted for the increase in *S. flexneri* cases between 2009 and 2011.

The increase in serotype 3a since 2009 was mostly attributable to diagnoses among men aged 30-50 years which constituted 65% (211/324) of all *S. flexneri* 3a reports with no or unknown travel history between 2009 and 2011. When focusing on the male adult cases with serotype 3a, the number of monthly *S. flexneri* diagnoses in 2007/2008 fluctuates between 1 and 7 cases. The number of monthly reports increases to between 5 and 15 from 2009 onwards. The following graph shows the number of monthly diagnoses from

Figure 3

Shigella flexneri cases by sex and age group, England and Wales, (A) 2001–2008 (n=2,026) and (B) 2009–2012 (n=1,239)



Source: National laboratory reporting database (LabBase 2), Health Protection Agency, Colindale, United Kingdom.

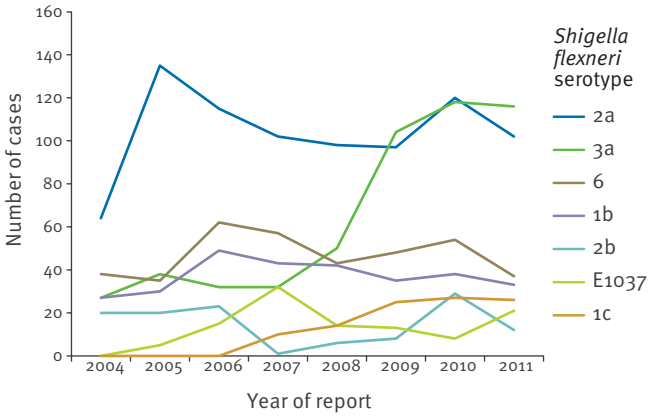
2007-2012 and a three-month moving average (Figure 5).

Control measures

The outbreak control team introduced control measures which focused on actions aimed at prompt and effective management of cases to prevent onward transmission. They included increasing awareness among clinicians and MSM and prompt diagnosis and treatment, increased testing of MSM with diarrhoea and treatment of laboratory-confirmed cases with ciprofloxacin [12] subject to antimicrobial sensitivity.

Figure 4

Shigella flexneri serotype by year of report for cases with *S. flexneri* infection with no or unknown travel history, England and Wales, 2004-2011 (n=2,350)



Source: National reference laboratory database (GDW- Gastro Data Warehouse), Health Protection Agency, Colindale, United Kingdom.

These actions also included recommendations regarding behaviours that may contribute to prevent further transmission:

- wash hands after using toilet, before preparing or eating food and after sexual activity;
- avoid anal sex, oral-anal sex, scat and rimming whilst symptomatic and until test for infection shows clearance;
- use of condoms, gloves, dental dams during sex;
- avoid sharing douching materials and sex toys;
- avoid swimming pools and spa centres whilst ill and for two weeks after recovery.

Work is ongoing to identify risk factors for infection and evaluate other possible control measures such as screening of asymptomatic contacts.

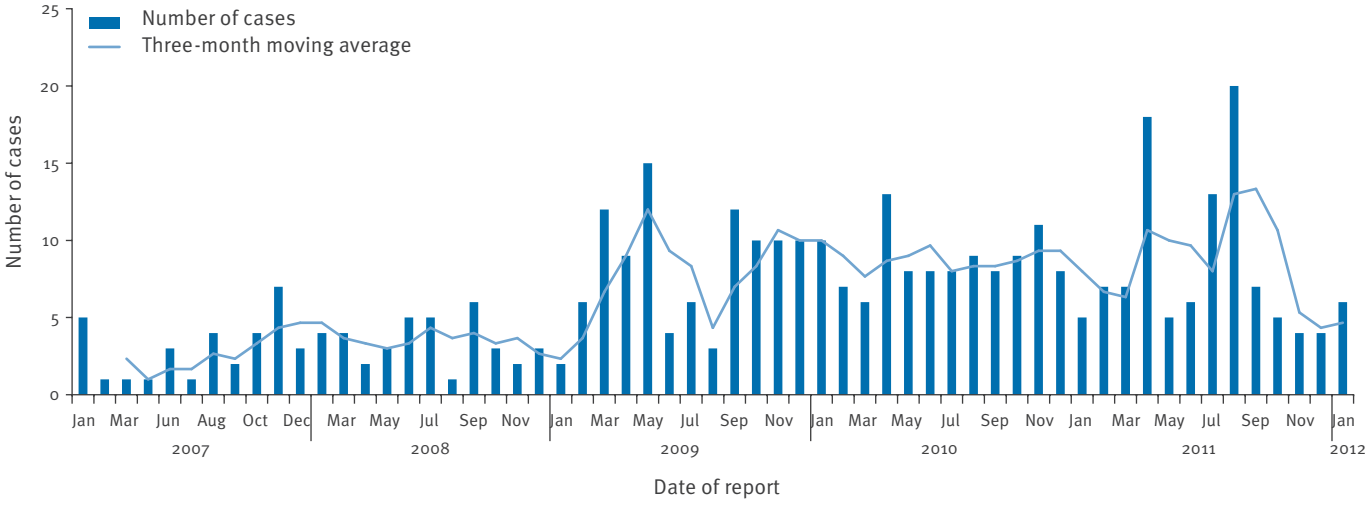
Discussion and conclusion

As the outbreak is still ongoing and no similar *S. flexneri* outbreaks have recently been reported by other countries, increased vigilance and monitoring by other European countries is recommended in order to promptly and effectively detect any change in the reported trends of *S. flexneri*.

Although some people may have been reluctant to disclose details about their sexual orientation, the enhanced surveillance revealed a strong association between UK-acquired *S. flexneri* and transmission in MSM. The outbreak will continue to be monitored through routine arrangements and information on cases occurring in MSM will continue to be collected in order to effectively describe the epidemiology of the disease in MSM and identify any potential risk factors to inform public health action.

Figure 5

Adult male cases of *Shigella flexneri* 3a infection with no or unknown travel history, England and Wales, January 2007–January 2012 (n=381)



Source: National reference laboratory database (GDW- Gastro Data Warehouse), Health Protection Agency, Colindale, United Kingdom.

Although the *S. flexneri* outbreak first emerged in 2009 and has been sustained since then, it has only been detected relatively recently. An evaluation of *Shigella* infection surveillance will therefore be carried out in order to identify factors leading to the delay in outbreak identification and to explore new approaches to routine surveillance of sexually-transmitted *Shigella* infection.

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Severe leptospirosis in a Dutch traveller returning from the Dominican Republic, October 2011

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Citation style for this article:
Arcilla MS, Wismans PJ, van Beek-Nieuwland Y, van Genderen PJ. Severe leptospirosis in a Dutch traveller returning from the Dominican Republic, October 2011. Euro Surveill. 2012;17(13):pii=20134. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20134

Article published on 29 March 2012

In October 2011, a case of leptospirosis was identified in a Dutch traveller returning from the Dominican Republic to the Netherlands. The 51-year-old man had aspired muddy water in the Chavón river on 29 September. Twenty days later he presented with fever, nausea, vomiting, diarrhoea, arthralgia, headache, conjunctival suffusion and icterus. *Leptospira* serovar Icterohaemorrhagiae or Australis infection was confirmed ten days later by laboratory testing.

We report on a patient diagnosed with leptospirosis following travel to the Dominican Republic. Only a few cases of leptospirosis have been described among travellers to the Dominican Republic [1]. This case serves as a reminder for physicians to consider leptospirosis in the differential diagnosis of febrile patients returning from the Dominican Republic.

Case report

At the end of September 2011, a 51-year-old Dutch male spent 14 days at a tourist resort in Punta Cana, Dominican Republic. During his stay he made several excursions, among which one was a swimming excursion to the Chavón river near the village Altos de Chavón. While swinging from a vine, he fell in the river. His travel companions covered his body and face with mud from the river bank, which caused the patient to aspire muddy water. Twenty days after this incident, when back in the Netherlands, he presented with fever, nausea, vomiting, diarrhoea, arthralgia and headache at the outpatient department of the Havenziekenhuis in Rotterdam. On physical examination conjunctival suffusion and icterus was noted. Laboratory results showed raised C-reactive protein (280 mg/L, norm: 0-10 mg/L), thrombocytopaenia ($44x10^9$/L norm: 150-400$x10^9$/L) and total bilirubin (104 µmol/L, norm: 0-17 µmol/L) without a marked increase in liver transaminases, and signs of renal dysfunction (creatinine 268 µmol/L, norm: 65-115 µmol/L). After admission, the clinical condition of the patient deteriorated with hypotension, progressive kidney failure and anuria for which he was admitted to the Intensive Care Unit. Because there had been typical exposure to mud, twenty days prior to the clinical manifestations, the working diagnosis was septicaemia due to leptospirosis.

The diagnosis was confirmed by the demonstration of specific agglutinating antibodies against *Leptospira* spp in a microscopic agglutination test (MAT), titer 1:320, and specific immunoglobulin M (IgM) antibodies (ELISA › 1:160) in a second sample taken 10 days after presentation. Interestingly, even though serology was negative in the serum sample taken on admission, a real-time PCR was positive [2,3]. The causative serovar was identified by the MAT as probably belonging either to the *Leptospira* serovar Icterohaemorrhagiae or Australis [4]. Other potential diseases such as malaria and dengue, were excluded. Blood cultures taken on admission remained negative.
He was treated with ceftriaxone intravenously and doxycycline orally. The patient's condition improved following intensive fluid resuscitation and infusion of vasopressors. His renal function had recovered completely after seven days and after 10 days, the patient left the hospital.

His fellow travellers remained asymptomatic throughout this period.

Background

Leptospirosis is a worldwide zoonotic infection with a much greater incidence in tropical regions [5,6]. An increasing number of imported cases of leptospirosis following international travel are being published [7]. High risk areas include India, Sri-Lanka, Thailand, Vietnam, Malaysia, China, Seychelles, the Caribbean, Brazil and the Pacific Islands. Leptospirosis is now considered an emerging disease in travellers [8]. Human infection results from exposure to infected urine from carrier mammals, either directly or via contamination of soil or water. Leptospirosis in travellers is usually associated with recreational activities that involve contact with freshwater, soil and animals such as jungle trekking and kayaking [9].

Conclusions

Statistics published by the Epidemiology Department of the Dominican Ministry of Public Health show that from January until mid-March 2012 there were 211 suspected cases of leptospirosis [10]. In 2011, there were a total of 891 suspected cases of leptospirosis in the Dominican Republic, a clear decrease compared with 2010 when there were 1,270 suspected cases [10]. As outbreaks often occur following natural disasters such as earthquakes, weather conditions as rainstorms and ensuing floods could have an impact on the incidence of leptospirosis in the Dominican Republic [11].

Physicians taking care of travellers returning ill with fever should consider leptospirosis a differential diagnosis in those who have travelled to areas where *Leptospira* spp are endemic and those who participated in high-risk activities. Given the potentially fatal course of severe leptospirosis, pre-emptive antibiotic treatment for leptospirosis should be considered without delay in febrile travellers returning from endemic regions, who have been exposed to freshwater and soil or have had skin contact with animals [12–15]. Travellers who plan to engage in water activities should be advised about preventive measures such as wearing protective clothing and shoes, and to cover up abrasions.

Acknowledgments

We would like to thank Mr. H. van der Linden from the National Leptospirosis Reference Laboratory of the Royal Tropical Institute Biomedical Research, Amsterdam, the Netherlands for providing information concerning the diagnostic tests.

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Risk perception and information-seeking behaviour during the 2009/10 influenza A(H1N1)pdm09 pandemic in Germany

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Citation style for this article:
Walter D, Böhmer MM, Reiter S, Krause G, Wichmann O. Risk perception and information-seeking behaviour during the 2009/10 influenza A(H1N1)pdm09 pandemic in Germany.
Euro Surveill. 2012;17(13):pii=20131. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20131

Article published on 29 March 2012

During the influenza A(H1N1)pdm09 pandemic in 2009/10, a total of 13 consecutive surveys were carried out of the general population in Germany to monitor knowledge, attitude and behaviour concerning the disease and vaccination against pandemic influenza in real time. In total, 13,010 persons aged 14 years or older were interviewed by computer-assisted telephone techniques between November 2009 and April 2010. During the peak of the pandemic, only 18% of participants stated that they perceived the risk of pandemic influenza as high; this proportion fell to 10% in January 2010. There was a significant difference in information-seeking behaviour among population subgroups concerning the disease and vaccine uptake. However, in all subgroups, conventional media sources such as television, radio and newspapers were more frequently used than the Internet. While the majority of participants (78%) felt sufficiently informed to make a decision for or against vaccination, overall vaccination coverage remained low. Among those who decided against vaccination, fear of adverse events and perception that the available vaccines were not sufficiently evaluated were the most frequently stated reasons. Such mistrust in the vaccines and the perceived low risk of the disease were the main barriers that contributed to the low vaccination coverage in Germany during the pandemic.

Introduction

After the first description of a novel influenza A(H1N1) virus in April 2009, the virus rapidly spread worldwide. While many countries experienced a first pandemic wave in the middle of 2009, Germany was initially affected by imported cases followed by an acceleration of cases mainly due to travellers and their contacts in the summer of 2009 [1]: at the end of September, there was an increase in the number of reported autochthonous influenza A(H1N1)pdm09 cases, followed by a sharp increase in the number of cases from October onwards, which peaked in the middle of November (week 46) [2].

In September 2009, the German Standing Committee on Vaccination (STIKO) recommended that people in target groups – people at occupational risk (including healthcare workers), persons with underlying chronic diseases and pregnant women – should be vaccinated against influenza A(H1N1)pdm09. The vaccination campaign officially started at the end of October 2009 (week 44), when pandemic vaccines became available. In Germany, an AS03-adjuvanted vaccine was almost exclusively used, with a one-dose recommendation for all age groups. With the availability of large numbers of vaccine doses, in mid-December 2009, the Committee expanded its recommendation to the general population, but still with prioritisation of the target groups mentioned above [3]. Although the vaccine was shown to be highly effective in protecting against pandemic influenza [4], vaccine uptake remained low among the general public and even among those in vaccination target groups [5].

Research into knowledge, attitude and behaviour in the context of a pandemic can not only guide communication and mitigation strategies during the event, but can also inform future pandemic preparedness planning. Data can be collected via online or telephone surveys, which – if analysed ad hoc – can provide insights into public perceptions related to the disease and implemented control measures in real time. In Germany, we conducted 13 consecutive cross-sectional knowledge, attitude and behaviour surveys to monitor the vaccination campaign against pandemic influenza in the general population in 2009/10. Our primary objective was to assess vaccine uptake in different target groups. Details of target group-specific vaccination coverage have been published previously [5]. Here we present data from the surveys related to public perception of the disease and relevant vaccination as

well as information seeking-behaviour during the pandemic. The analysis aimed to identify possible pivotal points and needs for future communication planning in situations with pandemic potential and immunisation campaigns.

Methods

Cross-sectional telephone surveys

A series of 13 computer-assisted telephone interview surveys took place from 16 November (week 47) 2009 to 14 April (week 14) 2010. The first nine were carried out every two weeks, until 10 March; the final four, from 22 March to 14 April (weeks 12–15) 2010, were weekly. The first survey took place about three weeks after the official start of the influenza A(H1N1)pdm09 vaccination campaign in Germany.

The survey methodology has been published previously [5]: in brief, each survey was conducted with a representative sample of approximately 1,000 households. The surveys included a core set of questions: other questions were changed, included or deleted in surveys over the study period to monitor new or upcoming topics of research or to adjust to changing situations. Because of that, each analysis refers to the particular surveys in which the questions of interest were included. The interviews were conducted by forsa (Gesellschaft für Sozialforschung und statistische Analysen mbH), a large market research company with extensive experience in health-related surveys, as part of forsa's daily omnibus survey in Germany, a continuing multi-topic survey primarily used for market research.

Interviews were performed according to the data protection standards used by forsa, which include obtaining oral informed consent before starting the interview. Trained interviewers surveyed randomly selected German-speaking individuals, aged 14 years and older, living in private households equipped with a telephone. In each household contacted, the last-birthday selection method was applied [6]. Interviews were usually conducted on workdays in the afternoon or evening, but appointments were also made if requested. The survey samples were weighted for region, age, sex and educational level on the basis of recent population projections of the Federal Statistical Office of Germany [7].

To monitor vaccine uptake as well as knowledge and attitude related to pandemic influenza, we used a core set of questions in all 13 surveys, e.g. questions on immunisation against pandemic or seasonal influenza, as well as questions designed to categorise interviewees into specific target groups for vaccination as defined by the German Standing Committee on Vaccination. Socio-demographic information (e.g. age, sex, educational level) was assessed as part of the omnibus survey. Furthermore, interviewees were asked to judge how high they perceived the threat imposed by pandemic influenza to their personal health, how well informed they felt about the disease and vaccination against pandemic influenza, the information sources they used during the pandemic and the perceived risk related to the vaccination.

Statistical analysis

Statistical analysis was performed using PASW version 18.0 for Windows (SPSS, United States). Univariable and multivariable analyses were performed using the complete set or subsets of survey data. A two-sided p value of less than 0.05 was considered to indicate a statically significant difference. Statistical independence was tested using logistic regression models. Multivariate analysis was performed using multiple logistic regression models with combined stepwise backward removal and forward selection. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Variables potentially associated with vaccine uptake ($p<0.2$ in univariable analysis) were entered into a multivariate logistic regression model in a first step, followed by stepwise backward removal of variables with a p value greater than or equal to 0.05 to produce a final model.

Variables were categorised as follows: age group (aged 14–24, 25–59, ≥60 years), sex (male/female), geographical region (west/east), level of education (low: nine years or less of school education; medium: at least 10 years of school education; high: university entrance diploma), community size (≤5,000; 5,001–20,000; 20,001–100,000; 100,001–500,000; >500,000 inhabitants), whether in a vaccination target group, as defined by German Standing Committee on Vaccination (persons with underlying chronic diseases, people at occupational risk and pregnant women).

For questions requiring agreement or disagreement, four categories were possible: full or partial agreement and full or partial disagreement. Data were weighted with respect to the inclusion probability depending on geographical region, age, sex and level of education of the participants. All statistical analyses were performed using the weighted data.

Results

A total of 13,010 telephone-interviews were conducted in the 13 cross-sectional surveys. The first nine surveys, conducted every two weeks, comprised 9,005 participants and the final four weekly surveys, which were identical, a total of 4,005. As the interviews were part of the omnibus survey, which has an ongoing inclusion of telephone numbers, a precise response rate cannot be determined. The average response rate in the omnibus survey was approximately 45% and the refusal rate 26%. The median age of all respondents was 48 years (range: 14–93) with 52.5% of the interviewed persons being female.

Risk perception related to pandemic influenza

During the first nine surveys, the 9,005 respondents answered questions about the perceived threat of pandemic influenza to their personal health. The first

survey took place at about the same time most influenza A(H1N1)pdm09 cases per week were notified to the national disease surveillance system in Germany (Figure). Risk perception (i.e. risk due to 'swine flu' perceived as great or partially great) fell in the general population from about 18% in November 2009 (week 47) to a plateau of approximately 10% in the surveys in December 2009 (weeks 51 and 53) and January 2010 (weeks 2 and 4). Over the same time period, there was an increase in the proportion of respondents who stated that their perception of risk was low, from about 34% in the initial survey (week 47) to approximately 65% in March 2010 (week 10). The risk perception over the first nine surveys among all interviewed persons, among those who were aged 60 years or older and among those belonging to the target vaccination groups is shown in the Figure.

In the final four weekly surveys, during March and April 2010, 70% of the 4,005 interviewees agreed fully and 10% agreed partially to the statement that in retrospect at no point in time had they felt a special threat to their personal health due to 'swine flu'.

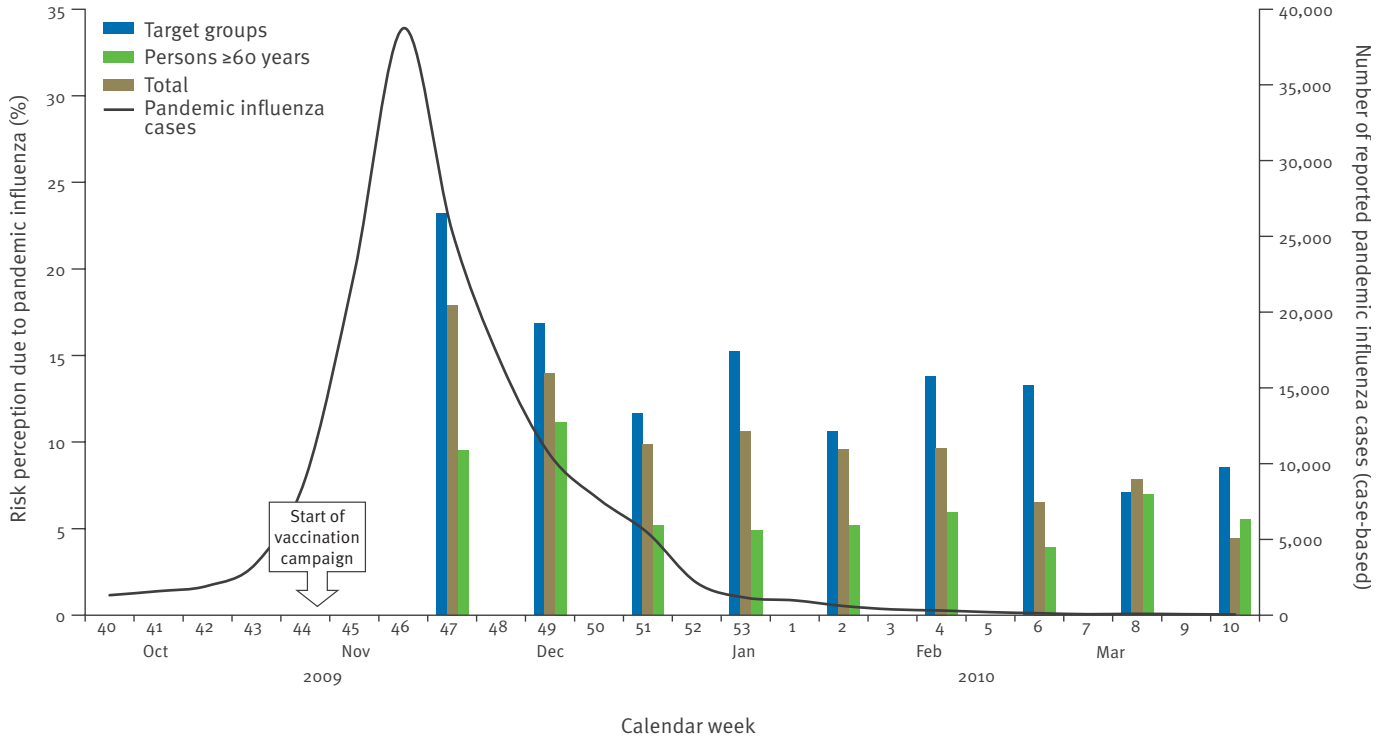
In two surveys in January 2010 (weeks 2 and 4), we asked participants about the potential influence of the media coverage on their risk perception related to pandemic influenza in Germany. Among the 1,000 respondents in the mid-January survey (week 2), 68.2% agreed fully and 16.1% agreed partially to the statement that media reporting about pandemic influenza had been exaggerated. Furthermore, 33.0% of the 1,004 respondents at the end of January (week 4) agreed fully and 12.0% agreed partially to the statement that media reporting about the vaccine had led to a feeling of uncertainty.

Informedness about pandemic influenza

In the first six surveys (those until the end of January 2010 (week 4)), we asked how well informed the participants felt about pandemic influenza. In the first survey, 17.7% of the 1003 respondents stated that they were 'not well' informed and 28.5% 'partially not well'. Over the time course of these six surveys, the proportion of 6005 respondents who did not feel well or partially not well informed fell to 10.2% and 21.5%, respectively. In the pooled data set of the first six surveys, the proportion of respondents who felt well or partially well informed increased by level of education (59.3% with a low level of education, 64.5% with a medium level and 69.7% with a high level; for comparisons at all educational levels, $p < 0.001$) and decreased with age (age group 14–24 years: 72.7%; 25–59 years: 64.2%; ≥60 years: 61.0%; for comparisons in all age groups: $p<0.001$). Respondents who were not immunised against pandemic influenza stated more frequently

Figure

Proportion of respondents who perceived a great or partially great threat due to pandemic influenza in the first nine surveys, by population subgroup, 16 November (week 47) 2009–10 March (week 10) 2010 (n=9,005) and epidemic curve of pandemic influenza cases (case reports)



Source of number of reported pandemic influenza cases (case based): [2].

to be not well or partially not well informed about the disease compared with those respondents who were immunised (35.9% v. 28.2%; p<0.05).

Information sources used to find out about pandemic influenza

Between mid-November and the end of December 2009 (weeks 47–53) – a period with substantial spread of pandemic influenza in the population – we asked 4,003 participants about the sources used to gather information about the disease. The main sources of information were the mass media, such as television and radio (71.2%; 95% CI: 69.3–73.0), as well as print media, such as magazines or newspapers (58.6%; 95% CI: 56.6–60.7). The Internet was used by 27.6% (95% CI: 26.0–29.4) as a source of information, but – when stratifying by age group – only by 10.2% (95% CI: 8.3–12.4) of persons 60 years and older. Friends and relatives were mentioned as an important source of information by 56.1% (95% CI: 54.1–58.1) and physicians by 31.0% (95% CI: 29.1–32.8). Some 3.1% (95% CI: 2.4–4.0) stated not to have used any kind of information source.

Respondents belonging to the vaccination target groups used physicians more frequently (38.0% v. 28.1%; p<0.001) and peers less frequently (51.4% v. 58.0%; p<0.01) as a source of information related to the disease when compared with the respondents who were not in a target group. Physicians were used as a source of information about the disease by 62.1% of respondents who had been vaccinated against pandemic influenza, in contrast to 28.8% of respondents who had not received the vaccine (p<0.001). There was, however, no statistically significant association between any source used to gather information on the disease in general and the uptake of influenza A(H1N1) vaccine.

Informedness and attitude related to pandemic influenza vaccination

In the final four surveys (n=4,005), we asked how well informed the respondents felt about issues related to pandemic influenza vaccination. In total, 78.4% (95% CI: 75.1–81.6) agreed fully or partially to the statement that they felt sufficiently informed during the pandemic to make a decision for or against vaccination. Only 23.8% (95% CI: 22.1–25.6) agreed fully and 11.3% (95% CI: 10.1–12.6) agreed partially that they lacked neutral and factual information. However, 55.3% (95% CI: 51.8–59.0) fully and partially had the feeling that official authorities had not informed the public openly and honestly about issues related to the vaccination.

Stratified analysis showed that 91.8% (95% CI: 87.6–94.6) of respondents who had been vaccinated agreed fully or partially that they were sufficiently informed to make a balanced vaccination decision, while only 78.1% (95% CI: 76.2–79.9) of those who had not been vaccinated felt well informed (p<0.001). There was also a significant difference in the number of respondents who agreed that official authorities had informed the public openly and honestly about pandemic influenza vaccination when comparing vaccinated with unvaccinated respondents (63.0% v. 41.1%; p<0.001).

Use of information sources related to pandemic influenza vaccination

Data on sources used to gather information on vaccination against pandemic influenza was available from the 4,005 persons interviewed in the final four surveys. There was a significant difference in information-seeking behaviour among population subgroups (Table 1). When compared with younger age groups, respondents aged 60 years or older obtained information significantly more frequently from conventional media sources such as radio, television, newspapers, and magazines. The Internet as well as information materials of official health authorities were less frequently used by all age groups compared with conventional media sources. Internet use for this purpose increased significantly with higher educational level. Physicians as a source of information related to vaccination were mentioned more frequently by older age groups and almost twice as frequently by vaccinated compared with unvaccinated respondents (Table 1). Persons who belonged to a vaccination target group used the Internet less frequently (21.6% v. 26.9%; p<0.01) and their physician more frequently (42.1% v. 29.8%; p<0.001) as source of information compared with respondents not in the target groups.

We used univariable and multivariable logistic regression models to explore potential associations between the source of information about vaccination and vaccine uptake by using data from the final four surveys (Table 2). After adjusting for possible confounders (i.e. age, sex, whether in a vaccination target group, education level, community size and region), we found that use of radio or television (OR: 0.62; 95% CI: 0.48–0.81) as well as family and friends (OR: 0.72; 95% CI: 0.55–0.94) as a main source of information were independently associated with lower vaccine uptake. In contrast, an association with vaccine uptake and the search for information about vaccination was found when physicians (OR: 2.77; 95% CI: 2.16–3.57) or official materials (OR: 2.07; 95% CI: 1.55–2.77) were used as a main source of information. Use of the Internet as a main information source for vaccination was not associated with pandemic influenza vaccination in our study population (Table 2).

Reasons for not being immunised against pandemic influenza

In all 13 surveys over the whole study period, we asked persons who were not vaccinated against pandemic influenza and did not intend to be the reason why they objected to vaccination. Fear of adverse events of the vaccine was given as a reason for not being vaccinated in approximately 20%; the perception that the vaccines were insufficiently tested was stated in 15%. An additional 14% stated that their decision against

the vaccination was triggered by 'public panicking and overhyping' and approximately 10% stated that they felt vaccination was just not necessary. Lack of information about the vaccine or information about possible side effects was mentioned in 2%. The proportion of respondents who stated they had a fear of adverse events decreased by age (chi-square test for trend, p<0.001) and was lowest in those aged 60 years or older (13.5%). In mid-January 2010, we asked the survey participants (n=1,000) if they believed that the adjuvant in the pandemic vaccine was safe. Of those, 8% agreed fully and 10% partially.

Discussion

Our survey results provide important insights into public opinion and information-seeking behaviour related to the influenza pandemic and vaccination campaign in Germany in 2009/10. The findings of the survey are generally in line with those conducted in other countries during the pandemic [8,9]. In Germany, vaccine uptake was particularly low, even in vaccination target groups, and communication practices might have contributed to this fact [5]. Our findings suggest that a perceived low risk related to the disease and concerns about the safety of available vaccines were the main barriers to pandemic influenza vaccination.

The first of the 13 consecutive surveys was carried out during the peak of the pandemic wave and at the early phase of the vaccination campaign. Therefore, we were not able to monitor trends in risk perception from the beginning of the pandemic in spring 2009. However, even during the peak of pandemic influenza in Germany, we observed that the level of perceived risk was low. Similar findings were reported from Australia in 2009, where risk perception was low even during times of high likelihood of acquiring the virus [10]. Risk perception in our survey fell further at the beginning of 2010 and was particularly low in persons aged 60 years and older.

According to the health belief model, risk perception (which is usually defined by the expected probability of an event and its severity) and believing that preventive measures are safe and effective are the main factors influencing a vaccination decision [11]. A literature review assessing factors that influence preventive behaviour during pandemic situations highlighted that perceived susceptibility to and severity of the disease as well as believing in the effectiveness of protective measures increased its implementation [12]. A low-to-moderate risk perception related to pandemic influenza and lack of concern was observed in surveys in various industrialised countries during 2009/10, for example in Italy [13], the Netherlands [14], Australia [15] and the United States [16].

Public risk perceptions may be directly modulated by media coverage, and media-triggered public concern was shown to be an important factor for health-related personal measures during the influenza pandemic as shown in studies in, for example, the United States [17] or France [18]. While there are studies showing that media coverage can have a positive influence on disease perception and willingness to be vaccinated against seasonal influenza [19,20], the reception of media output during an influenza pandemic needs to be analysed carefully [21]. In Europe, the initial media attention, related to the occurrence of a new pandemic influenza strain in 2009, was found to be high [22].

Table 1

Sources used to gather information on vaccination against pandemic influenza, by population subgroup, Germany, final four surveys, 22 March–14 April (weeks 11–15) 2010 (n=4,005)

Source of information[a]	Percentage of respondents										
	Total n=4,005	Vaccinated against pandemic influenza		Sex		Age group (in years)			Educational level[b]		
		Yes[c] n=324	No n=3,676	Male[c] n=1,948	Female n=2,057	14–24 n=555	25–59 n=2,261	≥60[c] n=1,170	Low[c] n=1,706	Medium n=1,094	High n=965
Radio or television	64.6	53.0	65.6***	63.7	65.3	51.9***	64.5***	70.9	68.3	65.8	59.5***
Newspapers or magazines	50.0	47.4	50.3	49.4	50.5	35.2***	49.6***	58.2	50.1	49.9	53.6
Family and friends	42.8	39.5	43.1	39.4	45.9***	47.0***	46.9***	33.1	38.6	46.6***	45.6***
Physician	34.0	66.9	31.1***	30.0	37.7***	26.0***	33.8**	38.3	36.6	35.2	31.6*
Internet	25.1	21.9	25.4	26.0	24.3	31.5***	31.1***	10.9	17.2	27.2***	37.2***
Information materials from official authorities	13.4	22.9	12.6***	11.5	15.2**	12.6**	16.4***	8.2	8.6	16.7***	19.1***
Other sources of information	2.8	3.5	2.7	2.2	3.3*	3.2*	3.5***	1.3	1.9	3.2*	3.2*
No active information-seeking	5.7	0.0	6.2	7.2	4.2***	12.1***	4.7	4.3	6.2	5.2	4.2*

* p<0.05, ** p<0.01, *** p<0.001.

[a] Multiple answers were possible.

[b] Low: nine years or less of school education; medium: at least 10 years of school education; high: university entrance diploma.

[c] Reference group.

Systematic content analysis, for example, of television reports in Australia [23] or print media in the United Kingdom [24] and in the German city of Bremen [25], did not show that reports on pandemic influenza were scaremongering. Our data, however, suggest a public sentiment of media exaggerating the situation in Germany. Use of television and radio as a main source of information was associated with lower vaccine uptake compared with use of other sources. This finding is consistent with studies showing that uncertainty about the pandemic situation and perceived exaggeration of the situation is associated with a reduced likeliness to implement the recommended behaviour [26].

In general, the Internet is regarded as an important source of information for the general public on health-related topics: therefore, relevant and high-quality information should be made available online [27]. Nonetheless, in our survey, use of the Internet was found to be low compared with other information sources. The Internet does not seem to be effective in reaching certain population groups such as elderly people or those with a low educational level.

Table 2

Univariable and multivariable analysis of the association of the source of information about the vaccine and vaccination against pandemic influenza, Germany, final four surveys, 22 March–14 April (weeks 11–15) 2010 (n=4,005)

Source of information	Used or not	Univariable analysis	Multivariable analysis[a]
		OR (95% CI)	OR (95% CI)
Radio or television	No	1[b]	–
	Yes	0.56 (0.46–0.72)	0.62 (0.48–0.81)
Newspaper or magazines	No	1[b]	–
	Yes	0.84 (0.67–1.05)	NS
Family and friends	No	1[b]	–
	Yes	0.75 (0.59–0.95)	0.72 (0.55–0.94)
Physician	No	1[b]	–
	Yes	3.37 (2.67–4.26)	2.77 (2.16–3.57)
Internet	No	1[b]	–
	Yes	0.93 (0.72–1.20)	NS
Information materials from official authorities	No	1[b]	–
	Yes	2.1 (1.66–2.78)	2.07 (1.55–2.77)
Other sources of information	No	1[b]	–
	Yes	2.08 (1.25–3.49)	2.26 (1.29–3.95)

CI: confidence interval; OR: odds ratio; NS = not significant.

[a] Adjusted for age, sex, whether in a vaccination target group, educational level, community size, region.

[b] Reference category.

Although Internet use was found to be lower than expected in our study, the impact of specific online communication, such as the use of social media, was not assessed. Nevertheless, the spread of information through informal online networks and peer-to-peer communication might have had considerable impact on vaccination decisions during the pandemic. This has been shown in Japan, where informal networks of communication were influential in sharing safety information on pandemic influenza vaccine [28]. A survey of Hong Kong adults supports the finding that trust in informal information sources may be linked to the perceived health risk related to pandemic influenza and avoidance behaviour [29]. Using family and friends as a main source of information was shown to be negatively associated with vaccine uptake in our study. This finding corroborates the hypothesis that peer-to-peer communication is of high importance in a pandemic [30].

Concern about the safety of the pandemic vaccines was identified as a major barrier to vaccination in our study population. This was consistently observed in many studies assessing factors influencing vaccination decision [11]. In Greece, for example, fear about vaccine safety was the most frequently mentioned reason against vaccination [31]. Although we found that the majority of respondents felt sufficiently informed to make a balanced vaccination decision, information about the safety and benefits of the pandemic vaccine was obviously not convincing enough to reach satisfactory immunisation rates in the population. In a situation of high uncertainty about risks, trust in public bodies may be a crucial factor for the success of public health measures. Building and maintaining trust should therefore be a long-term task, involving all stakeholders [30]. The observed mistrust in the safety and usefulness of the pandemic vaccines stresses that information campaigns primarily focusing on the safety of pandemic vaccines may not be sufficient in a situation of low risk perception related to the disease [32].

Physicians were considered an important source of information, in particular regarding vaccination decisions, among respondents who were in vaccination target groups. Therefore informing healthcare professionals about the risks and benefits of the vaccine can be regarded crucial to increasing vaccination coverage. Public trust in medical organisations was shown to be an important factor for pandemic influenza vaccination decisions in Switzerland [33]. In our study, being informed by physicians and use of information material of official authorities were independently associated with vaccination against pandemic influenza. Surveys in the United States showed that persons who reported use of information from healthcare providers and official sources were more frequently convinced about the seriousness of pandemic influenza and the usefulness of the immunisation [34]. In an Italian survey, not only concerns and risk perception, but also trust in the media and official bodies were associated with compliance to the recommended behaviour [35]. In our study,

however, a considerable proportion of participants had the feeling that official authorities had not informed the public openly and honestly about issues related to the vaccines.

A limitation of our study is that bias due to the telephone sample procedures cannot be excluded. Household-based telephone surveys may have limited access to certain groups such as people who use exclusively mobile phones or persons living in nursing homes. Furthermore, the survey represents only German-speaking persons: individuals without German-language skills might use different patterns of information sources. On the other hand, however, using a standard omnibus survey, which contained topics not related to the study, may have reduced potential bias due to rejection or higher interest in the study topic. Results of our surveys were furthermore weighted to control for possible selection biases.

In conclusion, on the basis of the results of our surveys – which began shortly after start of the vaccination campaign – we were able to demonstrate that the pandemic influenza vaccination campaign in Germany took place when public risk perception related to the disease was low, while scepticism and misconceptions about the pandemic influenza vaccine and implemented measures were frequent. These findings are in line with surveys of other countries conducted during the pandemic [8,9] but add the first insights into the situation in Germany, where vaccine uptake was particularly low. Rebuilding trust in recommendations of public health authorities and addressing common misinformation about immunisation against pandemic influenza will be a communication challenge when preparing for future pandemic situations and for vaccination policies in general [30]. The pre-pandemic development of tailor-made information strategies accompanied by surveys to monitor public perception implemented early in the pandemic should be considered for future pandemic preparedness planning and the mitigation of health threats on a population level.

Acknowledgments

The authors thank all staff of the Department for Infectious Disease Epidemiology at the Robert Koch Institute who were involved in the management of the influenza A(H1N1) pandemic.

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An outbreak of severe respiratory tract infection caused by human metapneumovirus in a residential care facility for elderly in Utrecht, the Netherlands, January to March 2010

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Citation style for this article:
te Wierik MJ, Nguyen DT, Beersma MF, Thijsen SF, Heemstra KA. An outbreak of severe respiratory tract infection caused by human metapneumovirus in a residential care facility for elderly in Utrecht, the Netherlands, January to March 2010.
Euro Surveill. 2012;17(13):pii=20132. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20132

Article published on 29 March 2012

Recognition of infections with human metapneumovirus (HMPV) among institutionalised elderly is rising. When HMPV was found to be the causative agent of an outbreak of pneumonia in a residential care facility for elderly in the Netherlands, an elaborate outbreak investigation was set up, including active surveillance for new cases. From clinical cases, defined by fever (› 38°C) and symptoms of respiratory tract infections, respiratory samples for analyses of viral pathogens by real-time Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR) and blood samples for determination of HMPV-specific IgM and IgG antibody titres were taken. Five staff members and 18 residents fulfilled the clinical case definition. Of those, five residents tested positive for HMPV by rRT-PCR. The combination of rRT-PCR and serology identified nine confirmed cases, six probable cases, six possible cases and ruled out two persons as cases. Among residents, the outbreak of HMPV had an attack rate, ranging from 5% for laboratory-confirmed cases, to 13% for clinical cases. This outbreak investigation shows that HMPV is a potential serious pathogen for institutionalised elderly.

Introduction

Outbreak description

In mid-February 2010, staff of a residential care facility for the elderly notified an outbreak of pneumonia to the municipal health service of the town of Utrecht, the Netherlands. At the time, in five weeks, nine of the 140 residents and two staff members had fallen ill with pneumonia. Three residents had been admitted to the hospital. One resident was admitted with cardiac failure and pneumonia, another with dyspnoea (oxygen dependent) due to a lower respiratory tract infection (RTI) (X-ray: possible lobar infiltrate) and the third resident was admitted among other things because of a deteriorating lower RTI (X-ray: lobar infiltrate). All three died in the hospital shortly after admission. No virological examination had been performed and a definite causative agent was not established for any of the three deceased patients. The other ill residents were not admitted to hospital but treated by general practitioners in the care facility, mostly with antibiotics. Although RTIs can be expected in winter season, the clinical presentation – especially the three deaths with a possible common causative agent – together with the number of cases, were found severe enough to justify an outbreak investigation.

This induced an inventory of clinical cases (onset of disease, symptoms, clinical diagnosis, treatment, date of birth and sex) and the active surveillance for new clinical cases among residents and staff members in this facility, from mid-February onwards. A clinical case was defined by fever (› 38°C) and clinical symptoms of RTI. Respiratory samples for analyses of viral pathogens were taken from three new clinical cases, five days after the initial notification. When laboratory investigations on 23 February 2010 identified human metapneumovirus (HMPV) as causative agent, an elaborate outbreak investigation among staff and residents was set up.

Residents, staff members and the general practitioners of the residents were informed about the outbreak and infection control measures were taken. These included: (i) isolation of the ill residents in their own apartments until symptoms resolved, (ii) use of a surgical mask by staff members while giving care to the ill residents as well as application of strict hand hygiene, (iii) all persons – staff members, family members, and other visitors - leaving the apartment of ill residents were advised to apply hand alcohol.

These measures were lifted on 15 March 2010 after two maximum incubation periods (12 days) without the occurrence of new clinical cases.

Background on human metapneumovirus

HMPV is a respiratory pathogen, which was first identified in 2001 in children with RTI [1]. It is a single-stranded RNA virus with a lipid envelope and belongs to the family *Paramyxoviridae*, subfamily *Pneumovirinae*. Phylogenetic analysis has identified two subgroups of HMPV, subgroups A and B, and two clades within each of these subgroups [2]. Seroprevalence data suggest that most children are infected by the age of five and re-infection occurs throughout life [1,3,4]. Most infections occur during late winter and early spring [4]. Depending on the region of the world, both HMPV subgroups A and B may co-circulate, but during an epidemic one subtype usually dominates [5]. Transmission is likely by direct (e.g. via hands) or close contact (e.g. via coughing or sneezing) with contaminated secretions, which may involve large particle aerosols, droplets or saliva. The clinical incubation period is not precisely known; estimates range from three to six days [6]. Clinical manifestations of HMPV infection are similar to those of respiratory syncytial virus (RSV). The majority of HMPV infections are self-limiting mild upper RTI, but in a minority it causes lower RTI such as bronchiolitis and pneumonia, requiring occasionally mechanical ventilation support. Risk factors for severe HMPV infections are age (< 5 years and > 65 years of age), compromised immune status and underlying pulmonary or cardiac disease [7,8]. Treatment is supportive and varies with the clinical manifestations. Ribavirin and polyclonal intravenous immune globulin (IVIG) are active against HMPV *in vitro* and reduce viral replication in experimentally infected mice, but clinical data on the effectiveness in humans are lacking [9,10]. Since the discovery of HMPV the majority of clinical publications concerns infections in children, but the number of publications on outbreaks of HMPV infections in institutionalised adults and elderly is rising [11-15]. However, no studies have been performed combining results of real-time Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR) and serology during outbreaks.

This article describes an outbreak of HMPV in a residential care facility for elderly, in which a combined approach of epidemiology and laboratory investigations (rRT-PCR and serology) gave insight in the extent of HMPV infection.

Methods

Laboratory investigation

Respiratory samples for viral analysis were taken from each new clinical case. Sampling consisted of a nasal swab and a pharyngeal swab which were transported to the laboratory in one viral transport medium (universal transport medium (UTM)). Viral analysis was performed with rRT-PCR.

Sampling new clinical cases for viral analysis continued until the outbreak was ended on 15 March 2010. Furthermore, cases positive for HMPV were periodically sampled until the last respiratory sample tested negative for HMPV, with a sampling interval of approximately eight days.

The initial viral analysis by rRT-PCR was performed by the laboratory of one of the local hospitals. In a later stage, all respiratory samples were analysed in one batch by the Erasmus Medical Centre, Rotterdam, which is one of the two national reference laboratories for respiratory viruses.

After viral DNA or RNA isolation from nasopharyngeal swab supernatant, a multiplex rRT-PCR respiratory virus panel was used to identify viruses (HMPV, RSV types A and B, rhinovirus, parainfluenza virus 1-3, adenovirus and influenza A and B viruses) as previously described [16-19].

To culture HMPV, it was propagated as described previously [8]. LLC-MK2 cells (monkey kidney cells, ATCC CCL-7) at 80–90% confluency were inoculated in culture medium supplemented with trypsin. Subsequently, each following day, cells were monitored for cytopathogenic effect and harvested when maximum cytopathic effect was observed. All isolations were performed in duplicates. Viral RNA was extracted, amplified by RT-PCR, sequenced and run on an ABI genetic analyser as described before with slight modifications [20].

To gain insight into the magnitude of the outbreak, all clinical cases – i.e. all clinical cases before and after outbreak notification – were requested to donate a blood sample for determination of HMPV-specific immunoglobulin (Ig) M and IgG antibody titres. A second sample was requested from the symptomatic staff members. Residents were requested to provide a second sample only if a HMPV infection was not probable or proven by the results of rRT-PCR or serology from the first sample.

HMPV-specific IgM and IgG antibody titres were determined using the direct immunofluorescent-antibody (IFA) test as described before [4,5]. Data are expressed as reciprocal anti-HMPV IgM and IgG antibody titres. All serological analyses were performed in duplicates. An anti-HMPV IgM antibody titre of 64 or higher was considered proof of HMPV infection. The same holds for a fourfold increase in anti-HMPV IgG antibody titres between the first and second blood sample taken (seroconversion). An isolated HMPV IgG titre of 256 or above was considered indicative of a recent HMPV infection.

Final case classification

Results of both analyses were combined into a final case classification for clinical cases: no proof of HMPV infection (serology and rRT-PCR negative), possible (insufficient laboratory investigations), probable (IgG titre first blood sample 256 or above), and confirmed

HMPV infection (rRT-PCR positive or IgM first blood sample positive (IgM titre 64 or above) or seroconversion (fourfold increase in anti-HMPV IgG antibody titres between the first and second blood sample taken).

Results

Outbreak

In all, 23 persons were included in the outbreak investigation: five staff members (one male, four female) and 18 residents (five male, 13 female). Mean ± Standard Deviation (SD) (minimum–maximum) age for staff members and residents, was 47.6 ± 3.6 (37–59) and 90.1 ± 1.1 (83–98) years respectively. Underlying conditions of the cases are shown in Table 1.

Table 1

Underlying conditions in clinical cases, outbreak of human metapneumovirus in a residential care facility for elderly in Utrecht, the Netherlands, January–March 2010 (n=23)

Underlying condition	Number of cases
Cardiac disease[a]	14
Cardiac failure[a]	6
Atrial fibrillation[a]	3
Angina pectoris[a]	2
Chronic obstructive pulmonary disease[a]	3
Hypertension	4
Cerebro vascular attack[a]	5
Transient ischemic attack[a]	3
Diabetes mellitus[a]	4
Renal failure[a]	1
Hypothyroidism[a]	1
Asthma[b]	2

[a] Underlying condition only in residents of the care facility for elderly.

[b] Underlying condition only in staff of the care facility for elderly.

Among the residents, there was no clustering of cases in wards or floors as they were scattered over 10 of the 12 floors of the residential care facility. Staff members were not only nursing staff. Twelve persons had an onset of disease after 17 February 2010 and therefore respiratory samples were taken. Among the new clinical cases, another two residents were hospitalised; one because of the seriousness of the RTI, the other because of another medical condition. Both were discharged in an improved condition after about 12 days. However, one patient died eventually.

Figure 1 shows the epidemic curve of the outbreak, as well as the timeline of outbreak management.

Real-time Reverse Transcriptase Polymerase Chain Reaction results

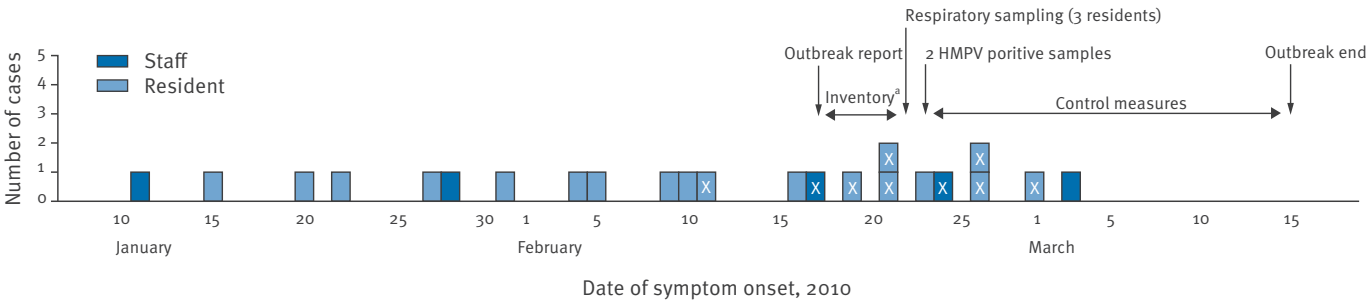
Five of 12 respiratory samples, which were all from residents, tested positive for HMPV by rRT-PCR. Follow-up by rRT-PCR was possible for four residents: nose and throat swabs were obtained with an interval of approximately eight days until a sample tested negative. As shown in Figure 2, these residents shedded HMPV for at least nine to 17 days after onset of disease.

rRT-PCR results of both laboratories were consistent (Pearson's r between the cycle threshold values (Ct-values) is 0.94, $p<0.001$, nine samples). There was a clear correlation between the Ct-values and the time from disease onset: the longer the period between onset of disease and respiratory sampling, the higher the Ct-value (Figure 3, R^2 linear = 0.39, $p<0.04$, 11 samples), indicating lower virus levels with time.

The virus was isolated from one respiratory sample from HMPV positive patient 3 (Figure 2). HMPV genotype A was assigned based on submission of the glycoprotein (G) gene sequence to a BlastN search (Genbank accession JN200816).

Figure 1

Epidemic curve and outbreak management, outbreak of human metapneumovirus in a residential care facility for elderly in Utrecht, the Netherlands, January–March 2010



HMPV: human metapneumovirus.

Confirmed cases are indicated by a "X".

[a] Inventory of clinical cases.

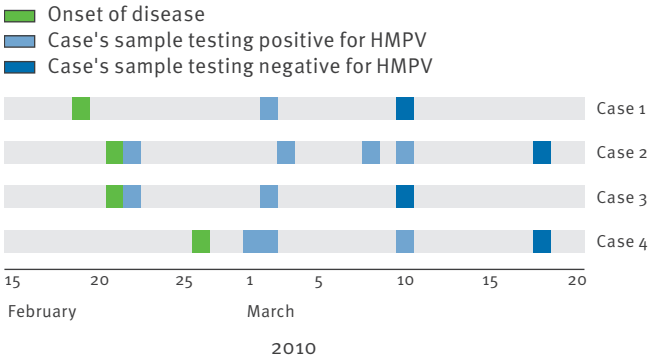
Serological results

The first serum sample was taken at a median of 23 days after onset of disease (range: 11–63, n=18). The second sample was taken at a median of 64 days after onset of disease (range: 59–113, n=9). As at that time, the HMPV genotype was unknown, both HMPV A and HMPV B infected LLC-MK2 cells were used to determine the antibody titres. As sequencing showed it was HMPV genotype A, only HMPV A-specific antibody titres are shown (Table 2). The titres of HMPV genotype B were similar or one step deviant from the titres of HMPV genotype A.

One of 18 clinical cases showed a positive HMPV-specific IgM antibody titre in the first serum sample; this case still had a positive IgM in the second sample. Anti-HMPV IgG antibody titres in both first and second sample were indicative of recent HMPV infection for six clinical cases. Seroconversion occurred in seven sera of nine persons tested twice (Table 2).

Figure 2

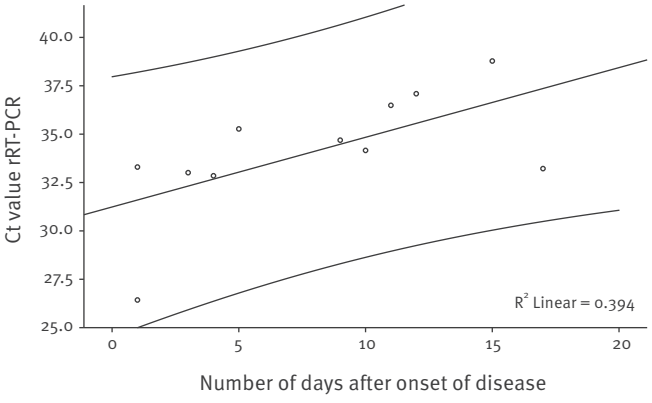
Follow-up of four human metapneumovirus positive cases, outbreak of human metapneumovirus in a residential care facility for elderly in Utrecht, the Netherlands, January–March 2010



HMPV: Human metapneumovirus.

Figure 3

Correlation between real-time Reverse Transcriptase Polymerase Chain Reaction for human metapneumovirus Cycle threshold-values and number of days after disease onset



Ct: Cycle threshold; rRT-PCR: real-time Reverse Transcriptase Polymerase Chain Reaction.

Final case classification

Table 2 shows the rRT-PCR and serological results as well as the final case classification of the 23 clinical cases. As the rRT-PCR results already identified five confirmed cases, the serological results increased that number to nine. Based on IgG level in the first serum sample, another six clinical cases could be classified as probable cases. The majority of the confirmed (seven of nine cases) and all probable cases (six cases) were residents. Nevertheless, the diagnostic approach identified two staff members as confirmed cases as well. For two clinical cases, both diagnostic results excluded a HMPV infection. Figure 4 summarises the results of the outbreak investigation.

Figure 4. Flowchart of the laboratory investigations and results, outbreak of human metapneumovirus in a residential care facility for the elderly, Utrecht, the Netherlands, January–March 2010

Given the numbers of possible, probable and confirmed cases, the attack rate of HMPV infection among residents in this outbreak was 5% for laboratory-confirmed cases (seven confirmed cases of 140 residents) and 13% for clinical cases (18 possible, probable and confirmed cases of 140 residents).

Discussion

This article describes an outbreak of HMPV in a residential care facility for elderly. Notifications of outbreaks of pneumonia in these kind of facilities for elderly are not very common in the Netherlands and HMPV as causative agent has not been described earlier.

Five of the 12 (42%) clinical cases, occurring after the outbreak was notified and from whom respiratory samples were taken, tested positive for HMPV by rRT-PCR. Our results are in agreement with those of Boivin et al., who, upon investigating a HMPV outbreak in a long term care facility in Canada, found six of 13 tested residents (46%) HMPV positive by rRT-PCR [11]. In a summer outbreak in a long term care facility in California, however, a lower proportion was found, with five of 20 cases (25%) testing HMPV positive by RT-PCR [13]. Higher proportions than in our study are nevertheless also reported concerning two other outbreaks where RT-PCR was used. In a hospital for older people in Japan, Honda et al. found that all eight inpatients (100%) in the same day-care room were RTI HMPV positive, while Tu et. al. found 10 of 13 patients (77%) HMPV positive, in a psychiatric ward of an armed-forces general hospital in Taiwan [12,15]. All studies included relatively small numbers of patients ranging from eight to 18 patients. The differences in proportions might partly be explained by the different settings (residential care facilities for elderly versus hospital settings). On the other hand, in this outbreak investigation we

sampled only staff and residents fulfilling the clinical case definition. Asymptomatic cases and less severe cases are therefore missed.

Follow-up respiratory samples showed that viral RNA remained detectable in residents during a relatively long period after disease onset, ranging from at least nine to 17 days. Whether this correlates with transmission of the virus is unknown. Because outbreak control measures were taken, the absence of new cases could not be used as a parameter for this. Alternatively, virus isolations by culture could be used as a surrogate parameter. However, isolation of HMPV by culture is relatively difficult due to its slow growth and mild cytopathic effects. Since viral culture remained negative in follow-up samples, it is possible that non-infectious viral particles/RNA fragments in cell debris from the lower lungs, could explain the positive rRT-PCR results in the follow-up samples.

We took infection control measures similar to those taken in case of RSV infection: clinical cases were cared for in isolation until clinical recovery and strict hand hygiene was applied. This approach seems justified given the probability of a relative long period of viral shedding. Also, after control measures were taken, new clinical cases only occurred in the following week, while they occurred during five weeks before the outbreak was notified. This is shorter than Boivin et al. reported [11]. In the later outbreak only droplet- and contact precautions were taken and new cases occurred for at least two weeks.

When serological results were combined with rRT-PCR results, four additional confirmed cases of HMPV infection and six probable cases were identified. The differences between rRT-PCR and serological results might be explained in various ways. Most likely, timing of sampling relative to onset of disease could explain these findings. Alternatively, sampling error or variations in the time of viral shedding might play some role. Possibly, more cases could have been confirmed as the sensitivity and specificity to detect IgM and IgG antibody titres with fixed and permeabilised infected cell monolayers is lower compared to enzyme-linked immunosorbent assay (ELISA), but HMPV ELISAs for both IgM and IgG were not in use as a diagnostic tool. Nevertheless, it is clear that a combined approach of serology and rRT-PCR has added diagnostic value.

For the early stage of an outbreak, serology by itself cannot be used as the interval between virus spreading

Table 2

Final case classification and laboratory results of clinical cases, outbreak of human metapneumovirus in a residential care facility for elderly in Utrecht, the Netherlands, January–March 2010 (n=23)

Case	Final case classification	HMPV rRT-PCR Ct-value	First serum sample Reciprocal IgG antibody titre	Second serum sample Reciprocal IgG antibody titre
1	Confirmed	26[a]	<16	256
2	Confirmed	33	<16 (IgM 256)	1,024
3	Confirmed	36	<16	1,024
4	Confirmed	33	<16	Deceased
5	Confirmed	38	<16	ND
6	Confirmed	Negative	<16	1,024
7	Confirmed	Negative	<16	512
8	Confirmed	Negative	<16	256
9	Confirmed	Negative	<16	64
10	Probable	ND	>1,024	ND
11	Probable	ND	>1,024	ND
12	Probable	ND	>1,024	ND
13	Probable	ND	256	ND
14	Probable	ND	256	ND
15	Probable	Negative	256	ND
16	Possible	Negative	16	ND
17	Possible	Negative	Sample not provided	Sample not provided
18	Possible	Sample not provided	Sample not provided	Sample not provided
19	Possible	Deceased	Deceased	Deceased
20	Possible	Deceased	Deceased	Deceased
21	Possible	Deceased	Deceased	Deceased
22	Non-case	ND	64	16
23	Non-case	ND	16	16

ND: not determined; HMPV: Human metapneumovirus; rRT-PCR: real-time Reverse Transcriptase Polymerase Chain Reaction.

[a] Viral culture positive.

and detection of HMPV-specific IgM and IgG antibodies is too long to manage the outbreak, especially considering immunosenescence in elderly [20]. Based on the present data, we would recommend a combined diagnostic approach, in which a direct IFA test is coupled to rRT-PCR. IFA is a rapid and useful test for the diagnosis of HMPV infections in outbreaks. However, the sensitivity of IFA is lower than that of rRT-PCR and needs to be validated before use [21]. While the results of the IFA, available within two hours, are validated by rRT-PCR, appropriate measures can be taken. Furthermore, standardised timing of sample collection (time after onset of disease, time intervals between samples) for serology clearly contributes to the final identification of cases in outbreak studies.

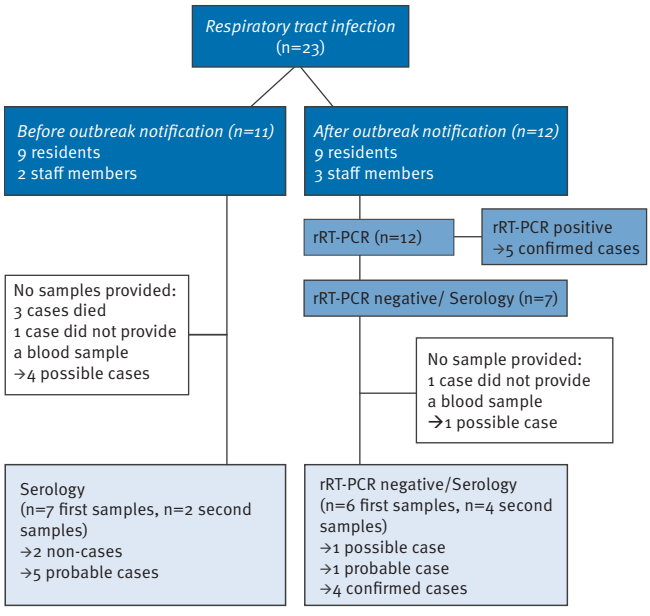
This outbreak exemplifies that HMPV can cause severe disease. The majority of the resident cases were treated for pneumonia and some of them were admitted to the hospital. Several studies have reported mortality among elderly due to HMPV [3,11,15,22]. Although none of the probable or confirmed HMPV resident cases in this outbreak died because of the HMPV infection, it is very likely that HMPV caused or contributed to the death of at least one of the three possible resident cases that were admitted to hospital and died there before the outbreak was notified. After all, the grand majority of the resident cases with laboratory results turned out to be probable or confirmed HMPV cases (13 of 14 clinical cases), making it highly probable that at least one of the three clinical cases, who were admitted to hospital and died there before the outbreak was notified, had a HMPV infection too.

A further question is how the virus was spread. As both residents and staff members were affected, both groups could have transmitted the virus to others. Direct spread among residents is not very likely as they all have their own apartment, but it cannot be ruled out as they do share common facilities. Staff members, on one hand, could have easily transmitted the virus as they do work over all floors, but on the other hand they form a small minority under the (probable or confirmed) final cases. Another possibility is that affected staff members who did not fulfil the clinical case definition (especially the fever criterion) were involved in the transmission, since symptoms of HMPV infection are dependent on age and health of the host. It is therefore possible that staff members – (much) younger and healthier compared to residents - were infected with HMPV, but developed only minor symptoms and continued to work and in doing so, could have spread the virus. Whether this hypothesis holds, can only be studied in an outbreak in which not only persons fulfilling the clinical case definition are included, but (a sample of) those not fulfilling that definition as well.

In conclusion, this article describes an outbreak of HMPV in a residential care facility for elderly with an attack rate of 5–13% among residents, with severe disease and probable mortality. It is of interest that follow-up of rRT-PCR positive cases suggests a relatively long period of viral shedding. This should be considered when applying infection control measures.

Figure 4

Flowchart of the laboratory investigations and results, outbreak of human metapneumovirus in a residential care facility for the elderly, Utrecht, the Netherlands, January–March 2010



rRT-PCR: real-time Reverse Transcriptase Polymerase Chain Reaction.

Acknowledgments

We thank residents and staff members of the residential care facility - especially Angelique van der Burgh and Els van Schoot -, Georgina Aron and Rik de Swart from the Erasmus Medical Centre, Rotterdam, Emma Millar from Queen's University Belfast in Belfast, Northern Ireland and Sjon Oudejans from the Diakonessenhuis, Utrecht for their technical assistance and/or advices in this investigation.

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