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ESCAIDE 2010 - an opportunity for sharing knowledge, building capacity and strengthening networks

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Between 11 and 13 November 2010 the European Centre for Disease Prevention and Control (ECDC) invites researchers to its fourth annual ESCAIDE conference in Lisbon. ESCAIDE is short for the "European Scientific Conference on Applied Infectious Disease Epidemiology", and this year's edition – just like the previous ones – has a dual aim: first, to provide a forum where exchange of knowledge in epidemiology, microbiology and other related fields is applied in support of prevention and control of infectious diseases. Second, to give the coming generation of European public health scientists within the European Programme for Intervention Epidemiology Training (EPIET), the European Public Health Microbiology Training Programme (EUPHEM) and national field epidemiology training programmes (FETP) an opportunity to present their work [1-2].

The past ESCAIDEs covered a wide range of speakers and subjects. In this issue of *Eurosurveillance* an article by Faber *et al*. highlights that physicians may misinterpret patients' expectations to be prescribed antibiotics. It demonstrates that most respondents from a general population sample either do not expect to receive antibiotics for a common cold or would follow the advice of their doctor. The paper, based on a presentation at ESCAIDE, was among the abstracts submitted for the conference that scored highest in the peer-review. It was therefore invited for submission by the editorial team [ref paper]. It serves as a good example of the high quality of contributions at the conference where in many cases the quality of presentations by the young EPIET fellows matched that of their more experienced peers. We are looking forward to this year's ESCAIDE which will provide a new batch of excellent scientific presentations of infectious disease workers from across the European Union and beyond. The call for late breakers for ESCAIDE 2010 opens on 3 September [3].

EUPHEM is the most recent member of the family of training activities funded through the ECDC. It was launched in 2008 as a project within the European Network for Diagnostics of Imported Viral Diseases Collaborative Laboratory Response Network [4], and aims at developing a European network of public health microbiologists to strengthen communicable disease surveillance and control. This is achieved by creating an integrated laboratory – field epidemiology network for outbreak detection, investigation and response. During the 2010 ESCAIDE, the first two fellows who have been the front runners for what will hopefully evolve to be the EPIET fellows' counterpart in the laboratory sphere will receive their diploma.

When he announced ESCAIDE earlier this year, Marc Sprenger, the ECDC Director, stated that "ESCAIDE helps to build and strengthen professional links across the public health community in Europe. It is here that ECDC and its partners can start to build the multi-disciplinary, multi-country approaches needed to strengthen Europe's defences against infectious diseases." Together with EPIET, EUPHEM and the national FETP's ESCAIDE nurtures networks, brokers knowledge sharing, supports European collaboration in public health, and brings new scientists to the fore. This will help create a better prepared and healthier Europe.

Members of the ESCAIDE scientific committee are: Andrea Ammon, ECDC, Arnold Bosman, ECDC, Viviane Bremer, ECDC/EPIET, José Luis Castanheira, Portuguese FETP, Johan Giesecke, ECDC (chair), Aftab Jasir, ECDC, Marion Koopmans, European Society for Clinical Virology, Davide Manissero, ECDC, Lorenzo Pezzoli, EPIET Alumni Network, Fernando Simon Soria, Spanish FETP, Ines Steffens, ECDC, Howard Needham, ECDC, Panayotis Tassios, European Society of Clinical Microbiology and Infectious Diseases.

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Pertussis outbreak in northwest Ireland, January – June 2010

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We report a community pertussis outbreak that occurred in a small town located in the northwest of Ireland. Epidemiological investigations suggest that waning immunity and the absence of a booster dose during the second year of life could have contributed to the outbreak. The report also highlights the need to reinforce the surveillance of pertussis in Ireland and especially to improve the clinical and laboratory diagnosis of cases.

Introduction

Pertussis is a notifiable disease in Ireland. The pertussis case definition used in Ireland includes compatible clinical symptoms alone (possible), clinical symptoms in combination with epidemiological link to laboratory confirmed case (probable) or laboratory confirmation (confirmed). Between 2005 and 2009, on average 81 cases of pertussis were notified annually nationwide. This corresponds to an average incidence rate of 1.9/100,000 population. The majority of cases were children aged less than six months (51% of all cases notified from 2005 to 2009). The Irish vaccination schedule comprises an acellular pertussis-containing vaccine at two, four and six months and a booster dose given when children are between four and five years old.

On 21 April 2010, a general practitioner (GP) in a small town in the north western region of the country notified the Department of Public Health (DPH) – Health Services Executive (HSE) North West of an increase in the number of patients presenting with pertussis-like illness. The age range was broad and the GP reported that the patients were mostly up-to-date with their vaccinations. On 19 May, the first case was confirmed by serology. The DPH launched an epidemiological investigation in order to manage the outbreak, describe the magnitude of the outbreak and develop a hypothesis regarding the cause of the outbreak.

Epidemiological and microbiological investigations

A possible case was defined as a person living or working in the small town or in the immediate area (consisting of 11 electoral divisions with a total population of 3,624) who was diagnosed with pertussis by a GP or who met the European Union/World Health Organization (EU/WHO) clinical case definition for pertussis i.e. cough lasting at least two weeks with one of the following: paroxysms of coughing, inspiratory whoop or post-tussive vomiting between January and June 2010. A probable case was defined as a person who met the possible case definition and had close contact with a confirmed case. A confirmed case was a person who met the possible case definition and had laboratory evidence of *Bordetella pertussis* infection (isolation of *B. pertussis* from clinical specimen, detection of nucleic acid or demonstration of a specific antibody response in absence of recent vaccination).

We undertook active case finding by contacting all GPs working in the surrounding area, as well as emergency and paediatric departments of the two nearest regional hospitals. For all cases notified by a GP, the presence of other cases in the close circle of family and friends was explored.

The contacted GPs and hospitals were asked to collect a swab specimen or a serum sample from any new possible case of pertussis that presented. GPs do not normally have the naso-pharyngeal swabs that are used for pertussis in their surgery. These swabs were supplied to them along with recommendations for collection and transportation. For serology testing, we used a single high titre of anti-pertussis toxin immunoglobulin G (IgG). The cut-off was set at 100 IU/ml. The laboratory where polymerase chain reaction (PCR) was carried out performed real time PCR testing (IS481-PCR) and also tested for *B. pertussis* toxin promoter and for *B parapertussis* (insertion sequence).

We interviewed all cases by telephone using a standardised questionnaire. We collected socio-demographic information, work/educational setting, clinical symptoms, complications secondary to pertussis, outcome and laboratory testing. We gathered vaccination history either from the Local Health Office records (for children under the age of 15 who were vaccinated locally), directly from the cases, or from the notifying GP.

Age-specific attack rates were calculated using 2006 census data [1].

Control measures

Letters were sent to local GPs, emergency and paediatric departments in the two regional hospitals and local ante-natal clinics in order to inform them about the outbreak and give advice about clinical features, treatment, chemoprophylaxis for vulnerable contacts and vaccination as recommended in the Immunisation Guidelines for Ireland [2].

Letters were also sent to local schools and crèches containing information about the outbreak and recommending that all children should be up-to-date with their vaccinations. Following the notification of a confirmed case in a maternity ward, letters were sent to all those who had been inpatients on the maternity ward at the same time.

Results

A total of 69 cases were identified from notification data and subsequent active case finding. Two cases were excluded because they were not reported by a GP and did not meet the clinical case definition. Finally 67 cases were included in the analysis. Four of them were probable cases, three were confirmed and the remainder were possible.

Of these 67 cases, 62 were notified by four different GPs (from two GP practices) and five further cases were identified in the close circle of notified cases.

Pertussis testing was carried out in four different laboratories. Seventeen patients were tested in total and three were confirmed (one by culture and two by serology). Of seven patients tested by serology, two had a positive result. Of ten patients tested by culture, one had a positive result. Four patients who tested negative by culture were further tested by PCR and all of them had a negative result. Of three negative serology tests for which the information was available, two were taken seven days after symptom onset and one was taken eight days after symptom onset. Of nine negative on culture, one had been taken more than one week after symptom onset and five had been taken more than 14 days after symptom onset.

Of 58 cases for whom the information was available, onset of cough was reported from January to June 2010 with a peak in week 21 (Figure 1).

Four cases were hospitalised in the local hospital: three children aged between four days and one month and one 60 year-old adult. This last case was hospitalised for pneumonia secondary to pertussis.

The male/female ratio was 0.6. Sixteen cases were aged between one and four years old which corresponds to an attack rate of 77 per 1,000 population. Another 16 cases were aged 10-14 years (attack rate:76/1,000 population). Twenty (30%) cases were older than 19 years (attack rate:7.6/1,000 population). Considering the number of cases by single year of age, the highest attack rates were in children aged under 12 months (130/1,000 population) and three years (149/1,000 population).

Figure 2 shows the number of cases by age group and the vaccine doses they received. Of five children aged less than six months, one child had received the recommended three priming doses.

Of 17 children aged between six months and four years, 15 had received the recommended priming doses. Of 22 children aged between five and 18 years old for whom the information was available, 20 had received the recommended four doses of vaccine. Vaccination status was unknown for all adults.

Of 51 cases who were interviewed more than 14 days after the cough onset, 50 reported a cough lasting more

Figure 1

Number of cases by week of symptom onset, northwest Ireland, January-June 2010 (n=58)

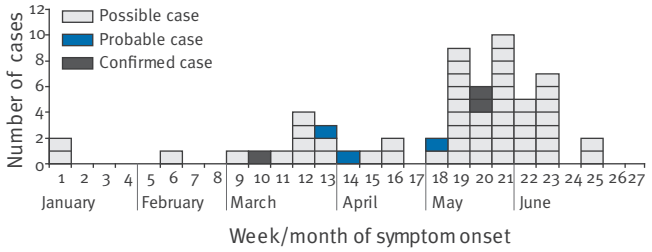
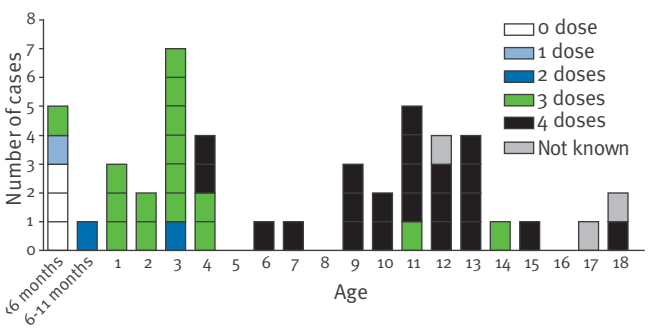


Figure 2

Distribution of cases by age group among children aged ≤18 years old, northwest Ireland, January-June 2010 (n=47)



than 14 days (median: 29 days, range: 14-99 days). Of 64 cases for whom the information was available, the most frequent reported symptom was paroxysmal cough (52 of 64). Reported symptoms varied according to age. Inspiratory whoop, post-tussive vomiting and apnoea were reported more frequently in children less than one year old than in the other age groups (Figure 3).

Discussion

In the light of these preliminary results, this outbreak seems to have occurred in a well-vaccinated community and to have spread mostly among children under six months of age, between one and four years old and among the 10-14 year-olds.

There may be more than one factor that contributed to the outbreak. As suggested by the analysis of vaccination data, waning immunity could explain the high number of adolescent cases. We could not verify this hypothesis in adult cases but waning immunity might also have contributed to infection in adults, among other factors.

In the 1990s and 2000s, findings from various pertussis surveillance systems demonstrated a change in the age profile of pertussis cases in countries with high vaccine coverage rates in young children [3-5]. A shift in the age group has been observed, with increasing pertussis incidence among adolescents and adults. The increase was attributed to improvements in the diagnosis and reporting of adolescent and adult cases, combined with waning immunity. The introduction of an immunisation programme reduces the amount of *B. pertussis* that is circulating in the population. This will result in less natural boosting of immunity amongst those whose immunity is waning. This waning of immunity has led to a recommendation in many countries for a vaccine booster dose for adolescents and adults. The duration of immunity is estimated to range from seven to 20 years after infection with *B. pertussis* and 4-12 years after vaccination with whole or acellular pertussis vaccine [6-8], thus making adolescents and adults more susceptible to pertussis disease. Waning immunity and the subsequent increase in disease is associated with considerable morbidity and economical costs and increases the probability of transmission of pertussis infection to vulnerable children. Various studies have shown that adolescent siblings and parents are often the major source of transmission of pertussis to infants [5,8,9].

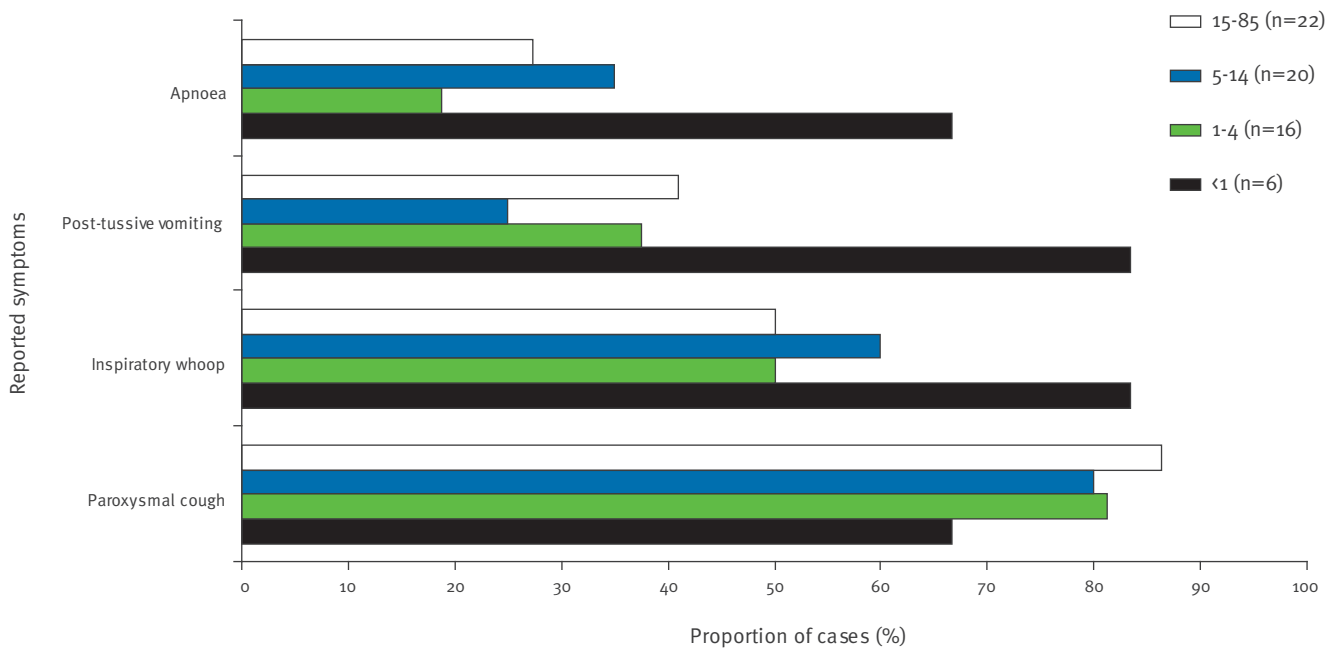
During the outbreak, five infants aged less than six months were diagnosed with pertussis. For three of them, a symptomatic contact was reported with onset of illness prior to their own (cousin and mother). It is likely that these contacts had transmitted pertussis to these infants.

Following the awareness of waning immunity, a booster dose at adolescence was introduced in the vaccination schedule in the United States (US), Canada and many European countries [10]. In Ireland, a booster dose is recommended since 2008 but has not been routinely provided through the national immunisation programme (usually administered in schools).

On the other hand, we observed a high incidence rate among children aged between one and four years old despite good vaccination coverage Most recent data available on immunisation coverage (Q1 2010) indicates that the vaccination coverage rate at both 12 and 24

Figure 3

Distribution of reported symptoms by age group, northwest Ireland, January-June 2010 (n=64)



months (93% and 97%) in the HSE North West region exceeds national average (89% and 94% respectively). Effectiveness of acellular vaccines in infants has been estimated to be high (71%-93%) [11]. Since 1996 acellular pertussis vaccines have been used in the childhood vaccination programme. The vaccine used since September 2008 (INFANRIX- HEXA).is a three-component pertussis-containing vaccine. Two vaccines are currently used in Ireland for the booster dose, either a two-component pertussis containing vaccine (TETRAVAC) or three-component pertussis vaccine (INFANRIX-IPV). Both vaccines are licensed for booster usage. In this investigation we did not seek information on the vaccine brand used. However, as this outbreak affected many age cohorts we do not have reason to suspect low vaccine effectiveness linked to a specific batch of vaccine as different vaccines and batches would have been used for the population affected. A more likely explanation may be waning immunity due to the absence of a booster dose in the second year of age. But as Ireland has never had a booster at this age it is not evident why this large outbreak should be occurring now, in this highly vaccinated population.

The duration of protection after the priming doses at two, four and six months is not clear [9]. Current vaccination schedules in the US, Canada and all European countries except the United Kingdom and Ireland include a booster dose between 10 and 24 months. At a recent meeting of the Strategic Advisory Group of Experts on immunisation (SAGE) of the WHO in April 2010, experts stated a preference for giving a pertussis booster dose in the second year of life [12].

The possibility that other pathogens, respiratory syncytic virus (RSV) and adenovirus, may have contributed to some of the cases reported cannot be ruled out. No samples from patients involved in this outbreak were sent for virological investigation. But outbreaks associated with these pathogens were not reported from other parts of the country and during this period the prevalence of RSV from respiratory samples taken at non-sentinel GP sites in Ireland was low, with just 5.4% of all samples positive for RSV, in comparison to 14.1% for the same time period in the previous influenza season. The peak period of detection for RSV in the 2009-10 season was December-January (unpublished data HPSC). The extent and development of this outbreak, together with the clinical presentation and also laboratory confirmation supports our hypothesis that most cases were likely to be pertussis.

An antigenic divergence between the circulating and the vaccine strains, as observed in the Netherlands [13], can not be excluded yet as a contributing factor in the outbreak. Further microbiological investigations are ongoing to explore this hypothesis.

In this outbreak, we found that symptoms varied according to age. In particular, the typical symptoms for pertussis (whoop and post-tussive vomit) are less common among older patients. Pertussis is thought to be underreported as a result of this atypical presentation in adolescents and adults [3]. As previously suggested [3], this highlights the need for a case definition for older individuals in order to improve the reporting. Findings from this outbreak, along with the outbreaks that occurred in California and Australia highlighting the fact that pertussis outbreaks still occur, despite vaccination programmes, and the need to report so that control measures can be taken [14,15], should be communicated to GPs in order to increase their vigilance and their awareness of the symptomatology of pertussis in adolescents and adults.

The large proportion of cases reporting apnoea in this investigation is surprising. The highest proportion was in the youngest age group (<1 year of age), but was also commonly reported in the older age groups. Apnoea associated with pertussis is infrequently reported in older age groups. The question regarding apnoea was asked as interruption of external breathing. Whether patients or parents of children responding to this question understood what was being asked needs to be considered as a reason for this finding as this may reflect a misinterpretation of the question.

One limitation in our findings is the low number of confirmed cases. Ninety percent of those tested by PCR or culture had a negative result. Although there might be some true negative patients, it is likely that some of them were false negatives. Indeed, the sensitivity of laboratory diagnostic methods for pertussis can be affected by various factors such as the sampling technique, timing of sampling since the symptom onset, delay in transporting the specimen, treatment prior to sampling, age and vaccination status [16,17]. Culture and PCR have a low sensitivity if the specimen is taken late in the illness. In the outbreak, the late collection of nasopharyngeal swabs may have contributed to the low positivity rate. Problems linked to sampling technique may also explain some negative results.

For serology testing, a single high titre of anti-pertussis toxin IgG has been showed to be useful in late pertussis diagnosis, with a sensitivity of 76% and a specificity of 99% using a cut-off of 100 IU/ml [18]. In the outbreak, some of the negative blood samples were taken within eight days from symptom onset, probably too early to have a detectable level of IgG. Clinicians need guidelines on appropriate samples to be referred for confirmation of pertussis. They should be encouraged to take a sample for culture and PCR at the early stage of infection; whereas serology testing to detect IgG antibodies to pertussis toxin should be recommended when patients present themselves more than two weeks from symptom onset.

The hypotheses that we developed in the descriptive investigation still need to be verified through rigorous analytical study. A retrospective cohort study is currently ongoing among school children in all local

primary schools. It will allow us to further explore the waning immunity in adolescents, to estimate the vaccine effectiveness and to address other contributing factors.

Conclusion

This pertussis outbreak occurred in a well-vaccinated community; this is a rare phenomenon that has not been reported in Ireland for many years. We hope that this descriptive study will inform both national vaccination policy and the management of possible future outbreaks. This outbreak was managed by raising awareness in order to promote early diagnosis, treatment and vaccination. Consideration should be given to what role vaccination could have had in preventing this outbreak, whether by giving the recommended adolescent booster or by giving a booster dose earlier than four or five years of age as in other countries. Further epidemiological and microbiological investigations of this outbreak are ongoing regarding the circulating strain of *B. pertussis*, vaccine efficacy and the timing of boosters in relation to infection.

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Spotlight on measles 2010: Excretion of vaccine strain measles virus in urine and pharyngeal secretions of a child with vaccine associated febrile rash illness, Croatia, March 2010

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We describe excretion of measles vaccine strain Schwarz in a child who developed a febrile rash illness eight days after primary immunisation against measles, mumps and rubella. Throat swabs and urine specimens were collected on the fifth and sixth day of illness, respectively. Genotyping demonstrated measles vaccine strain Schwarz (genotype A). If measles and rubella were not under enhanced surveillance in Croatia, the case would have been either misreported as rubella or not recognised at all.

Introduction

Vaccination against measles was introduced into the Croatian vaccination schedule in 1968 for all children at the age of 12 months and at first grade of elementary school. The vaccine containing the Edmonston-Zagreb measles virus strain was produced by the Institute of Immunology, Zagreb. In 1976, the monovalent measles vaccine was replaced by a trivalent measles, mumps, rubella (MMR) vaccine, containing the same Edmonston-Zagreb strain of the same producer. In 2008, 18 cases of vaccine-associated mumps were reported that has resulted from transmission of the mumps component (L-Zagreb) to close contacts of children who had received primary vaccination with this trivalent vaccine [3,4,11]. This vaccine was thereafter replaced by Priorix (GSK; containing the RIT 4385 mumps virus strain and the Schwarz measles virus strain) for the first MMR vaccination in January 2009. The MMR vaccine produced by the Croatian Institute of Immunology is still used for the second dose of MMR. Since the MMR vaccine used for primary vaccination was changed in January 2009, vaccine-associated mumps in contacts of vaccinees have no longer been reported [5].

No suspected measles or rubella cases were reported in Croatia during 2010. In the last five-year period, one local outbreak of rubella occurred in Croatia in 2007, affecting 39 adolescents and one outbreak of measles in 2008, affecting 51 people. The illness in the index cases of both outbreaks was imported. Independently of these two outbreaks, only five cases of measles and another five cases of rubella were reported in Croatia from 2005 to 2009, which were eventually discarded by serology or classified as imported. After receiving information on a measles outbreak in Roma children in Bulgaria in 2009 [6,7] and media reports on rubella cases in neighbouring Bosnia and Herzegovina, the Croatian Institute of Public Health sent a circular letter to healthcare workers in Croatia on 15 March 2010 to raise awareness of possible importations of measles and rubella.

Four suspected rubella cases were notified in Croatia in the second half of March 2010. Three cases were discarded based on negative serology for measles and rubella and lack of epidemiological link to a possible source. One case may have had a chance to be exposed to rubella but also had a history of MMR vaccination and is described here.

Case description

A healthy child (14 months-old) was vaccinated on 9 March 2010 with Priorix MMR vaccine according to the Croatian childhood vaccination schedule. The child had facial erythema without fever on 14 March and developed a macular rash and fever on 17 March. It was examined on 21 March at the county hospital and reported as a possible case of rubella to the epidemiology department at the County Institute of Public Health on 23 March.

Since rubella and measles are under enhanced surveillance according to the national action plan for measles and rubella elimination, an epidemiological investigation was initiated, and serum, urine and throat swab specimens for laboratory testing were obtained. The investigation found no similar cases among contacts of the patient. A source of rubella infection was not

identified, however, possible exposure to rubella or measles virus could not be completely excluded, because the child had travelled abroad during the two weeks preceding the illness.

A serum sample and throat swabs were taken on 23 March and a urine specimen on 24 March. On 26 March, the rash was still present. Serum was obtained again from the convalescent child on 11 April. In addition, a serum sample from the asymptomatic pregnant mother was obtained on 24 March.

Laboratory investigation

Serologic tests of the patient and mother were performed at the World Health Organization (WHO) national measles laboratory, Virology Department, Croatian Institute of Public Health. For the detection of specific measles and rubella IgM and IgG antibodies we used commercial ELISA (Rubella IgM/IgG: Dia Sorin; Measles IgM/IgG: Genzyme Virotech GmbH). For detection of specific mumps IgM and IgG antibodies, a commercial immunofluorescence test was used (Euroimmun). Throat swab and urine were initially tested for measles virus at the Department of Molecular Diagnostics, Croatian Institute of Public Health using real-time RT-PCR (Applied Biosystems), using the primer/probe set for the measles virus nucleoprotein (N) gene [2].

The child's paired sera were tested in parallel. The first serum tested negative for IgM and IgG antibodies against rubella virus and mumps virus, while measles antibodies were equivocal for IgM and negative for IgG. The child's second serum obtained on 11 April also tested negative for both IgM and IgG rubella antibodies, while measles antibodies were negative for IgM, but IgG-positive, and mumps antibodies were postitive for IgM as well as for IgG. The mother was negative for IgM and positive for IgG antibodies against both measles and rubella virus (the mother's vaccination status could not be determined with certainty). The child's throat swab was negative in RT-PCR for measles RNA, while the urine tested positive.

An additional RT-PCR was performed, targeting the 3'-end of the N gene [1]. PCR products were obtained from throat swab and urine, sequenced and compared using the BLAST algorithm, and finally identified as Schwarz vaccine strain (genotype A).

Discussion

We demonstrated excretion of the Schwarz measles vaccine virus in a child with a vaccine-associated febrile rash illness in urine and in pharyngeal excretions.

Virus excretion in vaccinees has been reported before [8-10], but to our knowledge, this is documented for the first time for the Schwarz vaccine strain. Interestingly, although the blood for serology testing was obtained 14 and 32 days after vaccination, the child still had no antibodies to rubella virus in either serum sample. It is unclear why there was no seroconversion to rubella 32 days after vaccination, although this is not an unusual finding. The dynamics of measles and mumps antibodies were as expected for someone who had either been vaccinated or had natural infection, indicating that the child did not have impaired antibody production kinetics in general.

According to WHO guidelines for measles and rubella elimination, routine discrimination between aetiologies of febrile rash disease is done by antibody assays, not necessarily by virus detection [12]. However, in a patient recently MMR-vaccinated, only molecular techniques can differentiate between wildtype measles or rubella infection or vaccine-associated disease.

This case report demonstrates that excretion of Schwarz measles virus occurs in vaccinees. Also, it demonstrates a need to strengthen surveillance of measles and rubella cases continuously, also in countries that are currently approaching elimination of measles and rubella.

Competing interests:
Maja Santak is an employee of the Institute of Immunology, Zagreb, the national vaccine producer.

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Antibiotics for the common cold: expectations of Germany's general population

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Physicians mention patients' expectations as a reason for prescribing antibiotics for common (viral) upper respiratory tract infections despite clinical evidence against their use and the physicians' better judgement. We aimed to assess the prevalence of such expectations and factors of influence (knowledge and attitudes) in Germany's general population. In November 2008, 1,778 persons registered with a large market research company were invited to complete an online questionnaire on expectations concerning prescription of antibiotics and on knowledge and attitudes regarding the effectiveness and use of antibiotics for upper respiratory tract infections. A total of 1,076 persons aged 15–78 years participated (response: 61%), of whom 91.8% reported using antibiotics 'only if absolutely necessary'. Prescription of antibiotics was expected by 113 (10.5%) of the 1,076 respondents for the common cold and by 997 (92.7%) for pneumonia. In a logistic regression analysis, predictors for expecting a prescription for antibiotics for the common cold included the following opinions: 'common cold or flu can effectively be treated with antibiotics' (prevalence: 37.6%; odds ratio (OR): 9.6; 95% confidence interval (CI): 3.8 to 24.3) and 'antibiotics should be taken when having a sore throat to prevent more serious illness' (prevalence 8.6%; OR: 7.6; 95% CI: 3.9 to 14.5). Among those expecting a prescription (n=113), 80 (71%) reported that they would trust their physician when he or she deems a prescription unnecessary; a further eight (7%) would be unsatisfied, but would accept the decision. Our results suggest that only a minority expects antibiotics for the treatment of cold symptoms. Physicians should be educated that their decisions not to prescribe antibiotics for the common cold, even when against patients' expectations, are apparently accepted by the majority.

Introduction

Most respiratory tract infections (e.g. common cold, influenza and sinusitis) are self-limiting and viral in origin. Thus, antibiotics are rarely necessary or effective [1-3]. While overall figures of outpatient antibiotic use in Germany fall within the lower third of those of European countries [4], 28% of German respondents in the recently published Eurobarometer on antimicrobial resistance had taken antibiotics in the past year and more than a third had taken them for a viral infection such as a cold or influenza [5]. In a direct observation study conducted in general practices in Germany, 18% and 64% of patients with common cold and sinusitis respectively were prescribed antibiotics [6]. These unnecessary prescriptions are thought to largely contribute to the development of antimicrobial resistance and increasing numbers of infections without treatment options [4].

As a reason for these prescriptions against their better judgment, physicians mention pressure exerted by their patients to receive antibiotics even for minor ailments or diseases of viral origin (such as influenza or the common cold) [7]. Doctors feel the need to give in to this pressure due to time constraints or to avoid losing the patient to another practice.

Public knowledge and attitudes concerning antibiotic use and action differ greatly between countries in Europe and between groups of different socio-economic background. People in northern European countries and those with a higher level of education are among the best informed about the effects and sensible use of antibiotics, whereas there are generally higher levels of misconceptions in southern and eastern European countries and among those with a lower level of education. These geographical and socio-economic differences in knowledge and attitudes can in part explain differences in observed use of antibiotics [5,8].

Large campaigns, educating the public about antibiotic action and responsible antibiotic use, have therefore been conducted in various countries including Australia, Belgium, Canada, the United Kingdom and the United States [9,10] as well as at the European level [11], aiming at decreasing unnecessary antibiotic use and thus slowing down the development of antibiotic resistance.

Little is known about the prevalence of expectations regarding the prescription of antibiotics for upper respiratory tract infections in Germany and possible determinants of these expectations. With this survey, we try to explore knowledge, attitude and expectations of Germany's general public in order to guide decisions on further preventive measures such as public awareness campaigns.

Methods

Design, sample size, questionnaire design

We conducted a cross-sectional study among a sample of the German general population using an Internet-based questionnaire. A sample size of 1,000 was calculated to yield a precision of 3.1 on a confidence level of 95%, which was judged to be sufficient for the purposes of this study.

In total, 1,778 individuals were selected from a panel of approximately 30,000 Internet users, who registered with a large market research company and had given their consent to be contacted for purposes of (market-) research-oriented studies. Upon invitation via email, participants were able to log on to a website and complete the online questionnaire during a 10-day period in November 2008. They received a small remuneration for their efforts in completing the survey.

The questionnaire consisted of closed questions (multiple-choice, Likert scale) on expectations of prescription of antibiotics from physicians and knowledge and attitudes regarding effectiveness of antibiotics and antibiotic use for upper respiratory tract infections. Questions were mostly selected from published studies with similar objectives (e.g. [8,10,12]) and slightly rephrased according to the objectives of this study. Detailed demographic data had been recorded at the time of the participant's registration and kept in a separate database with the market research company. The definition of levels of education, as used in this study, was as follows:

- low – maximum of nine years of basic school education;
- medium – 10 years of extended school education;
- high – 12 or 13 years of extended school education, including persons who went on to university.

Participants' answers were directly recorded into a database, merged with demographic data and exported

Table 1

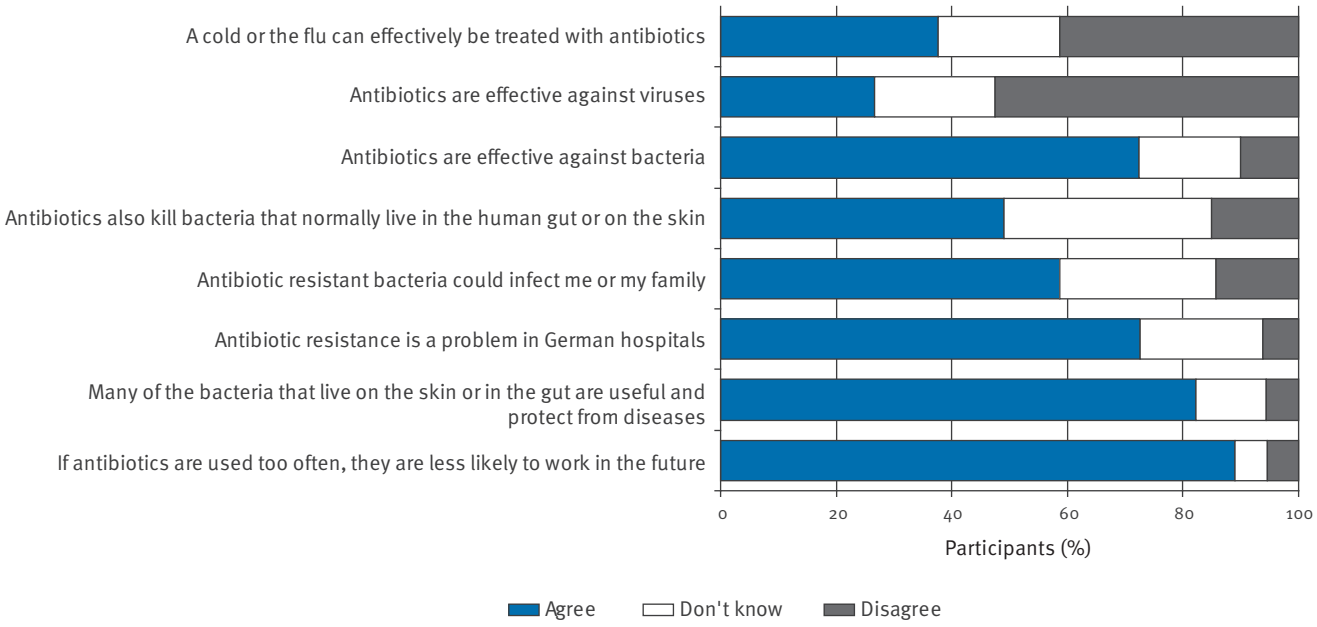
Demographic characteristics of the study participants in 2008 (n=1,076) and general public, Germany

Characteristics	Number (percentage) of study participants	Percentage of general public aged ≥15 years[a]
Male	589 (54.7)	48.9
Age (years)		
15–19	95 (8.8)	7.4
20–29	213 (19.8)	13.8
30–39	251 (23.3)	14.5
40–49	271 (25.2)	19.5
50–59	164 (15.2)	15.7
≥60	82 (7.6)	29.1
Level of school education		
Low	156 (14.5)	48.7
Medium	276 (25.7)	27.6
High	644 (59.9)	23.7

[a] Data for 2007 according to the German Federal Statistical Office [14].

Figure 1

Relative frequency of participants' responses to statements concerning knowledge of antibiotic action and resistance and normal flora, Germany, 2008 (n=1,076)



to a single database that was then checked for missing data and monotonous answers (e.g. yes/no only). Variables were dichotomised if needed for the analysis (e.g. 'agree fully' and 'agree somewhat' = 'agree', 'disagree fully' and 'disagree somewhat' = 'disagree').

Statistical analysis

We calculated relative frequencies of responses (total and stratified by demographic characteristics or particular items in the questionnaire). Scores were calculated for: (i) knowledge of antibiotics and (ii) responsible antibiotic use, summing up the number of correct responses to statements or answers indicating responsible views of antibiotic use, respectively. The chi-square test, t-test or Cuzick's test for trend was applied to test for significant differences between subgroups.

Determinants (demographics, knowledge and attitudes) for expecting a prescription of antibiotics for the common cold were sought using logistic regression analysis. Variables associated with these expectations in the bivariate analysis ($p<0.2$) were entered into the model and retained if the adjusted p value was less than 0.1 (stepwise backward elimination). Logistic regression analysis was conducted with a separate set of variables using mean substitution of missing values (separately for the outcomes 'respondent expects antibiotics' versus 'respondent does not expect antibiotics') [13].

All statistics were conducted using STATA 10.1.

Results

Of 1,778 invited, 1,076 persons between the age of 15 and 78 years (54.7% male) participated, resulting in an overall response of 61%. Compared with Germany's general population, there was no considerable difference in our sample concerning the distribution of persons across Germany's 16 Laender and the size of places of residence (scale of five ranks), but higher

Table 2

Number of correct responses (to eight knowledge statements)[a] and number of responses indicating responsible antibiotics use (to eight attitude statements)[b], by participants' demographic characteristics, Germany, 2008 (n=1,076)

Characteristics	Knowledge		Attitudes	
	Mean	95% CI	Mean	95% CI
Sex				
Male	5.12	4.94–5.29	6.20	6.06–6.34
Female	5.25	5.07–5.44	6.39	6.26–6.52
Age (years)				
15–19	4.17	3.74–4.59	5.77	5.43–6.12
20–29	4.94	4.65–5.23	6.21	6.00–6.42
30–39	5.35	5.11–5.60	6.34	6.15–6.54
40–49	5.62	5.38–5.86	6.50	6.32–6.68
50–59	5.48	5.16–5.79	6.26	6.00–6.51
≥60	4.35	3.85–4.86	6.26	5.96–6.55
Level of education				
Low	4.38	4.06–4.71	5.88	5.59–6.17
Medium	5.00	4.73–5.26	6.24	6.04–6.43
High	5.45	5.29–5.60	6.41	6.29–6.52
Total	**5.18**	**5.05–5.30**	**6.29**	**6.19–6.38**

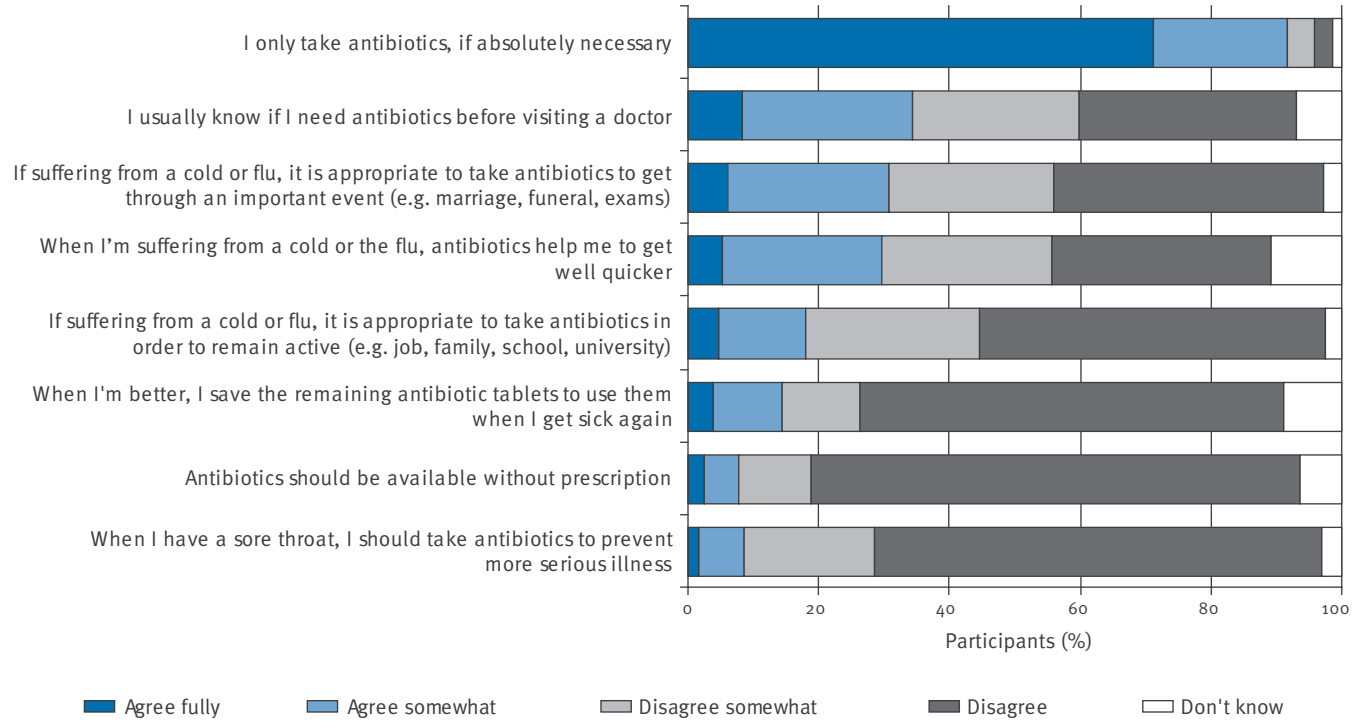
CI: confidence interval.

[a] See Figure 1.

[b] See Figure 2.

Figure 2

Relative frequency of participants' responses to statements concerning attitudes towards antibiotics and antibiotic use, Germany, 2008 (n=1,076)



age groups, women and persons with a lower level of education were under-represented (Table 1).

Knowledge and attitudes concerning antibiotics and respiratory tract infections

The majority of participants knew that antibiotics are effective against bacteria (72.3%) but not viruses (52.6%), knew about antibiotic resistance (89%) and acknowledged it to be a problem in German hospitals (72.6%). However, only 445 (41.4%) knew that antibiotics are not effective against the common cold or influenza (Figure 1).

The mean number of correct responses to eight statements on antibiotic knowledge was 5.2 of eight (65%). Participants with a high level of education responded to more statements correctly than those with a medium or low level of education (Cuzick's test for trend: p<0.001). Persons of younger (15–29 years) or older (≥60 years) age had lower scores in the questions on antibiotic knowledge (Table 2), also after stratification by level of education (data not shown).

When asked about views on antibiotics and antibiotic use, most participants (91.8%) reported that they use antibiotics 'only if absolutely necessary', and disagreed with the statement 'antibiotics should be available without prescription' (86.0%). However, 34.4% thought they knew if they needed antibiotics before visiting a doctor and 30.8% considered it appropriate to take antibiotics to get through an important event when suffering from a cold or influenza (Figure 2). Overall, self-reported views on antibiotics were more sensible or responsible in persons with higher levels of education and least in participants less than 20 years of age (Table 2).

Prevalence of expectations

Participants were asked on two occasions during the survey whether they expect their physician to prescribe antibiotics for the common cold: the first question dealt with general expectations when consulting their physician because of the common cold or influenza. Most respondents reported that they consult in order to 'be examined, receive advice or a sick certificate' (47.3%) or for symptomatic treatment (44.4%). A wish for antibiotics was mentioned by 83 (7.7%) respondents. In the second question, participants were asked whether they would expect a prescription of antibiotics for certain common respiratory infections (along with their typical symptoms). In this question, 113 (10.5%) reported to expect antibiotics for the common cold (sore throat, blocked nose, cough), while 46.9% and 92.7% did so for influenza (fever, fatigue, head- and muscle aches, cough) and pneumonia, respectively. For the common cold, the prevalence of self-reported expectations of receiving a prescription of antibiotics depended on level of education in the bivariate analysis (19.9%, 12.0% and 7.6% for low, medium and high level of education, respectively, p<0.01). No other significant associations with demographic data (age group, sex, place of residence, migration background, household income, type of health insurance, occupational group) were seen after stratification by level of education (data not shown).

Association of expectations and knowledge and attitudes

In the multivariable analysis, the strongest predictors for expecting a prescription of antibiotics for the common cold were holding the following opinions: 'a cold or the flu can effectively be treated with antibiotics' (prevalence: 37.6%; odds ratio (OR): 9.6; 95% confidence interval (CI): 3.8 to 24.3) and 'when I have a sore throat, I should take antibiotics to prevent more

Table 3

Multivariable analysis: factors associated with self-reported expectations for antibiotic prescription for the common cold, Germany, 2008 (n=1,076)

Factors	Odds ratio	95% CI
Knowledge and beliefs		
A cold or the flu can effectively be treated with antibiotics	9.58	3.77–24.31
When I have a sore throat, I should take antibiotics to prevent more serious illness	7.56	3.94–14.51
Many of the bacteria that live on the skin or in the gut are useful and protect from diseases	0.21	0.08–0.55
I only take antibiotics if absolutely necessary	0.26	0.11–0.62
When suffering from a cold or flu, it is appropriate to take antibiotics to get through an important event	2.26	1.28–4.00
Antibiotics should be available without prescription	2.65	1.25–5.59
Antibiotic resistant bacteria could infect me or my family	3.25	1.28–8.21
When I'm suffering from a cold or the flu, antibiotics help me to get well quicker	2.18	1.15–4.15
Antibiotics are effective against viruses	2.01	1.07–3.79
If antibiotics are used too often, they are less likely to work in the future	0.31	0.10–0.94
Characteristics		
Antibiotic use during the last year	1.86	1.07–3.22
Reported suffering from cough, cold, sore throat or fever at the time of the investigation	1.77	1.03–3.06
Level of school education: high	0.55	0.32–0.94

CI: confidence interval.

serious illness' (prevalence 8.6%; OR: 7.6; 95% CI: 3.9 to 14.5). The full results are shown in Table 3.

Confidence in the physicians' decisions

Among those expecting a prescription of antibiotics for the common cold (n=113), 80 (71%) reported that they trust their physician when he or she deems a prescription unnecessary. A further eight (7%) would be unsatisfied but accept the decision, whereas 14 (12%) reported that they would win over the doctor to prescribe and three (3%) would consult another doctor. In a more general question, 99 of 1076 (9.2%) reported that they felt they were not taken seriously or were not receiving proper treatment if they were not prescribed antibiotics for a cold or influenza.

Discussion

We found that 10.5% of respondents expected a prescription of antibiotics for the common cold and that such expectation was associated with a lack of knowledge of correct indications for antibiotic use and antibiotic resistance. Of those expecting antibiotics from a consultation, 77.9% reported that they trusted their physician when he or she deemed a prescription unnecessary or would at least accept such a decision.

Strengths and limitations

This is, to our knowledge, the largest study specifically investigating public views and knowledge of common respiratory tract infections and antibiotic use in Germany. The use of an online access panel allowed us to achieve a high response and to gain insight into the views and expectations of a wide range of population groups before they visit a doctor. Our study has limitations: firstly, the shortage of participants with a lower education level might bias the overall results towards better knowledge and more responsible views than actually present in the general population. We therefore presented stratified results whenever appropriate. Secondly, asking the general public might introduce a bias towards a lower prevalence of expectations of receiving a prescription of antibiotics when compared with asking patients. We therefore included a question on the presence of common cold or influenza symptoms at the time of investigation, which allowed us to partially compensate for this effect. Finally, as with all questionnaire studies, participants may give answers that they consider are socially desirable, which might introduce a bias towards more responsible use of antibiotics.

Patients' expectations

The existence of patients' expectations regarding the prescription of antibiotics and their influence on the decisions of doctors to prescribe is unequivocal [7,15,16]; however, the prevalence of such expectations varies considerably depending on the setting or type of study. It can be as high as 50% in United States adults consulting for cold symptoms [17] or as low as 1.2% in the Dutch general population [12].

Overall, our results indicate a sensible approach to antibiotics among Germany's public. Only a minority reported that they expected a prescription of antibiotics for cold symptoms and most reported to be taking antibiotics 'only if absolutely necessary'.

This is remarkable in light of the overprescription of antibiotics and the common belief that patient expectations at least partly drive it. However, our findings are in line with several studies that show that most patients seek information, reassurance or a diagnosis rather than a prescription of any kind [18] or a prescription of antibiotics in particular [19,20]. Real expectations of patients regarding the prescription of medication seem to be much less prevalent than expectations perceived by the doctor and furthermore their presence less predictive of the decision to prescribe [21-23]. Cockburn *et al*. found that when a patient expected a prescription he was three times more likely to receive it, but when the general practitioner thought the patient expected medication, the patient was 10 times more likely to receive it [22]. A study conducted in general practices in Germany showed that nearly all patients who, in their doctor's opinion, expected a drug left the surgery with a prescription. However, doctors accurately perceived the patient's wish for a drug prescription in only 41% of cases [24].

Furthermore, if patients do expect a prescription for cold symptoms, they do not necessarily expect a prescription of antibiotics. Van Driel *et al*. suggested that patients with acute sore throat and who hope for antibiotics are actually seeking treatment for pain [19]. This corresponds well to results of our survey, where 44% of respondents reported to expect symptomatic treatment for cold symptoms (e.g. lozenges, painkiller, cough medication) while only 7.7% reported to expect antibiotics for these symptoms.

In contrast to the observed low prevalence of expecting antibiotics for the common cold, nearly half of the participants in our study reported to expect a prescription of antibiotics for influenza. Given the existence of antiviral medication used for the treatment of influenza, it is unclear whether this question was not specific enough or whether influenza is much more frequently expected to be treated with antibiotics. But even if an individual patient has such expectations and the physician denies an actual wish for a prescription of antibiotics, he or she must not necessarily worry about losing the patient to another practice. The results of our study indicate a high level of confidence towards physicians and their decisions among Germany's general public. Less than 3% of those reporting to expect an antibiotic for cold symptoms stated that they would consult another doctor if their request were denied. Studies conducted in general practice settings showed similar results and concluded that a medically justified refusal to prescribe antibiotics had, in most cases, no negative effect on the consultation or its assessment by the patient [15,24,25].

Misconceptions and their implications

Misconceptions concerning the appropriateness and effectiveness of antibiotics for different indications seem to be quite common among Germany's public, comparable with results found in similar studies conducted in the United Kingdom [10] or the Netherlands [12]. In our multivariable analysis, these misconceptions were clearly associated with the expectation of receiving antibiotics for the common cold. The two 'items' most strongly associated were both related to the plain beliefs that antibiotics can be used to effectively treat the common cold or influenza and if they are used for a sore throat they could prevent more serious illness. It therefore seems to make sense to educate the public on antibiotic effectiveness, correct indications and risks of antibiotic mis- or overuse. If this is considered, efforts should be focused on the group where relevant expectations are most prevalent: those with a lower level of education. However, simply educating the public may not be effective in reducing the level of prescribing. A large household survey conducted in the United Kingdom demonstrated that those with a greater knowledge of antibiotics were no less likely to be prescribed an antibiotic [10]. According to a systematic review of 39 studies focusing on interventions to improve antibiotic prescription practices in ambulatory care, multifaceted interventions involving informing patients, communication training of physicians and educating the public were more successful [26]. In a cluster-randomised study conducted in more than 100 general practices in Germany, an intervention focusing on doctor–patient communication and patient empowerment even reduced antibiotic prescription rates for acute cough by 40% after 12 months [23].

Conclusions and recommendations

Our study suggests that there may be several opportunities to reduce unwarranted use of antibiotics and thus ultimately reduce further development of antibiotic resistance. Expectations that antibiotics will be prescribed for the common cold are generally not widespread and are most likely less prevalent than believed by general practitioners.

Physicians should therefore carefully explore if a perceived wish for antibiotics really exists in an individual patient. It may turn out that the consulting patient actually seeks symptomatic relief, reassurance or just a sick certificate.

Existing erroneous expectations might be caused by misconceptions of what can be achieved by taking antibiotics for cold symptoms and what risks are involved (e.g. adverse effects or development of resistance). With the high level of confidence physicians enjoy among the public, they may often be able to convince patients of alternative strategies and should not overly worry that they may displease their patients by not yielding to their requests. Change, however, does not come easily and multifaceted approaches are needed to tackle the problem of overprescribing and antibiotic resistance.

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Micro-simulation of a smallpox outbreak using official register data

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To explore the efficacy of four vaccine-based policy strategies (ring vaccination, targeted vaccination, mass vaccination, and pre-vaccination of healthcare personnel combined with ring vaccination) for controlling smallpox outbreaks in Sweden, disease transmission on a spatially explicit social network was simulated. The mixing network was formed from high-coverage official register data of the entire Swedish population, building on the Swedish Total Population Register, the Swedish Employment Register, and the Geographic Database of Sweden. The largest reduction measured in the number of infections was achieved when combining ring vaccination with a pre-vaccination of healthcare personnel. In terms of per dose effectiveness, ring vaccination was by far the most effective strategy. The results can to some extent be adapted to other diseases and environments, including other countries, and the methods used can be analysed in their own right.

Introduction

Should an infection of a contagious disease occur, the potential threat must be met by swift countermeasures. In Sweden, relatively accurate and complete population data as well as environment data are available from governmental institutions. We have used these official register data as part of the input to our computer-based micro-simulation model of the spread of infectious disease. We have studied different pathogens and scenarios, but this report concentrates on our results for smallpox, which is an example of a predominantly airborne, fairly contagious vaccine-preventable disease for which reliable data on some basic parameters exist [1]. To explore the value of a micro-level representation, meaning that we explicitly represent each of the micro-units – here individuals – instead of aggregating them into groups, we performed a number of simulation experiments on the efficacy of various policy interventions for smallpox outbreaks. To the best of our knowledge, our model is the first based on real register data at the level of individuals [2].

A large number of models have been produced to describe the spread of infectious disease, in order to better understand the mechanisms behind incidence and speed, as well as to evaluate countermeasures. In 1905, William Hamer put forth the so-called mass action principle by concluding that an epidemic process is in part governed by the degree of contact between infectious and susceptible individuals. The principle states that the speed of an outbreak's development is proportional to the product of the number of individuals in these two groups. It is true under the most simple assumption possible concerning the structure of human contacts that everybody is equally likely to meet anybody else, so-called homogeneous mixing [3]. Even today, most models assume homogeneous mixing. The widely used SIR model [4], for instance, contains three groups of individuals: susceptible, infectious, and recovered/removed (SIR). The numbers of individuals in the three groups are functions of time, and the process is often described using partial differential equations [5,6]. Macro-models of this simple kind, in which the behaviours of individuals are not modelled, can be shown to be sufficient for some diseases, such as measles [5,7]. For diseases that are less infectious a close contact between the infectious and the susceptible is required for transmission. Macro-level models assume homogenous mixing, which means that the chance for any two people in the model to meet is equally great – not the case in reality, where geography and contact patterns make it much more likely to meet a family member or a neighbour than a distant stranger. It has recently been established that contact patterns may influence epidemics significantly [8,9]. Real contact networks are highly structured into families and other social groupings, and the rate of contacts varies considerably in the different settings. To identify and to model the key elements in social structures and behaviour are major challenges in disease modelling: levels of detail need to be neither too low nor too high [10]. The computer readily lends itself to random simulations, due to the conceptual ease with which different

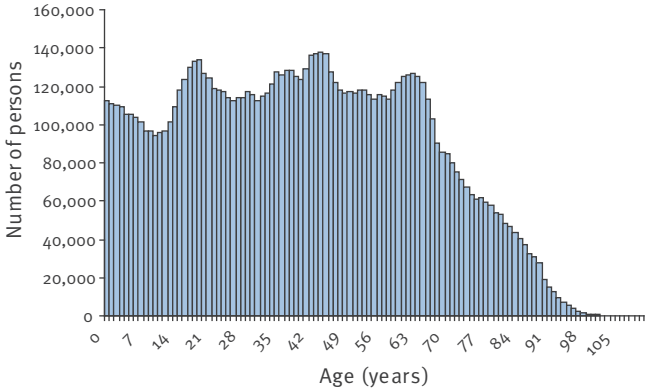
assumptions can be implemented, forming different scenarios.

Compared with other models [11,12-14], our model stands out because all individuals – as well as their homes, workplaces, and certain behaviours – are explicitly represented. What is more, the underlying data are real in so far that each individual's home, family, and workplace is modelled on official register data. In addition, all dwellings and workplaces are spatially explicit – i.e. represented by their real geographical coordinates. This explicit representation allows for exploration of tailored interventions; towards individuals within particular sectors of the work force, geographical regions, or specific age groups.

In a step towards an individual-based model, a pattern of contacts may be devised. This enables us to model the application of control measures such as ring vaccination. Through certain assumptions, it is possible to mimic the effects of contact tracing [15], without explicitly modelling a contact network. The model of Eubank *et al*. [12] is the most detailed in its population structure and to some lengths mimics a real population by using extremely detailed transportation data.

Figure 1

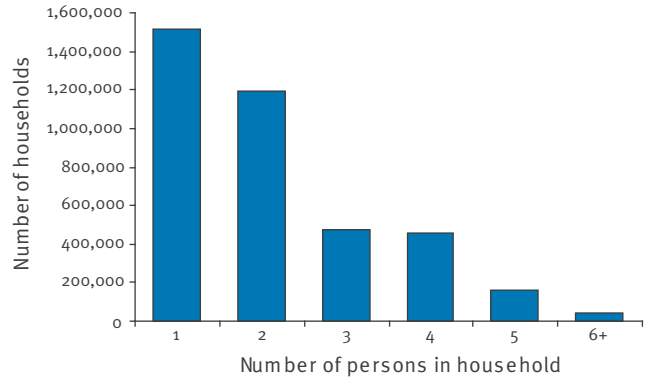
Age distribution of the Swedish population, 2009



Source: Statistics Sweden, 2010.

Figure 2

Household size distribution, Sweden, 1990



Source: Statistics Sweden, 1990.

It is through that dataset possible to connect people to places and so generate a contact network. Halloran *et al*. [16] also use an individual-based approach with a population structured in groups at various levels, such as homes, schools, and clinics. Within each group, contacts take place through homogeneous mixing.

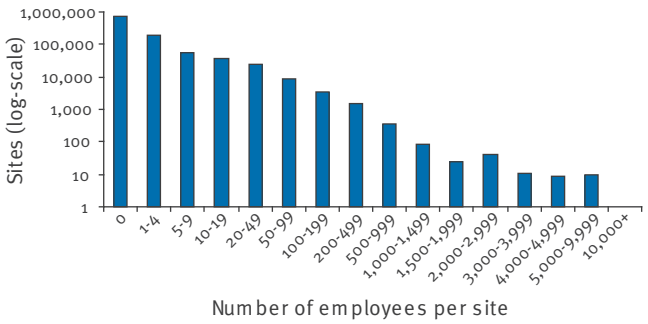
Method

Modelling the population

'Microsim' is a structured micro-model for simulating outbreaks of infectious disease [17,18]. It represents the entire Swedish population, with geographically explicit connections to family members, dwellings, and workplaces. Microsim is built to run on a standard personal computer. Updating the status of nine million people in the model is time consuming; thus we put much effort on increasing the speed of execution. A simulation run over 150 days takes about one hour to run, which we found acceptable. The Microsim model

Figure 3

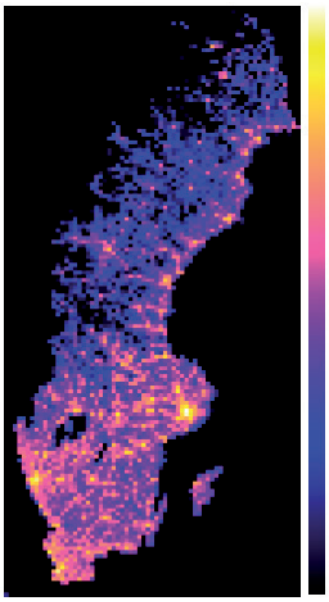
Size distribution of workplaces (number of employees at workplace sites), Sweden, 2009



Source: Statistics Sweden, 2010.

Figure 4

Spatial distribution, Swedish population, 2002



Brighter colours indicate higher density.
Source: Statistics Sweden, 2002.

specification and code is available from the authors upon request, but access to population data might hinder replication experiments. The model is stochastic, meaning that it includes randomness. Two consecutive runs will generate different outbreaks even when all parameters are the same since there is an element of randomness included in many of the individual choices: if a person travels, goes to hospital or stays home from work. The time representation is discrete with a resolution of one hour. The population data are compiled from three official data registers [19]: the Swedish Total Population Register of December 1999, the Swedish Employment Register of December 1999, and the Swedish Geographic Database of January 2000. The age distribution of the Swedish population is shown in Figure 1, the family size distribution in Figure 2, and the workplace size distribution in Figure 3. In Figure 4, the spatial distribution of the population is plotted.

The three registers were linked by Statistics Sweden at the level of individuals by the unique personal identification number of each individual. The identification number was removed before the dataset was delivered to us; we have thus worked with an anonymised dataset of the total population, in which individuals are connected to workplaces and dwellings. Individuals with same family identity belong to the same family and share a dwelling. The contacts between individuals through dwellings and workplaces form a mixing network that enables the spread of disease. Individuals move to different locations during the day and contact other people. The model predicts transmission on the basis of probabilities that depend on the numbers of infectious individuals present at a particular place. Schools, emergency wards, and infectious disease departments are also represented, making it possible to model and evaluate specific countermeasures. People may, for example, seek medical care when sick with smallpox, increasing the risk of transmission in hospitals.

Modelling the disease

We divided the incubation and symptomatic phases into two parts. We assumed that vaccination is effective only in the first three days of incubation in order to demonstrate the efficacy of different vaccination strategies. Likewise, we assumed that patients are highly infectious for the first four days of symptoms, after which their infectivity decreases. An individual can hence pass through up to six phases with different characteristics in the form of time, health status, infectivity, and more (Table 1). The relevant time-distributions are either uniform or point distributions, with the exception of the second incubating period [11,20-22]. It is assumed that 30% of the unvaccinated individuals will die, with death occurring seven to 14 days into the symptomatic phases.

Micro-modelling individual behaviour

The behaviour of the simulated individuals is defined by a simple set of rules for daily routines or special circumstances. In the morning, each individual checks his/her state of health, which determines activity for the next eight hours. For the working population, or children attending school or day care, this means moving to another location. The probability of making longer journeys within the country is set to 0.03 (3%), based on the average value for daily domestic journeys in excess of 100 km (215,000: probability 0.025, or 2.5%, rounded up to include shorter journeys between regions). Each day, we assume that 5% of the total population are prevented from attending work or school by illnesses other than smallpox. We assume that 1% of the population will seek medical care daily (in 1999 there were 25 million visits to doctors in Sweden [365 days; 9 million inhabitants]) [23]. This amounts to 4,500 emergency room (ER) and hospital visits daily. The daily routine of individuals infected with smallpox and still in incubation is unaffected on the first day of the prodromal phase. On the second day of the prodromal phase, 50% are assumed to be healthy enough to proceed as usual. A further assumption is that 25% will seek medical care and spend the rest of the prodromal phase at home. The remaining quarter will also stay at

Table 1

Features of smallpox during its six phases

Phase	Time/time distribution	Health status	Infectiousness	Other
Incubating 1	3 days	Healthy	None	Vaccination is effective
Incubating 2	4–16 days, distribution according to Figure 1	Healthy	None	Vaccination has no effect
Prodromal	3–5 days, uniform distribution	Influenza-like symptoms increasingly severe	25% during the last 2 days	Patients staying at home/visiting ER during this phase[a]
Symptomatic 1	4 days	Pox erupt	Full	Patient admitted to DID
Symptomatic 2	16 days	Pox dry out	50%	
Immune/ deceased	Death occurs 7–14 days into this phase in 30% of cases, uniform distribution	Recovered or deceased	None	Patient returns home

DID: department of infectious diseases; ER: emergency room.

[a] Stage 1: day 1, 100% go to work, none visits ER. Stage 2: from day 2 to the day before the last day, 50% go to work, 50% are ill and stay at home (25% of these visit an ER). Stage 3: last day, those who have not visited an ER before do so now.

home but wait until the last day of the prodromal phase before seeking medical care. On the last day of the prodromal phase, those who continued their daily routines will visit an ER. The events of the symptomatic phase are determined by awareness of an imminent smallpox epidemic. Until three patients have been confirmed with smallpox, it is assumed that an infected individual will wait one day before visiting the ER. The next day, this individual will be transferred to a department of infectious diseases (DID) and stay there for the duration of infection. Once three smallpox patients have been confirmed, all those entering the symptomatic stage will go to the nearest ER immediately.

Modelling places

The places where contacts occur and transmission may take place are of two basic types: regular and random. Regular places are based on register data, and represent contacts for which empirical data are available. The homes and workplaces represented in Microsim are collected from the register data, including geographical coordinates. The resolution of the coordinate system (Cartesian) is 100 metres. Workplaces also include schools, day care centres, and hospitals. Schools and day care centres differ from each other in that the contact rate is higher in day care centres. Workplaces, including schools, are further divided into departments. We assume that a department consists of 25 people, roughly the size of a school class. In comparison, the actual mean (and median) size of a workplace in Sweden is 15, given that one-person companies are excluded from the model (since such workplaces play little or no part in spreading the disease).

Hospitals are special cases in that they will sometimes have an ER or a DID, and sometimes both. These are both represented as departments where people work, as in other workplaces, but also as places where symptomatic smallpox patients are present. Our register data do not connect children to schools and day care centres since the employment register applies only to adults. Instead, we assign children to schools on the basis of proximity and size – i.e. the number of employed adults. Random noise in this assignment accounts for children attending schools other than the one closest to their home.

The second basic type is comprised of places where people meet haphazardly – for example, brief contacts in such places as shopping centres and airports. We used two random place types: neighbourhood and travel. We chose a partition of Sweden into 81 regions, defined by workplace attachment, 'local workforce region' [24]. This partition is useful because it means that most travelling, to and from work, is done within these defined regions, and is thus modelled implicitly by the daily movement to and from work. Travel between regions (and to a small extent within the region) is defined as 'travel' in our model and is not connected with the workplace or school. We defined one travel destination for each of the 81 regions. This putative place gathers everyone who travels within or to this region each day. The travel destination mimics the meetings that take place on public transportation such as trains, buses, and aeroplanes. The activity of travelling means one-day journeys in which the traveller is included in the list of travellers for this region, with the possibility of being infected by other travellers in the region as well as infecting them. The destination of a journey is determined on the basis of probability by using a gravitation model based on the number of people in the region and the distance from the dwelling of the traveller. Short trips are more likely than long ones, and trips to a densely populated region are more likely than to one that is sparsely populated. 'Neighbourhood' is a proxy for random encounters in the immediate vicinity. These encounters could take place at grocery stores, cinemas, on public transport, or in other places where many people meet. The underlying assumption for this is that it is more likely for a person to meet someone from his or her immediate area than from far away. When transmission has occurred in a dwelling, a neighbourhood list is created and filled with a number of individuals. The probability that an individual will be added to this list decreases with distance. For computational efficiency reasons, the lists are created once only for each neighbourhood and filled with 1,000 individuals from which the contacts are picked at random when transmission is simulated.

Modelling transmission

In Microsim, individuals are assigned to workplaces and to homes in periods of eight and 16 hours, respectively. The risk of infection differs for contacts depending on where they take place, following an assumption about the closeness of contacts and duration of each individual contact. The closeness of contact is assumed to be highest at home, followed by day care centres, schools, and workplaces, in descending order. For ERs, DIDs, as well as for the places of neighbourhood and travel, the ordering of the risk of infection is not as intuitive. The risk was assumed to be quite high in ERs, motivated by the closeness to other people in a crowded waiting room and the long duration of contact when waiting to see a doctor. In DIDs, the risk for transmission is much smaller since the risk awareness is high and the staff are likely to take precautions, such as wearing masks. The risks for neighbourhood and travel were obtained by calibration (Table 2) – that is, we tested different values and used the infectiousness values that produced the desired outcome in terms of number of infections from that type of place. In the past smallpox has spread between regions and countries, even though it is known that those with the infection are often very ill. Our way to represent this somehow contradictory behaviour is by setting a low risk for travelling when infectious but a high risk for infection when the infectious person does indeed travel. A highly infectious person might not feel ill when beginning a journey. Such a person might both develop symptoms while travelling, and expose many fellow travellers on a train or bus. Note that the infection risk

for homes is doubled in the simulations, since individuals are assumed to spend 16 hours at home and only eight at work. The risk of infection is much higher within a department than between departments of the same work place. We assume no prior immunity; thus everybody is susceptible to the infection at the outset.

Disease transmission is modelled to occur twice daily. The actual risk of contracting the disease for a susceptible individual during the duration of stay, the infection risk, or *IR*, is calculated for each department and home and is given in Equation 1. Every place type is associated with a basic per contact transmission risk, *pr*. The risks for different place types are listed in Table 2. The basic transmission risk is modified by the current disease phase of the infectious individual in the guise of a phase coefficient *p* and, if applicable, a coefficient *d*, corresponding to the department to which the infectious individual belongs. The relative infectiousness in prodromal and symptomatic phases is presented in Table 1. Parameter *d* equals 1 if the susceptible and the infectious individual belong to the same department, otherwise it is lower. The complement of the resulting risks is multiplied over the infectious individuals at that place to produce the complement of the infection risk.

$$1 - IR_j, \text{ where } IR_j = \prod_{n=1}^{i} 1 - p_i d_{ij} pr_i, \text{ for } 1,\ldots, \text{i, j.}$$

In Equation 1, above, i designates the infectious individuals and j the susceptible individual under consideration. The assignment of the base risk variables is not trivial. When values exist, they are contradictory or do not lend themselves to implementation models, especially at the micro-level. Initially, we used parameters taken from the model of Halloran *et al.* [16] as their model was conceptually the closest one to Microsim. We then calibrated our model, adjusting the parameters to achieve a predetermined goal value of transmissibility, as well as reasonable results in terms of numbers of infected at the different place types. The estimations were based on experiences from previous epidemics, such as the smallpox outbreak in Stockholm in 1963 [25]. The values used for our experiments are found in Table 2. The place type distribution – places where infections took place (the majority in ERs and DIDs) – is shown in Table 3.

We calculated transmissibility using an algorithm [6], essentially starting a simulation with 500 randomly picked initially infected individuals in a totally susceptible population, and counting the number of secondary cases. We iterated 500 times, each time with a new set of 500 infected individuals. Interpreting our transmissibility values in the light of analyses of historical smallpox data, we note that historical data show R_0 to have a value of 3.5–6 [26,27]. In Sweden today, where every second household consists of a single person and half the population lives alone or with one other person, the social structure implies that we should end up well below the low end of this interval. Our transmissibility value of 2.25 was hence deemed reasonable.

Modelling vaccination policies

We assumed that the vaccine grants immunity to 80% of those inoculated and we disregarded any adverse effects. The vaccination policies we set out to compare were the following:

- ring vaccination (Ring)
- targeted vaccination of medical care personnel at risk for exposure (Care)
- mass vaccination (Mass)
- pre-vaccination of medical care personnel at risk for exposure + ring vaccination (Combo)

The Combo policy was included because the National Board of Health and Welfare considered the scenario of an outbreak starting in neighbouring countries, with some time permitted to vaccinate medical care personnel in Sweden, as likely and thus of interest. The population in Sweden is nine million. Some 10,500 people work in ERs and DIDs, and are considered to be at high risk of exposure.

Ring vaccination involves tracing the contacts of infectious people as they are identified, including family

Table 2

The risk of infection with smallpox during a contact[a], for each place type

Place type	Basic infection risk
Home	0.25
Day care (within group)	0.1
School (within class)	0.05
Work place (within department)	0.05
Between groups, classes and departments	0.001
Emergency room	0.2
Department of infectious diseases	0.01
Neighbourhood	0.02
Travel	0.2

[a] The duration of a contact is eight hours at day and 16 hours at night. The high infection risk at home is a combined result of the close type of contact and the duration. Travel risk includes car, bus, train, and flight travel. Some forms of travel are of long duration in small compartments, hence the relatively high risk assigned.

Table 3

Distribution of locations where transmissions of smallpox took place in the vaccination policy experiments

Location	Base	Ring	Care	Mass	Combo
Dwelling	1,953	431	499	142	139
School/day care	36	10	10	4	6
Office	44	7	16	7	4
Travel	4	0	0	0	0
ER/DID	4,700	852	636	429	55

DID: department of infectious diseases; ER: emergency room.

members and colleagues, which are readily available in the model. We assumed that this process is 100% successful and that immunity from vaccination is generated immediately. Both of these assumptions are optimistic, admittedly, and these assumptions should be subjected to sensitivity analysis in longer series of experiments.

In the mass vaccination strategy, we included a capacity at the hospitals and care centres that limited the number of vaccinations to be administered each day. We assumed that a tenth of the nurses could be assigned to the vaccination programme, each able to administer 80 doses a day. This equates to a theoretical maximum of 720,000 patients per day. With the exception of the pre-vaccination part in the Combo policy, which takes place at the start of the simulation, all programmes are launched after the first case has been identified at a DID.

Figure 5

Incident cases of smallpox over 100 days from the first 99 runs without interventions (Base)

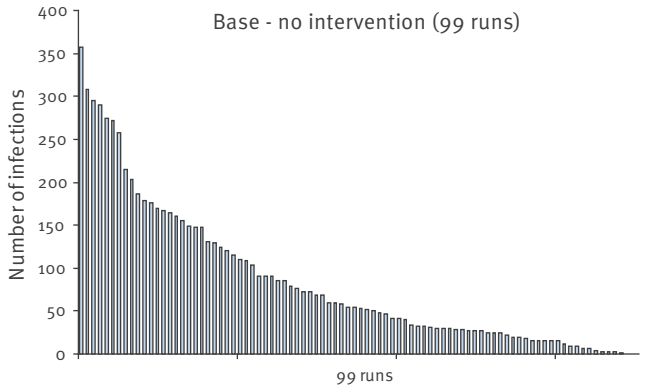


Figure 6

Variation in numbers of smallpox infections – intervention experiments

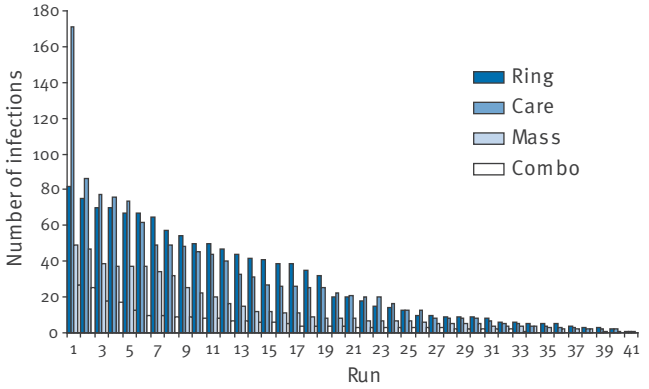


Table 4

Number of cases in the policy experiments, based on 41 simulation runs per policy*

Policy experiment	Base	Ring	Care	Mass	Combo
Average	176	30	30	14	6
Minimum	49	1	1	1	0
Maximum	834	82	171	49	27
Standard deviation	163.3	25.2	32.7	13.9	6.4
Reduction (%)	0	83	83	92	97

Experiments

Baseline values were recorded by running the simulation without intervention. We made 500 runs with different random seeds. Each run had a single individual initially infected, also picked at random. A random seed determines a vector of random numbers that are used throughout the simulation run for all kinds of stochastic events in the model, such as if an individual will travel or not on a particular day. If the same seed is used in several runs, the same random numbers would be generated and the simulation would repeat itself. By using 500 distinct seeds we generated a spectrum of possible scenarios. Each scenario was run for 100 days, which was deemed sufficient for evaluating policies. Longer runs, at the time of these experiments, exceeded the computer's memory capacity, hence a few outbreaks were not taken into full account because they had not finished by the 100th day. These computational complexity issues have since been fixed, and the model is currently optimised for 300-day runs, even if no more than 100 days are typically required. Of the 500 runs, 41 predicted the infection of 49 or more individuals. These runs were classified as outbreaks and their random seeds were recorded for further use in the policy comparison. A vaccination policy had to reduce the size of these 41 outbreaks to be considered effective. On average, 172 individuals (family, and colleagues from the same office department) were vaccinated in the Ring vaccination policy. The Care policy vaccinated 10,530 individuals (the same number in each experiment). The efficacy of policies was compared in terms of the difference in numbers of individuals infected. We therefore conducted four further experiments seeded with the same seeds recorded from the 41 outbreaks. We also recorded and compared the per dose reduction in incidence.

Results

In order to demonstrate the viability of our microsimulation model, our prototypical experiment set-up yielded the following results.

Figure 5 shows 99 base simulations, illustrating the variation in outbreak magnitude when no interventions were applied (range 0 to 357 infections). In Figure 6 the numbers of infections in each simulation run are shown for the different policies. The runs are sorted from the largest to the smallest number of cases, and the same random seed is used for the four different policy simulations. The results of our intervention experiments are shown in Table 4.

All strategies reduced the numbers of infected from base line values significantly: ring vaccination by 84%,

the care policy by 86%, mass vaccination by 93%, and the combo policy by 97%. The outcomes of the care policy and ring vaccination were not significantly different. Mass vaccination was significantly better than both, but the policy of combining ring vaccination with a pre-vaccination of the care personnel at most risk for exposure (combo) was significantly better than vaccinating the whole population (mass). This assumes that a vaccination of the care personnel is started after the first identified case and that the logistic restrictions described earlier apply.

Further comparisons can be made by examining the vaccination efficacy in terms of the numbers of doses required to prevent one case. It is evident that the combination policy is far more effective than mass vaccination. That the extra doses required to carry out ring vaccination were well spent is indicated by comparing the combined policy to the care policy. In terms of per dose effectiveness, ring vaccination is by far the most effective.

One motivation for vaccinating the highly exposed medical care personnel is the high rate of transmission assumed to occur at ERs and DIDs (where our model includes the personal protective equipment of staff only indirectly). Tables 3 and 4 illustrate how this assumption is represented in our model and explains the success of these strategies in terms of numbers infected and vaccination dosage.

Discussion

An outbreak simulation must take into account not only the numbers of those infected and their mortality but also the costs of vaccine doses and their distribution and the high-risk environment for medical care personnel. Note that we have considered neither adverse effects nor their consequences in our model. We have endeavoured to demonstrate here the general utility of our model and, although the results are subject to an array of assumptions and provisos as far as the parameter values are concerned, these results reflect those of other smallpox simulation studies [11,13,14,16,28].

In order to compare resources required, we calculated the per dose incidence reduction. Ring vaccination is the most effective in this sense. This was expected as only those who have been exposed to the index case are vaccinated. But since vaccine effectiveness is not 100%, and since there is no immunity outside the circle of contacts of the index case, the epidemic is allowed to continue. It is a feature of the model that it allows for interactive testing of different thresholds, that is, for the percentage of contacts that must be found for the policy to be effective.

When running our experiments, we saw that the results are very sensitive to the underlying assumptions. Here, a central variable is transmissibility, and the value of this seemingly simple variable is hard to determine. It is very difficult to assign exact probabilities to risk for disease transmission during a contact, since there are no data on number and nature of contacts. Historical records of outbreaks are of little help, since the reported values are a result of both the agent's inherent properties as well as external factors, such as the density of the population and factors such as healthcare and social structure. A related complicating factor challenging our assumption about a fully susceptible population is immunologic memory – that is, the possible presence of residual antibodies after vaccination [29,30].

Other important assumptions are those concerning an infected individual's behaviour, such as going to work or staying at home when ill, or whether an individual will visit an ER or not. To make explicit these assumptions, which are indeed central to the results, we added a graphical interface to the simulation programme. Through this, a user may easily set transmission rates and other variables. Further, a user can select whether a simulation should be run for the whole country or for a certain region only. Also, the number of repetitions and policy interventions may be selected. These features also make our model easier to adapt to the environments presented in other countries, or for use in a limited geographical region, such as a particular city or an island. That said, the availability of register data varies immensely between countries, and only systematic validation of experiment results can determine the utility of a model such as ours for other countries or regions.

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* Erratum: The title of Table 4 was corrected after publication of the article, on 3 September 2010.

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ESCAIDE 2010 - call for late breakers

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The 2010 European scientific conference on applied infectious disease Epidemiology (ESCAIDE) will take place in Lisbon, Portugal, from 11-13 November.

A so called 'Late Breaker' session will be organised at ESCAIDE. The aim of this session is to give speakers an opportunity to give oral presentations of important new findings of recently conducted studies which could have immediate implications for public health.

The call to submit abstracts to the ESCAIDE 'Late Breaker' session opens on 3 September. Please visit the conference website, www.escaide.eu, to read more about the eligibility criteria for abstract submission. The deadline for submitting abstracts to the Late Breaker session is Friday 24 September.