Effective control measures limited measles outbreak after extensive nosocomial exposures in January-February 2008 in Gothenburg, Sweden

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In January-February 2008, one imported case of measles initiated a series of exposures with around 380 nosocomial secondary contacts. Susceptible individuals were traced early and control measures were initiated that managed to limit the consequences considerably. Only four secondary cases were identified by the end of March. This minor outbreak illustrates the importance and efficiency of early control measures as well as the fact that the risk of measles outbreaks still exists in a country that has high measles, mumps, rubella vaccination coverage among children.

Introduction

Measles is one of the most contagious viral diseases and transmission in the community can only be prevented with efficient vaccination programmes. Such programmes have already reduced the incidence of measles in the European region. However, measles elimination in Europe is hindered by recurrent outbreaks in non-immune sub-populations. Non-immune subpopulations exist in all European countries due to:

- sub-optimal immunisation programmes with late implementation of measles, mumps, rubella (MMR) vaccination in a two-dose schedule,
- lack of catch-up campaigns for non-immune individuals of all ages,
- populations refusing MMR vaccination for a variety of reasons,
- and the window of susceptibility in infants between waning of maternal antibodies and the time when the first dose of MMR is provided.

Measles vaccination was introduced in Sweden in 1971. The vaccination coverage was initially only 40-60% [1] before the combined MMR vaccine was introduced in 1982. MMR has since then been offered in a two-dose schedule at 18 months and 12 years of age with a high vaccination coverage (>95%).

On 1 January 2007, the age for the second dose of MMR was lowered in Sweden from 12 years of age to 6-8 years since cases between the ages of six and 12 years had been observed in smaller outbreaks during the previous decade. At the same time it was decided to allow for the first dose to be given at any point between the age of 12 and 18 months. Under certain circumstances, such as international travelling or outbreak limitation, MMR may be provided between the ages of nine and 12 months.

Between mid-January and late March 2008, five cases of measles were notified to the medical officer in the Department of Communicable Disease Prevention and Control in Gothenburg, Sweden. All cases were unvaccinated. While four of the above patients were seeking medical attention for their measles infection, they exposed other patients, accompanying family members, and staff in the hospital or out-patient areas to measles on four separate occasions. Extensive nosocomial exposure of susceptible individuals to measles necessitated the implementation of control measures. These measures, described in the following, substantially limited the number of secondary measles cases.

Methods

Case definition

Measles is a notifiable disease in Sweden by the Swedish Communicable Diseases Act (2004:168). Case investigations include demographic characteristics, results from clinical and laboratory investigations, history of previous natural measles infection and vaccination. Contact-tracing of non-immune and exposed household-, school-, day care-, community- and nosocomial contacts should, if possible, be performed. A clinical case is defined as one having fever, a generalised maculopapular rash and one of the following: cough, coryza or conjunctivitis. A confirmed case is a clinical case with either laboratory confirmation (positive measles-specific IgM antibody test or positive PCR) or an epidemiological link to another case (two epidemiologically-linked cases are considered confirmed).

Prophylactic treatment

Prophylactic treatment should be offered to exposed non-immune children and adults. If less than 72 hours have passed since exposure, non-immune individuals should be either MMR vaccinated or offered immunoglobulin. If more than 72 hours but

less than seven days have passed since exposure, non-immune individuals should be offered immunoglobulin. The general immunoglobulin dose recommended for post measles exposure is 0.25 mL/kg up to a maximum of 15 mL intramuscularly, and for immunocompromised individuals, 0.5 mL/kg up to a maximum dose of 15 mL [2].

Laboratory investigations

Serological investigations (measles-specific IgM and IgG) are performed in the regional virus laboratories while virus isolation and molecular typing is performed by the national MMR laboratory at the Swedish Institute for Infectious Disease Control [3-4].

Results

Five cases of measles in unvaccinated individuals were notified to the Medical Officer in the Department of Communicable Disease Prevention and Control in the region Västra Götaland, Sweden between mid-January and late March 2008. Two cases were adults, aged 39 and 44 years, and three cases were children, aged 11 years, nine years and 18 months. Four of them were epidemiologically linked and the fifth case, for whom no epidemiological link has been established, had a link to the current outbreak through molecular typing of the isolated measles virus strains.

Index case

The index patient, an unvaccinated 11-year-old girl born in Sweden, developed fever and respiratory symptoms six days after returning from a visit to Paris, France, in mid-January 2008. On the third day of illness a rash was noted, and on the fourth day, she visited the paediatric emergency department at a local hospital. After 30 minutes in an open waiting room, she spent another five hours in an examination room without ante-room. During this period, a large number of young infants, children, accompanying parents and several hospital staff were present in the emergency department and the waiting room (Figure 1). Measles-specific IgM antibodies confirmed the measles diagnosis.

First generation of new cases

The first generation of cases included the index patient's younger sister, nine years old, and two visitors in the emergency department where the index patient sought medical attention, a 39-year-old pregnant woman and an 18-month-old boy.

Second generation of new cases

The second generation of cases included only one adult woman, 44 years old who had the same measles virus genotype and an onset of illness consistent with this outbreak. However, the source of her infection remains unknown and no epidemiological link has been established with the other cases.

Contact tracing and prophylactic treatment

Contact tracing and prophylactic treatment was initiated on the day the index patient was diagnosed with measles. All contacts to the index and subsequent cases were listed, traced and questioned about previous natural disease or immunisations against measles. On four separate occasions patients, accompanying family members and hospital staff in hospital and out-patient areas were exposed to measles, including a large number of susceptible and vulnerable individuals, i.e. pregnant women, infants and young children (Figure 1).

Immediate family of index case

A younger unvaccinated sister was exposed to the index case and developed measles nine days after the index case. During her incubation period, she was kept at home to avoid transmission of measles to non-immune class/schoolmates.

School of index case

The index case attended a school for children aged 12-16 years. The index case had attended school the day before developing fever, cough and coryza. Three unvaccinated children were identified in the school. Their parents were informed about the situation and the children were offered MMR vaccination. All children 11-12 years old had received only one dose of MMR at the age of 18 months and were due for the second dose the week after the index case fell ill. The second dose was given as planned. No further cases of measles evolved among the schoolmates.

Paediatric emergency department

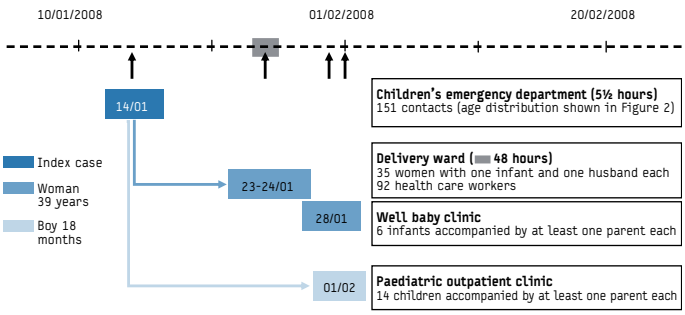
Altogether 151 visitors were exposed during the index patient's stay in the emergency department (see Table: nosocomial exposure I). All those that were uncertain of their immunity to measles, including those with no history of measles or incomplete MMR vaccination were offered post-exposure prophylactic treatment (see age distribution in Figure 2). By the time this could be arranged, 72 hours had passed and it was therefore too late for prophylactic MMR vaccine. Instead, polyvalent immunoglobulin (Beriglobin® CLS Behring 165 mg/mL) was administered to 61 contacts. Thirteen people who had only received the first dose of the MMR vaccine (MMR-I) were considered semi-immune and were therefore offered a second dose (MMR-II).

Delivery unit and postnatal ward

Among those exposed in the paediatric emergency department was a 39-year-old woman in late pregnancy. Due to natural immune suppression during pregnancy, she was considered immunocompromised and therefore received the maximum dose of 15 mL immunoglobulin. Nine days post exposure (six days post prophylaxis), she was admitted to the delivery unit for 48 hours and gave birth to a healthy full-term child. On the fourth day post partum the mother developed fever, cough and bilateral conjunctivitis. Since measles virus may be spread as early as several days before

Figure 1

Time line of nosocomial measles transmission and exposed contacts, Gothenburg, Sweden, January-February 2008 (n≥388)



Due to post exposure prophylactic treatment only two secondary cases were generated out of 74 susceptible contacts. These two, however, exposed approximately 237 persons (on three separate occasions).

onset of rash, the woman could have been contagious at delivery. Her child was given immunoglobulin prophylaxis of 0.25 mL/kg on the seventh day following birth. In retrospect, 35 pregnant women were identified as having been admitted to the delivery and postnatal ward during the same 48-hour-period in which the woman who developed measles had been a patient. In addition, their newborn infants, the accompanying family members that visited the delivery ward and postnatal ward, and the 92 hospital staff that had been on duty could theoretically have been exposed (see Table: nosocomial exposure II).

All 35 post-partum mothers were contacted and asked about their immunity to measles (i.e. previous natural disease or vaccination). Seventeen were uncertain of their status; therefore serology was performed on their antenatal sera. Laboratory results obtained for three of the women showed no measles-specific IgG antibodies. As a precaution only, since more than seven days had passed, the infants of these non-immune mothers were given immunoglobulin.

Seven hospital staff in the delivery and postnatal wards did not know their immune status and were temporarily suspended from further work (1-3 days) pending serology results. Serology result later revealed that all seven were immune.

Well baby clinic

Before measles was suspected, on the second day from onset of symptoms of fever, conjunctivitis and cough in the mother, the above 39-year-old measles case and her newborn child, visited the well baby clinic for a routine check-up of the baby at the same time as six other families (see Table: nosocomial exposure III).

Measles was initially confirmed in this woman by PCR performed on the nasopharyngeal aspirate and later by the development of measles-specific IgM (21 days post exposure and eight days after initial symptoms).

Paediatric outpatient clinic

Two weeks after visiting the emergency department, all immunoglobulin-treated individuals were contacted a second time (see the chapter on 'Follow-up' below). It was then noted that an 18-month-old boy was ill, with onset of fever and cough on day 14 after exposure (27 January). At this time, there were no signs of rash or conjunctivitis. On the scheduled follow-up in the department of infectious diseases on 2 February, he still had mild symptoms of fever and coryza. Viral PCR on a nasopharyngeal aspirate revealed respiratory syncytial virus and measles virus. It was interpreted as a mild case of measles, modified by the immunoglobulin but still contagious.

The family had visited a paediatric outpatient clinic on 1 February due to fever and coryza (see Table: nosocomial exposure IV). A further fourteen children (aged five months to 14 years), eight of whom were considered as non-immune to measles, were exposed in the paediatric outpatient clinic. However, at the time of diagnosis it was too late for immunoglobulin treatment of the exposed; therefore all these children were informed about the risk and symptoms of measles and followed clinically. No further cases of measles were identified.

Follow-up of immunoglobulin- treated individuals

Two weeks after visiting the emergency department, all 61 immunoglobulin-treated individuals were contacted a second time. It was then concluded that all were asymptomatic except for the 18-month-old boy mentioned above and the 39-year-old woman who had recently given birth. Her newborn child did not develop any symptoms. All immunoglobulin-treated individuals older than 12 months are still to be contacted again in three months for administration of MMR vaccine.

TABLE

Individuals, treatments and outcome at four nosocomial exposures to measles, Gothenburg, Sweden, January 2008 (n≥388)

	Exposed individuals	Susceptible and IgG-treated individuals	Number of measles cases among IgG-treated individuals
(I) Children's emergency department	151[a]	61[a]	2
(II) Delivery ward:			
mothers with infants	70[b]	3	0
accompanying spouses	35	0	0
hospital staff	92[c]	0	0
(III) Well baby clinic	≥ 12[d]	10	0
(IV) Paediatric outpatient clinic	≥ 28[d]	0	0

[a] Including 10 non-immune hospital staff.

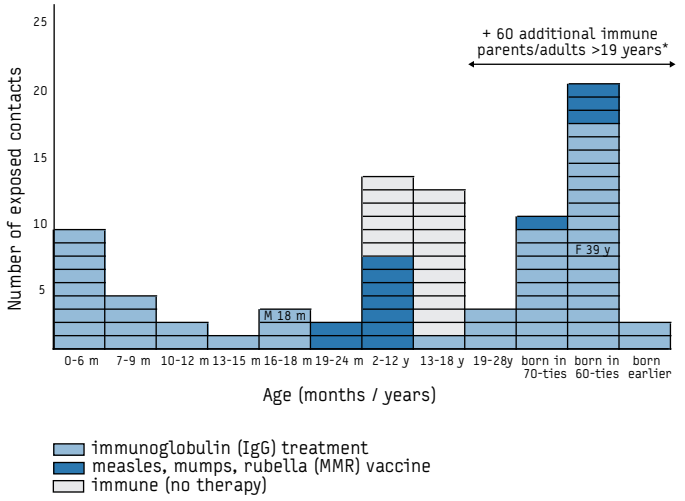
[b] Seventeen women with unknown immunity were tested, three were susceptible and their infants IgG-treated.

[c] Seven with unknown immunity were tested and temporarily suspended from work pending serology result.

[d] We estimated at least one parent accompanying each child to the clinic; the exact figures are not known.

FIGURE 2

Children, siblings, parents and hospital staff exposed to measles in the children's emergency department by age, Gothenburg, Sweden, January 2008 (n=151)



* The exact age of these 60 people was not known.

Of 151 exposed individuals, 74 were non-immune (10 hospital staff excluded from above chart) and were given post-exposure prophylaxis on the third day (>72 hours post exposure): Sixty-one were given immunoglobulin and 13 who had had one dose of MMR vaccine were given a second dose. Among those treated with immunoglobulin were an 18 month-old boy (M 18 m) and a 39 year-old pregnant woman (F 39 y) who later developed clinical illness.

Molecular typing of isolated measles virus strains

Serum and/or nasopharyngeal aspirate samples from four of the five patients with clinical symptoms of measles were available for laboratory investigations. In all four cases, measles-specific IgM or measles virus nucleic acid was identified. The patient without laboratory verification was the younger unvaccinated sister of the index case with an epidemiological link. Molecular typing of the isolated measles virus was performed on PCR products either from serum samples (in two cases) or from the nasopharyngeal aspirate (in one case). In all three individuals, identical sequences of the nucleoprotein gene were obtained and measles virus genotype D4 was identified. Molecular typing was instrumental in linking one of the cases to the current outbreak, since no epidemiological link could be established.

Organisation of control measures and use of media contacts

The implemented control measures involved a prompt and early response with regards to contacting susceptible, exposed individuals within hospital or out-patient settings. It required close multidisciplinary cooperation to identify and question all exposed individuals, initiate laboratory investigations and administer the recommended prophylaxis. Regular telephone conferences were held exchanging information and keeping all participants updated. Press releases were sent out and notices published on the website of the department of communicable disease prevention and control in Gothenburg. All general practitioners, emergency wards, infectious departments, paediatric departments, well baby clinics and paediatric outpatient clinics received continuous information via fax and mailing lists. Information about the nosocomial spread was disseminated through the media (television, local newspapers), alerting the general public to the symptoms of measles. In cases of a suspected measles infection, the public were advised to first contact the emergency medical services by telephone and if possible seek infectious disease departments where isolation routines are well established. The measles situation in Gothenburg was also continuously reported on the national level in the weekly newsletter EPI-aktuellt published by the Swedish Institute of Infectious Disease Control in Stockholm [5-7] to inform all health-care professionals in Sweden and increase their awareness of measles.

Discussion

In total, at least 388 people were exposed to measles in the context of the described outbreak. Seventy-four individuals were given immunoglobulin, another 13 individuals were offered a second dose of MMR vaccine, and three children in the index case's school were offered their first dose of MMR vaccine. Four of the exposed people developed measles. One of them was isolated at home, and one was not reached by the control measures, while two others were identified in time and received immunoglobulin treatment, but developed a milder form of the disease.

The number of measles cases reported in Sweden has varied from one to 77 cases per year during the last decade. The vaccination coverage in Sweden for one dose of MMR is over 99% and for two doses over 95%. No catch-up programme has ever been implemented targeting non-immune individuals, e.g. those that are too old to have been offered measles or MMR-vaccine or those that at one point in their life refused to be immunised but later may have been willing to receive the vaccine. In a recent study on measles-specific antibodies in antenatal sera from individuals born between 1965 and 1970, 7% of all women were susceptible to measles [8].

The five cases described here represent three different non-immune sub-populations in Sweden; the two adults had never contracted measles at the time it was circulating endemically and were too old to have been offered measles vaccination within the paediatric immunisation programme; the two older children belonged to a family that refused MMR vaccination; and the youngest child was still in the window of susceptibility as it had not yet received the first dose of MMR.

Nosocomial transmission generating clusters of secondary cases have recently been described [9, 10]. Physicians who seldom or never see measles cases in their practice, often have the misconception that measles is a mild disease. Reports from several recent outbreaks, however, describe a high (for European standards) mortality, and morbidity with frequent respiratory and central nervous system involvement [11-13]. Due to various complications, hospitalisation and additional supportive therapy is required in up to one third of the cases [14]. It is therefore very important to provide efficient protection at least for people at a high risk of developing serious disease, i.e. non-immune pregnant women, their newborn children and other immunocompromised individuals. A recent review of cases of measles in Sweden in 2005/2006 showed that more than half of all patients were hospitalised, often with pneumonia (unpublished data, Swedish Institute for Infectious Disease Control), suggesting that all measles-exposed individuals, irrespective of age, benefit from control measures.

Studies performed in the post-vaccination era indicate that young adults have lower antibody levels than the same age group at the time when wild type virus was still widely circulating [15,16]. Consequently, this decrease could also affect the amount of protective antibodies in the IgG fraction of pooled plasma obtained from vaccinated donors. In fact, none of the immunoglobulin preparations available on the Swedish pharmaceutical market today has measles prevention as an approved indication any longer. Nevertheless, we only observed two mild secondary cases, which did not require hospitalisation, among those treated with immunoglobulin in the course of the outbreak described here,

The lower antibody levels in young females, due to vaccine-induced immunity, also affect the time infants are protected by maternal antibodies [8]. The possible need for lowering the age for the first dose of MMR must be followed. It would be advantageous to have vaccines that are not affected by the amount of maternal antibodies and that could be given at any age. As the current live attenuated vaccines probably will continue to be used, the need for a third dose of MMR for young adults also ought to be assessed. Evaluating measles-specific antibodies in antenatal sera is an alternative strategy to identify susceptible women that could then be followed up by post-partum vaccination.

It is important to identify the non-immune sub-populations in a country. Different methods may be called for in different settings. Sero-epidemiological studies of the population and sub-populations may be helpful. A vaccination registry could in the long term be instrumental. Many countries are currently introducing a booster dose for diphtheria, tetanus and pertussis at the age of 14-15 years. This opportunity should be used to check whether all school children have received all doses of the recommended vaccines – including the MMR vaccine. Those who are behind in their schedules should be offered a final opportunity to receive the vaccines they have missed or refused earlier. However, it is vital

to exclude pregnancy before providing the live MMR vaccine to fertile young females.

Another important issue we observed in this outbreak was the lack of awareness among the healthcare workers of their own immune status, especially of those working in units where non-immune or immunocompromised patients are treated. It has previously been observed that employees working in medical facilities are at higher risk of being exposed to measles. Those that contract the disease may further transmit it and recommendations for preventive measures have therefore been given [2]. What preventive strategy that is most cost-effective, may be discussed in each institution and may differ between countries. Medical history should be obtained upon employment, and adequate immunisation recommended to those that are not immune, especially if they are likely to work with susceptible risk groups such as non-immune children, immunosuppressed transplant recipients or patients with malignant disorders. Alternative suggestions involve testing such people for their immune status upon employment or providing a booster dose of MMR, which would facilitate management, should any future exposure occur.

The genotype D4 identified in this outbreak has been reported from several European countries already in 2005/2006 [17]. Nine different measles virus genotypes were identified during this period throughout the World Health Organization (WHO) European Region, but all major epidemics were associated with the genotypes D4, D6 and B3. Highly mobile and unvaccinated communities have caused a massive spread of measles virus D4 throughout the whole region and this genotype is still causing outbreaks.

In conclusion, limiting outbreaks of measles with control measures is possible and should be done in order to avoid serious complications in the affected individuals, to prevent larger outbreaks, and to prevent the disease to become endemic again. In children with a recent history of travelling, both within and outside Europe, who develop a rash, a possible measles infection should be considered, and they should be kept in isolation until diagnosed. Finally, offering MMR-vaccination free of charge to susceptible individuals of all ages would significantly help to reach the goals set by WHO Regional Office for Europe to eradicate measles from the European region by 2010.

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This article was published on 24 July 2008.

Citation style for this article: Follin P, Dotevall L, Jertborn M, Khalid Y, Liljeqvist JÅ, Muntz S, Qvarfordt I, Söderström A, Wiman Å, Åhrén C, Österberg P, Johansen K. Effective control measures limited measles outbreak after extensive nosocomial exposures in January-February 2008 in Gothenburg, Sweden. Euro Surveill. 2008;13(30):pii=18937. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18937