Further efforts needed to achieve measles elimination in Germany: results of an outbreak investigation

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Objective To determine morbidity and costs related to a large measles outbreak in Germany and to identify ways to improve the country’s national measles elimination strategy.

Methods We investigated a large outbreak of measles in the federal state of North Rhine-Westphalia (NRW) that occurred in 2006 after 2 years of low measles incidence (< 1 case per 100,000). WHO’s clinical case definition was used, and surveillance data from 2006 and 2001 were compared. All cases notified in Duisburg, the most severely affected city, were contacted and interviewed or sent a questionnaire. Health-care provider costs were calculated using information on complications, hospitalization and physician consultations.

Findings In NRW, 1749 cases were notified over a 48-week period. Compared with 2001, the distribution of cases shifted to older age groups (especially the 10–14-year group). Most cases (n = 614) occurred in Duisburg. Of these, 81% were interviewed; 15% were hospitalized and two died. Of the 464 for whom information was available, 80% were reported as unvaccinated. Common reasons for non-vaccination were parents either forgetting (36%) or rejecting (28%) vaccination. The average cost per measles case was estimated at €373.

Conclusion An accumulation of non-immune individuals led to this outbreak. The shift in age distribution has implications for the effectiveness of measles control and the elimination strategy in place. Immediate nationwide school-based catch-up vaccination campaigns targeting older age groups are needed to close critical immunity gaps. Otherwise, the elimination of measles in Germany and thus in Europe by 2010 will not be feasible.

Background

Germany, with 82 million inhabitants, is committed to the WHO goal of eliminating indigenous measles transmission in the European Region by 2010.1,2 WHO recommends that at least 95% of children receive two doses of a measles-virus-containing vaccine (MVCV) – the first at 12 months of age and the second before school entry;7 and that older children who are susceptible also be targeted for a two-dose vaccination.2 A nationwide two-dose routine measles vaccination schedule was implemented in Germany in 1991.3 Since 2001, the first dose has been recommended at 11–14 months and the second at 15–23 months of age.3–5 Childhood vaccination is usually performed by paediatricians or general practitioners and is free of charge. Vaccinations are not mandatory in Germany, but status is routinely documented from vaccination cards presented at school entry examinations. In 2001, measles became a notifiable disease in Germany, which resulted in strengthened surveillance.

The number of measles cases notified in Germany decreased from 6037 in 2001 to a historical low of 122 in 2004.7 In 2005, a resurgence was observed due to outbreaks in two states (776 cases). The highest attack rate occurred in children aged 1–4 years in Hesse and 5–9 years in Bavaria.4 In 2006, a large outbreak occurred in the densely-populated state of North Rhine-Westphalia (NRW), with 18 million inhabitants. The epidemiological distribution of measles in Germany is a determinant of measles elimination in Europe because Germany has the largest population in the European Union; regions with high population densities; and geographic, economic and migratory characteristics conducive to measles importation and exportation.4–6

In a school-based retrospective cohort study during the initial phase of the 2006 outbreak, we demonstrated a vaccine effectiveness of 98.1% in students with one MVCV dose and of 99.4% with two doses.5 Low or diminishing vaccine effectiveness in older age groups was thus ruled out as an explanation for the outbreak. Here we describe the NRW outbreak in detail, present outbreak-related morbidity and costs in Duisburg (the most severely affected city in NRW), and identify areas for improvement in the national measles elimination strategy.

Methods

Case definition

A case was defined as a person with generalized maculopapular rash (≥ 3 days), fever and either cough, coryza or conjunctivitis.2 Cases that occurred less than one maximum

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incubation period (18 days) apart in the same city or district were considered to be epidemiologically linked and related to the outbreak.

Data collection

District public health offices routinely notify measles cases to the Robert Koch Institute (RKI) in Berlin via their state authority. We analysed data from all measles cases during the NRW outbreak and compared the age distribution of these cases with data from 2001. We compared district-level measles vaccination coverage at school entry from 1995 and 2005.

All notified patients in Duisburg were contacted to be interviewed with a standardized questionnaire that covered demographic characteristics, clinical symptoms, date of rash onset, measles vaccination status, reasons for non-vaccination, physician consultations and hospitalization, as well as contact details relevant for disease transmission. Interviews were conducted face to face during home visits or by telephone through staff from the district public health office, the state public health institute or the RKI. If at least three attempts to contact the patient by telephone failed, the questionnaire was mailed. Parents were interviewed if the patient was <18 years old. By using the same identifier as for routine surveillance, it was possible to retrieve and analyse a minimum dataset on non-responders. All private physicians and hospitals in Duisburg named in the questionnaires were asked to provide information on antibiotic treatment and on the results of serological testing.

Laboratory investigations

The results of serologic tests for immunoglobulins M and G (IgM and IgG, respectively) specific to measles virus (MV) performed in local laboratories were obtained from hospitals and private physicians. In addition, serum samples were sent by district public health officers or private physicians to the National Reference Centre for Measles, Mumps and Rubella (NRC MMR), where they were tested for the presence of MV-specific IgM and IgG and MV ribonucleic acid (RNA). MV-specific IgM and IgG in serum were determined by commercially-available enzyme immunoassays (Enzygnost, Dade Behring, Germany); MV RNA was detected in urine, throat swab and oral fluid using a nested reverse transcriptase polymerase chain reaction (RT–PCR) to amplify a highly conserved part of the MV nucleoprotein gene. Genotyping of MV was performed as previously described.

Statistical analysis

Data were entered into EpiInfo, version 3.3.2, (Centers for Disease Control and Prevention, Atlanta, GA, United States of America) and analysed with SPSS, version 13.0, for Windows (SPSS Inc., Chicago, IL, USA). All cases that met the clinical case definition, except those with both negative PCR and serology results, were included in the final analysis. Proportions were compared using the $\chi^2$ test, and continuous variables with a non-parametric distribution were compared using the Mann–Whitney U test.

Health-care provider costs

The hospital where all encephalitis cases in Duisburg were treated provided information on hospitalization costs. These were calculated according to the measles-specific diagnosis-related groups (DRGs) used in Germany as a classification and remuneration system for hospitalized patients. The costs for private physician consultations and serological testing were calculated according to the German Scale of Medical Fees, under the assumption that all physicians charged for a physical examination. We estimated the costs of antibiotic treatment using the price of a standard oral cephalosporin according to the German Red List Formulary.

Outbreak-related costs for the district public health office included the salaries of employees assigned full time to outbreak-response tasks for the duration of the outbreak, costs for MVCV doses administered and costs for serological testing.

Results

A total of 1749 measles cases were notified in NRW with disease onset between the 2nd and 48th calendar weeks of 2006, with a maximum of 154 cases in week 14. The main cities affected were Duisburg (614 cases; incidence 122/100 000), Mönchengladbach (173; incidence 66/100 000) and Mülheim (87; incidence 51/10 000). In total, 51/54 (94%) districts in NRW reported measles cases.

The largest number of cases ($n = 431$) occurred among children aged 10–14 years. In comparison to 2001 data, the age distribution of cases shifted to older age groups, with the highest incidence increase among children 10–14 years of age (Fig. 1). Despite the lower incidence in children less than 5 years (Fig. 1), the incidence among infants (i.e. children less than 1 year of age) was higher in 2006 than in 2001 (82 and 25/100 000 infants, respectively).
MV genotyping revealed genotype D6 in 119 of 125 cases (GenBank accession number DQ903070), with nucleotide sequence identity with the virus responsible for the concurrent Ukrainian outbreak.\textsuperscript{13,14} MV genotype D4 was detected in four patients from Siegburg district.\textsuperscript{14}

In 1995, one-dose MCVV-coverage at school entry ranged from 80% to 90% in 37 of 47 NRW districts for which data are available (including Duisburg). Only two districts had a coverage > 90%. In 2005, all but one district had a one-dose vaccination coverage of > 90%, and 23/54 (43%) had a coverage > 95%.\textsuperscript{3} Coverage with two-dose MCVV was 74.7%. No differences in coverage were observed between districts with low (<1/100 000) and high (>10/100 000) measles incidence during the 2006 outbreak.\textsuperscript{8} The vaccination status for 12% of the 182 245 children examined in 2005 was unknown.

\section*{Outbreak investigation in Duisburg}

\subsection*{Outbreak description}

In 2006, 614 measles cases were notified in Duisburg between weeks 2 and 32. Of these, 499 (81%) were interviewed. Of 109 physicians contacted, 96 (88%) returned the questionnaire and provided further information on 381 (76%) interviewed cases. The two largest hospitals in Duisburg provided data on 88 (18%) interviewed patients who were either hospitalized or had been seen in an outpatient department. Serological testing of 154 (31%) patients in local laboratories revealed detectable measles-specific IgM titres, indicative of acute measles infection, in 147 (96%) cases. The NRC received clinical material from 25 interviewees, of whom 23 (92%) were positive for MV RNA. Serum was available for 14 of these patients, and IgM was detected in all sera. MV genotyping revealed genotype D6 in all 20 interviewees investigated. MV genotype D6 was confirmed in a further 10 of 11 additional PCR-positive samples from Duisburg patients who had either refused the interview (6 patients) or had not been notified to the local health office (5 patients).

The median age of interviewed patients in Duisburg was 11 years (range: 0–53 years), and 255 (51%) were male. Patients attended 24 kindergartens (49 cases), 40 elementary schools (87 cases) and 42 secondary schools (208 cases) in Duisburg. The largest clusters occurred at secondary schools, comprising 55 (the first case cluster) and 33 cases.

\subsection*{Non-responder analysis and estimate for underreporting}

Compared with patients who were interviewed, the 115 patients not interviewed were more likely to be male (61% versus 50%; \(P = 0.045\)) and young (median age 7 years versus 11 years; \(P = 0.009\)). Among those not interviewed, 15.7% were hospitalized for a median duration of 4 days (total 82 days), compared with 15.0% of interviewed patients (\(P = 0.96\)). The diagnosis was confirmed by serum testing in 33 (29%) patients not interviewed; in 6 of these, genotyping revealed the D6 genotype.

An outbreak investigation with active case finding was conducted at one large Duisburg school (the first case cluster).\textsuperscript{7} Of the 55 measles cases identified, 36 (65%) had been reported to the local health office.

\subsection*{Disease complications}

All interviewed patients fulfilled the clinical case definition for measles. Otitis media was reported by 91 (19%) patients, pneumonia by 35 (7%), and encephalitis by three (0.6%), of whom two died. Measles-related complications were more common in younger children: otitis media (22% in infants, 21% in 1–14 year-olds, 10% in > 14 years; \(P = 0.008\)) and pneumonia (17% in infants, 7% in 1–14 years, 4% in > 14 years; \(P = 0.015\)). The two patients with encephalitis who died were aged 2 months and 2 years; the patient who survived was aged 19 years. Antibiotic treatment was reported in 32% (112 out of 353) of patients for whom information was available. Overall, 77 (15%) interviewed patients were hospitalized for a median duration of 6 hospitalization days (range 2–97) and a total of 693 days. The Duisburg outbreak resulted in 2854 school days missed (311 schoolchildren with measles) and 301 work days lost (30 employed adults with measles).

\subsection*{Vaccination status of cases}

Of 464 patients for whom information was available, 373 (80%) were reported as unvaccinated, 62 (14%) as having received one MCVV dose and 29 (6%) as having received two doses. Seven patients or parents refused to answer this question, and 28 did not know the vaccination status. The proportion of unvaccinated patients was similar across age groups. Parents of 272 (73%) children stated the reasons for non-vaccination (Table 1), the most common ones having been parents either forgetting about (36%) or being opposed to vaccination (28%).

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Reason for not being vaccinated} & \textbf{Number} & \textbf{Percent} \\
\hline
Parents forgot about the vaccination & 115 & 36.4 \\
Parents rejected the vaccination & 88 & 27.8 \\
Afraid of side-effects & 41 & – \\
Generally against vaccinations & 38 & – \\
Believed measles were not harmful & 9 & – \\
\hline
Family doctor or paediatrician recommended against vaccination & 53 & 16.8 \\
Underlying diseases of the child & 19 & – \\
Held opinion “it is not necessary” & 15 & – \\
Concerns about side-effects & 4 & – \\
No reasons given & 15 & – \\
\hline
Child was too young for vaccination (< 12 months) & 41 & 13.0 \\
Vaccination was not offered by family doctor or paediatrician & 19 & 6.0 \\
\hline
\end{tabular}
\caption{Reasons for not being vaccinated against measles given by parents of 272 unvaccinated measles patients in Duisburg, North Rhine-Westphalia, Germany, 2006}
\end{table}

\textsuperscript{8} More than one reason was given by 44. Patients with missing data \((n = 33)\) or who answered “don’t know” \((n = 68)\) were excluded.

\textsuperscript{9} In 18 of these 19 cases, the reasons provided were not considered true contraindications by the outbreak investigation team (e.g. eczema, “often sick”). In one child an immunodeficient was considered a true contraindication.
Outbreak response

One of the first responses to the outbreak in Duisburg was a public awareness campaign at the most seriously affected school during week 10. During week 14, an outbreak investigation was launched at the same school and students were advised to consult the family doctor if fewer than two MCVV doses were recorded on their vaccination card. Local health authorities conducted a large awareness campaign with media support, recommending physician consultation for possible vaccination. No citywide vaccination campaign was launched, due to limited personnel at the district public health office and to the hope that transmission would stop during the Easter holiday (weeks 15–16). However, 3 weeks after the holiday, the number of measles cases again increased (Fig. 2). In this second outbreak phase, the district health authority checked the vaccination cards of children at other affected schools and advised unvaccinated children to stay home for 14 days.

Health-care provider costs

Health-care provider costs for the 614 measles patients in Duisburg were estimated at €229 000 (Table 2). Over half of them were incurred by the 95 hospitalized patients (cost per average case: €1877), of whom one who had encephalitis received >3 weeks of intensive care with artificial ventilation (cost: €35 623). The average cost per measles patient was €373. The cost for the district public health office was €89 400 and included costs for personnel (€85 000), MCVV (€2300) and serological testing of school teachers (€2100). Taking these costs into account, the average cost per measles patient would increase to €520.

Discussion

The 2006 measles outbreak in NRW must be regarded as a wake-up call. It illustrated the impact measles can have even in an industrialized country facing measles elimination – in the city of

Table 2. Cost items used to calculate health-care provider costs during measles outbreak in Duisburg, North Rhine-Westphalia, Germany, 2006 (n = 614)

<table>
<thead>
<tr>
<th>Cost item</th>
<th>Cost (€)</th>
<th>Number of cases</th>
<th>Total cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interviewee</td>
<td>Non-responder</td>
<td></td>
</tr>
<tr>
<td><strong>Total costs for hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles without complications</td>
<td>1 325.0</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td>Measles with pneumonia</td>
<td>2 038.0</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Measles with otitis media</td>
<td>1 088.0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Measles with encephalitis</td>
<td>2 867.0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Measles with complicated encephalitis</td>
<td>4 384.0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Measles with fatal encephalitis, ICU</td>
<td>35 623.0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Outpatient consultation</strong></td>
<td>46.5</td>
<td>477</td>
<td>115</td>
</tr>
<tr>
<td><strong>Serological tests at local laboratory</strong></td>
<td>29.4</td>
<td>154</td>
<td>33</td>
</tr>
<tr>
<td><strong>Laboratory confirmation at NRC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serological tests</td>
<td>29.4</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>PCR</td>
<td>58.3</td>
<td>59</td>
<td>36</td>
</tr>
<tr>
<td>Genotyping</td>
<td>116.6</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td><strong>Antibiotic treatment</strong></td>
<td>20.0</td>
<td>122</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td>499</td>
<td>115</td>
<td>229 122</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; NRC, national reference centre; PCR, polymerase chain reaction.

* For each patient, up to four specimens (serum, urine and oral fluid samples, throat swab) were tested. The number indicates the number of tests performed.
Duisburg two children died, 95 patients (including those not interviewed) were hospitalized for a total of 775 days and the financial costs were high.

Although vaccination coverage of children at school entry has increased in Germany over the past decade, these data are only collected from children presenting their vaccination record. The proportion of unvaccinated children is probably higher among those not presenting their records; therefore, official coverage estimates are likely to be too optimistic. Also, increasing vaccination coverage has led to a decrease in endemic MV circulation. Thus, fewer unvaccinated children have had contact with wild-type MV, with a resulting accumulation of susceptible adolescents at risk for outbreaks. Mathematical modelling has shown a clear threshold value for the fraction of susceptible individuals (approximately 4.3%) below which only minor outbreaks occur. A shift in age distribution of measles cases towards older age groups has also been described in other countries. In the ongoing outbreak in Switzerland, 58% of the 1405 patients notified between November 2006 and 13 February 2008 were aged ≥ 10 years. In 2007, an outbreak occurred in Bavaria, Germany; of the 95 notified cases, 31% occurred in individuals ≥20 years old and 97% occurred among unvaccinated individuals.

Outbreaks affecting teenagers and young adults pose several challenges for control strategies because these individuals are highly mobile and have more social contacts beyond their school and family than young children. This explains why neither the 2-week Easter holiday nor prohibiting unvaccinated students from attending affected schools were sufficient to stop the outbreak. Despite well-publicized advice to the population to check and update their vaccination status, the outbreak lasted >30 weeks. Due to logistics and failure by health authorities to realize the magnitude and impact of the outbreak, further control measures were not implemented. WHO does not recommend supplementary immunization activities during outbreaks but makes an exception if these are in closed communities or institutions. A report from Africa showed that mass vaccination campaigns could slow down epidemic spread even in urban settings. The timely closure of immunization gaps at schools affected initially and among unvaccinated siblings at home might have prevented a significant number of cases. As an additional measure, unvaccinated contacts of cases should be confined to their homes for the duration of the incubation period to prevent further transmission, even if they received post-exposure vaccination. Such a policy has been implemented in the federal state of Lower Saxony.

This study is limited by the fact that the assessment of the cases’ vaccination status was based on parental or patient report rather than on examination of the vaccination record. However, vaccination coverage was similar to that found in an investigation of the Duisburg school, where 83% of measles cases with vaccination cards had never been vaccinated. Parental forgetfulness, followed by rejection of vaccination, was the most common reason given for non-vaccination. This suggests that a community-wide reminder, recall, and outreach system might improve vaccination coverage, as has been shown in other settings. It is worrisome that 17% of parents of unvaccinated cases claimed physicians had advised against vaccination without a clear contraindication. These data must be interpreted cautiously, as they are based solely on parental reporting, but they suggest a possible need for better education of physicians. Introduction of mandatory vaccination or the imposition of sanctions on families with unvaccinated children (as suggested by other authors) is likely to be legally and culturally unacceptable in Germany. However, this should not serve as an excuse for not being able to eliminate measles by 2010 because other measures can also significantly increase vaccination coverage. Requiring a physicians’ certification of adequate vaccination status upon entry into day care is one example that was implemented by the German state of Schleswig-Holstein in 2000 and that could be applied in other states. Immunization coverage can also be increased by providing incentive payments to private practitioners to immunize children; this was successfully implemented in Australia, which also provided immunization-linked incentive payments for lower-income parents. The possibility of linking the rather extensive maternity and parental payments in Germany to immunization status should be considered.

The American continent was declared free from endemic measles transmission in 2002. Europe remains far from attaining this goal, as exemplified by this measles outbreak and large outbreaks in the Ukraine (2005–2006; >44,000 notified cases), Switzerland (2006–2008; >1400 cases) and Austria (2008; >200 cases). In England, measles vaccination coverage fell below 85% in children aged 5 years from 2001–2002 to 2004–2005, and vaccine uptake problems were noted, particularly in London. Despite the 2004–2005 measles-mumps-rubella “capital catch-up campaign” in London, an MCVV coverage of only 77% was observed in 2005–2006, and 187 measles cases were reported in 2007, all of them by the end of August. Thus, Germany is not alone in facing problems in eliminating measles. The German surveillance system is fairly sensitive due to mandatory, countrywide reporting (including that of clinically diagnosed cases without laboratory confirmation). Nonetheless, underreporting may be substantial. Several European Union countries rely exclusively on reporting from laboratories, voluntary reporting, sentinel-based systems or combinations thereof, all of which presumably have lower sensitivity.

Changes in measles epidemiology similar to those observed in NRW occurred in the American continent 20 years ago and inspired the development of successful elimination strategies, including catch-up and follow-up vaccination campaigns. At present, Germany has no comprehensive strategy to close immunity gaps, which should include catch-up vaccination campaigns in specific age groups, as recommended by WHO. The grave consequences of the 2006 outbreak led to a school-based vaccination campaign among older children in NRW. An evaluation of vaccine uptake is underway. In Germany, outbreak-response efforts and vaccination campaigns have often been limited to awareness campaigns and recommendations due to logistic constraints and the reluctance of the public health service to impinge on personal autonomy. This limited approach proved insufficient in the NRW outbreak. To eliminate measles from Germany and Europe by 2010, stringent measles-control measures will be needed, and they should include high levels of routine coverage with two doses of measles vaccine, vaccination
of susceptible older population groups through additional vaccination campaigns, and implementation of timely steps to halt transmission as soon as a case is identified. These measures will require stronger political commitment and increased resources for the public health service.

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تعتبر حملة التطعيم واحدة من أهم التدابير المتخذة لمكافحة الأمراض المعدية، خاصة في البلدان النامية حيث الظروف الرغوية ضعيفة. إن تحقيق الهدف النهائي للقضاء على الحصبة في ألمانيا يتطلب اتخاذ إجراءات عديدة لزيادة نسب التزوعد الانتباهية في المجتمعات الريفية والUGC. cosìل على مستوى départements، بل جداً في المناطق الريفية. حيث أن نسبة التوافر لللقاحات تتراوح بين 60% إلى 70% في بعض المناطق الريفية، بينما تصل إلى 90% في المناطق الحضرية. هذه النتائج تتعارض مع الهدف النهائي للقضاء على الحصبة في ألمانيا بنهاية القرن الحالي.

الاستنتاج:
إذاً، فإن التخلص من الحصبة في ألمانيا يتطلب جهدًا مشتركًا بين السلطات الصحية والمجتمعات المحلية. من خلال استخدام الاستراتيجيات الفعالة مثل الحملات التثقيفية والتطعيمات المناسبة، يمكن تحقيق الهدف النهائي للقضاء على الحصبة في ألمانيا بحلول القرن الحادي والعشرين.


