

TWO OUTBREAKS OF MEASLES IN GERMANY 2005

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Measles re-emerged in some counties in Germany in 2005, despite increasing vaccination coverage rates in children at school entry in recent years, which had led to decreasing incidences (with the lowest incidence ever recorded, 0.2 cases per 100 000 inhabitants in 2004).

Regional outbreaks have been detected by the mandatory reporting system in the states of Hesse and Bavaria. Although both outbreaks led to similar incidences in the affected areas (14 and 12 cases respectively per 100 000 inhabitants) they differed in age distribution, transmission patterns and measles virus genotype.

In Hesse, 223 cases were submitted, from which 160 belonged to 41 clusters mainly defined by family or household contacts. Attack rate was highest in children aged between 1–4 years (102 cases per 100 000). Results of measles virus diagnosis showed genotype D4 and identical nucleotide sequences for all analysed cases from Hesse.

In Bavaria, 279 cases were submitted, most of which had occurred in schools and preschool facilities. Age-specific attack rate was highest in children aged between 5–9 years (129 per 100 000). Laboratory diagnosed viruses were identified as genotype D6 and were identical at the nucleotide level.

In both outbreaks the vast majority of cases (95% in Hesse and 98% in Bavaria) were in unvaccinated children, but vaccination coverage differed in the affected areas and was slightly lower in Bavaria than in Hesse. Local accumulation of unvaccinated children and their concentration in schools and kindergarten preceded the outbreak in Bavaria.

Despite high average vaccination coverage levels, local variations may lead to regionally limited outbreaks.

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Introduction

In Germany, two doses of MMR vaccine have been recommended since 1991. The current schedule has been in place since 2001, and recommends that the first dose is given at age 11 to 14 months and the second dose at age 15 to 23 months. Vaccination is mainly done by private physicians. Vaccination coverage and measles control remain regionally different in the federal states. Nationwide measles surveillance started in 1999 with a sentinel group of paediatricians and general practitioners (GPs), which was kept in place when statutory reporting was introduced by law in 2001. Case reports in both systems are made according to the clinical case definition. Laboratory testing of suspected measles is mostly offered and carried out in a decentralised fashion by private laboratories. However, the National Reference Centre for Measles, Mumps and Rubella (NRC MMR) at the Robert Koch-Institut (RKI) plays a major role particularly in genotyping of measles viruses (MVs).

The epidemiological situation has changed in recent years. Until 2002 endemic circulation and regional outbreaks of measles were

observed by sentinel and mandatory surveillance in the western part of the country [1,2]. Only sporadic cases occurred in the eastern part (territory of the former German Democratic Republic) due to higher vaccination coverage [1,2]. Since 2003, the incidence of reported cases nationwide has dropped below 1 per 100 000 inhabitants [3]. Vaccination coverage registered at school entry has steadily increased from 89% and 15% (for the first and second dose, respectively) in 1998 to 94% and 66% in 2004. However, there are differences in vaccination coverage at regional and local levels. At the beginning of 2005 two measles outbreaks were detected by the surveillance system in counties of the federal states of Hesse and Bavaria. In this report both outbreaks are described including genetic analysis of the detected MVs in order to illustrate how and why regionally limited outbreaks may still occur.

Methods

Both outbreaks were detected by the mandatory reporting system which is based on the Protection Against Infection law (“Infektionsschutzgesetz”) [4]. According to this law, physicians must report every suspected measles case, and laboratories must report every confirmed measles case, to the local health department. At the local level, which consists of 431 county health departments nationwide, reports are checked to see whether they fit the case definition, whether clinical and laboratory reports may be linked, and whether further cases have occurred which have not been reported yet. Case data are electronically submitted to the health departments of Germany’s 16 federal states and from there to the RKI. Cases are listed according to the reporting week, which is given by data entry at local level.

Each measles case submitted must meet one of the three following diagnostic categories:

- Clinically diagnosed case: fever and rash and at least one of the symptoms cough, coryza, conjunctivitis, Koplik spots
- Clinically and laboratory confirmed case: clinically diagnosed case with laboratory confirmation
- Clinically and epidemiologically confirmed case: clinically diagnosed case without laboratory confirmation but with an epidemiological link to a laboratory confirmed case

In the following report a case is defined as any submitted case, regardless of diagnostic category, unless another explanation is given.

Local health authorities carried out outbreak investigations by interviewing physicians and family members in order to detect further cases and contacts. In order to stop transmission they began campaigns in schools and kindergartens, aimed at informing parents and getting susceptible children vaccinated by their family physicians.

After detection of the first contact cases, the federal health authorities, together with the NRC MMR, encouraged public health officials and physicians in the affected areas to carry out laboratory investigations. Tests were carried out in local private laboratories and in the NRC MMR. Local laboratories generally test sera for measles specific IgM and IgG antibodies by commercially available enzyme immunoassays. Information on the total number of tested but not confirmed suspected measles cases is available only from the NRC MMR.

In the NRC MMR antibody tests were carried out as well as detection of MV RNA in clinical samples (throat swabs, urine and oral fluid) by RT-PCR, as described previously [5]. In order to trace the transmission pathways of the virus, samples from 38 cases were

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genetically characterised by sequence analysis of the variable part of the N-gene (456 nt), as described previously [6]. Assignment to measles virus genotypes was performed by phylogenetic analysis as recommended by the World Health Organization [7].

Results

Outbreaks in Hesse

From January to May 2005, a total of 223 cases were reported from four neighbouring counties (the cities of Offenbach, Frankfurt, Wetterau and Giessen) and the nearby city of Wiesbaden accounting for an incidence of 14 cases per 100 000 inhabitants in this area. During the same period, a further 29 sporadic cases were reported from 11 counties of Hesse, but 10 counties of this federal state had no measles cases.

Age-specific attack rates were highest in children aged between 1-4 years (102 per 100 000), followed by those aged 5-9 years (83 per 100 000) [FIGURE 1]. Although the incidence in adults was only about two per 100 000, the rate of admission to hospital was 34% in patients aged 20 years and older. A fourteen year old girl died.

The vast majority (n= 209; 95%) of cases were in unvaccinated people.

The first clusters of measles cases were reported in the cities of Offenbach and Frankfurt, mainly in families considered to be hard to reach by the health services. A case report of a hospitalised patient in

January led the public health authorities to identify further patients with cases which fit the clinical case definition but who had not seen a physician. Nineteen of the cases reported in January 2005 had experienced onset of disease in 2004.

Measles cases were next reported from the adjacent county of Wetterau, where several families were affected, followed by reports from the county of Giessen and finally from the city of Wiesbaden [FIGURE 2].

One hundred and sixty cases from the five counties were scattered in 41 clusters with clinically and epidemiologically confirmed cases, mainly defined by family or household contacts. Despite interviews with patients, parents and other carers and guardians, and physicians, no connections between the clusters themselves or between the clusters and the remaining single cases were detected.

A diagnosis of measles was laboratory confirmed in 67 cases. The NRC MMR obtained samples from 29 suspected measles cases in the state of Hesse and confirmed measles diagnosis in 18 cases, all of which were distributed in the five counties affected by the outbreak. Results of MV genotyping available for 12 patients from Hesse showed that these cases were exclusively caused by MVs of the same genotype D4. Moreover, these MVs also showed identical nucleotide sequences and thus belonged to a homogeneous genetic group.

Outbreak in Bavaria

From March to July, 279 cases were submitted from eight counties in the south of Bavaria, in and around the city of Munich, leading to an incidence of 12 cases per 100 000 inhabitants in the region [FIGURE 3]. During the same period, 25 sporadic cases were submitted from 13 further Bavarian counties. No cases of measles were reported in the remaining 75 counties.

FIGURE 1

Measles outbreaks 2005 in Hesse and Bavaria (Germany): age-specific incidence by region

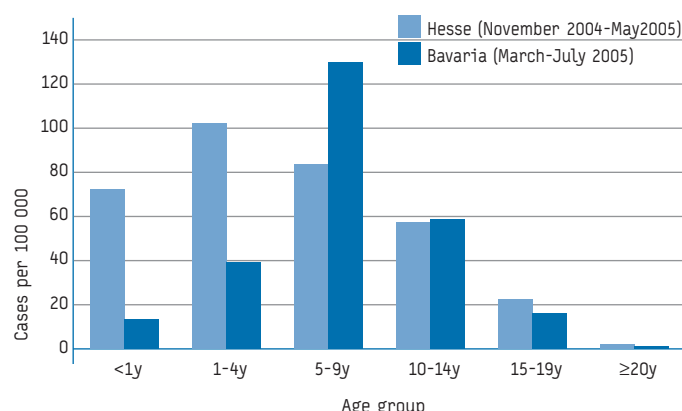


FIGURE 2

Number of cases of measles according to date of onset and reporting week respectively in the affected counties of Hesse, Germany

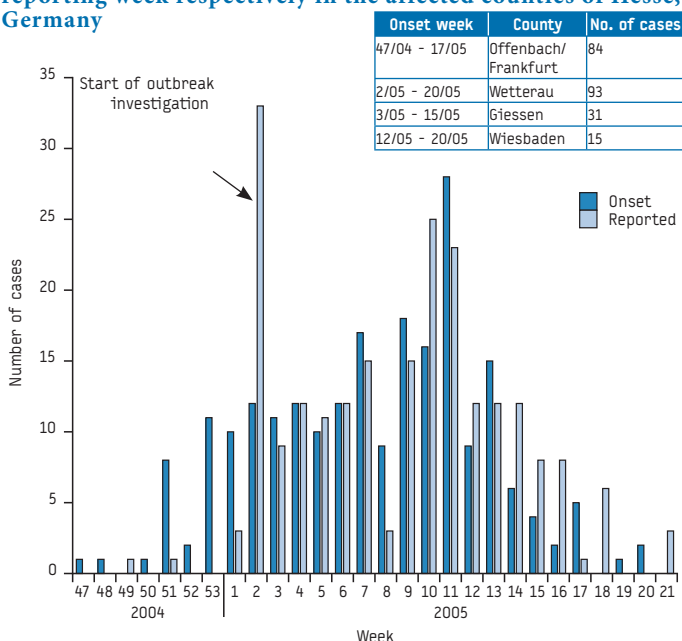
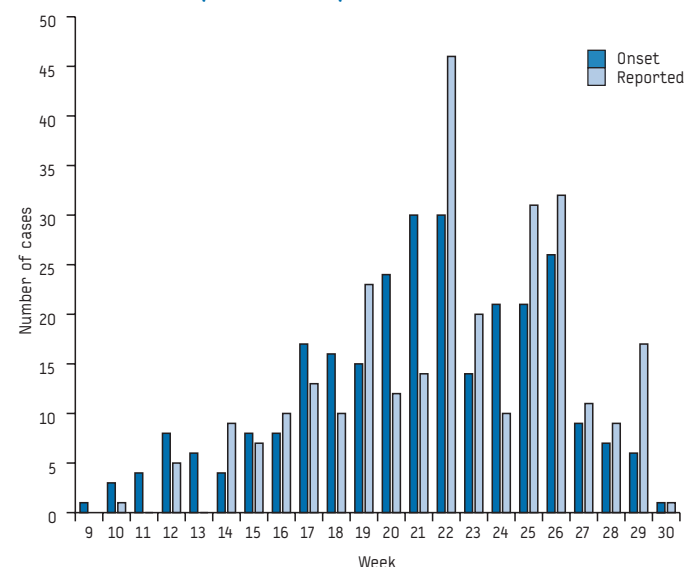


FIGURE 3

Number of cases according to date of onset and reporting week respectively in eight affected counties in southern Bavaria, Germany, March-July 2005



The outbreak mainly affected school aged children (5-14 years old) (n=208; 74%) but about 12% of cases were in adolescents and adults (n=16), and 7 out of 11 hospitalised cases were in patients aged 20 years or older.

Age-specific incidence was highest in children aged between 5 and 9 years (129 cases per 100 000 children), followed by those aged between 10 and 14 years (58 per 100 000) [FIGURE 1].

As the attack rates indicate, most of the cases were related to outbreaks in schools or preschool facilities: 45 cases occurred in a primary school in Munich, 52 cases in children from several counties who attended the same Montessori school, 42 cases in children in four kindergartens, and 38 cases in four further schools in different communities. Investigations of the local health authorities showed

possible transmission between these outbreak settings. This was also confirmed by laboratory results.

Seventy of the reported outbreak cases were laboratory confirmed, 26 of these were tested in the NRC MMR, and MVs from 17 cases representing all local clusters were genotyped. All of these viruses were identified as genotype D6 and were identical at the nucleotide level. This indicates the presence of the same chain of transmission of a D6 virus within the Bavarian outbreak.

Most of the cases (n=273; 98%) were in unvaccinated people, including eight children who were initially reported as vaccinated, but vaccine had been given during the incubation period, which was too late to prevent the disease. The genetic identification of four of these cases revealed measles wild-type virus (D6). In six cases, vaccination status remained unknown.

One measles case in Austria could be traced to the Bavarian outbreak, but no information on the genotype was available.

Discussion

Although vaccination coverage seemed to be high on average, regional outbreaks still occurred. In the affected region in Hesse, vaccination coverage at school entry is on the same level as the nationwide average proportion: 95% and 65% for the first and second dose, respectively. This might explain why most of the cases observed where either single cases or part of small clusters. Virus circulation was ultimately limited because vaccinated people were well protected and this led to the interruption of the transmission chain. The age distribution of the cases in Hesse and the peak at age 1-4 years suggest that vaccination is not given at the recommended age which was below two years of age for two doses. Some of the affected families were part of a particular community where most families had several children, avoided seeking medical care, are difficult for healthcare services to reach, and do not bring their babies to healthcare services for routine checkups. Missing vaccinations for the children of such families are usually detected and given later in childhood (for instance at medical examination before school entry), leaving the very young unprotected, and therefore susceptible children may accumulate. Additionally, coverage of the second dose of vaccine is generally still too low to make up for primary vaccine failures and to use the early second chance to be effectively immunised. Unfortunately, vaccine coverage data by age are not available. The registration of coverage at school entry is too late to assess whether children were immunised appropriate to age and to identify target groups for catch up vaccination.

Vaccination coverage in Hesse is slightly higher than in Bavaria (91% and 59% for the first and second doses, respectively) and, moreover, there are great regional and local differences in vaccination coverage in Bavaria. In the affected Bavarian counties, coverage is below the Bavarian average (personal communication, Dr. Hautmann, Bavarian Landesamt für Gesundheit und Lebensmittelsicherheit). This may explain why it took a longer time for a similar number of people to be infected in a smaller area in Hesse in comparison to Bavaria.

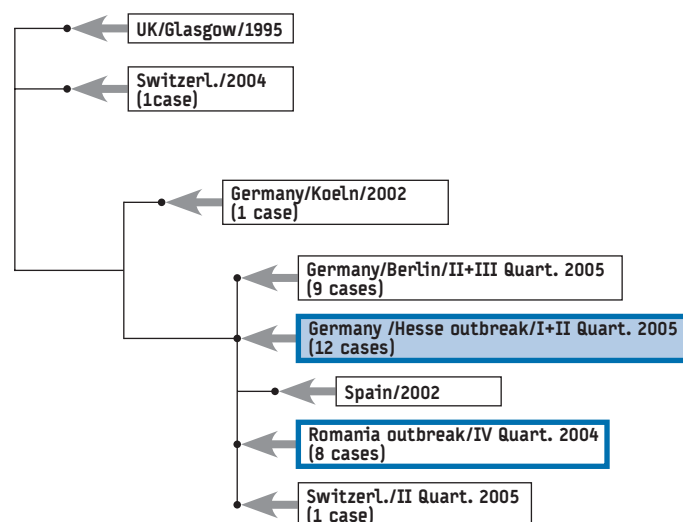
However, the older age of the Bavarian measles patients demonstrated that clusters of unvaccinated people may benefit from herd immunity until the virus arrives. Public health authorities had observed a concentration of unvaccinated children in single communities and certain schools and childcare facilities (most of which had connections with the anthroposophic teachings of Rudolf Steiner) in the outbreak areas in advance but their vaccination recommendations, although publicised in local newspapers and handouts to parents and carers in schools and kindergartens, were apparently ignored. This might have led to the accumulation of measles-susceptible people and the rapid spread of infection.

The virus of the observed transmission chain in Hesse differs from the previously detected D4 viruses. No identical nucleotide sequence could be found in the published data so far. Interestingly, the NRC MMR as the WHO regional reference laboratory had investigated clinical material from eight cases belonging to a measles outbreak in Romania in the fourth quarter of 2004. The detected D4 MVs share the nucleotide sequence with the D4 viruses which emerged in Hesse in the 1st quarter of 2005 and in Berlin in the 2nd quarter of the same

year [FIGURE 4]. Therefore, it can be assumed that the detected D4 MVs in Germany were possibly imported from Romania. This assumption is supported by the public health authorities in Hesse, who informed about possible contacts of cases in Hesse to Romania.

FIGURE 4

Tracing the transmission pathway of the genotype D4 MV detected in the federal state of Hesse in 2005, Germany



Note: The phylogenetic tree is based on the 456 nucleotide sequence encoding the carboxy-terminal of the MV nucleoprotein. MV sequences derived from cases that occurred in Europe during the period 1995–2005 were incorporated.

The genotype D6 MVs in Bavaria share their sequence with those of 4 measles cases from Switzerland also investigated at the NRC MMR, which occurred in the first quarter of 2005. Moreover, the only case confirmed by the NRC MMR in 2004 (second quarter, federal state of North-Rhine-Westphalia) belonged to the same variant of genotype D6. During the 1990s, MVs of genotype D6 were not only endemically circulating in Germany but also widely distributed throughout Europe [6,8-11]. Furthermore, sequence data published in the GenBank indicate that the same genetic variant of D6 was also circulating in several regions of Russia in 2003 and 2004. Therefore, the appearance of a D6 virus in Bavaria might be due to a continued limited circulation of this genotype in central Europe or might likewise be caused by virus importation.

Conclusion

The mandatory reporting system already in place enabled health authorities and epidemiologists at all levels of public health to detect and combat outbreaks of measles.

Laboratory investigation plays an important role in measles surveillance and control, and is particularly indispensable for tracing transmission chains in outbreaks. Genetic characterisation of the detected viruses revealed that the outbreaks in Hesse and Bavaria were associated with distinct MV genotypes. These data demonstrate that both outbreaks were caused by independent transmission chains of the MV. While the outbreak in Hesse was possibly due to imported measles, the origin of the Bavarian outbreak could be either imported or indigenous.

Besides the different MV genotypes, the spread of infection also appeared to be different in both outbreaks. While in Hesse, frequent small clusters and single cases were observed in outbreak settings such as families and households, in Bavaria it was mainly childcare facilities where measles susceptible children were concentrated that were affected. It can be assumed that although vaccine coverage was high at average, regional and local variations in vaccination coverage lead to distinct epidemiological situations.

In the two outbreaks two different groups of 'hard-to-reach' populations were involved: people who did not generally seek medical care, and people who are selective about the medical services they use and often refuse vaccination, especially for measles. Special attention

should therefore be given to identifying target groups and to find appropriate ways to reach them by additional immunisation initiatives. This includes assessment of vaccination coverage at an earlier age.

Generally, coverage of the second dose of measles vaccine still needs to be improved at all local, regional and nationwide levels.

The outbreaks provide evidence that, despite the decline in measles incidence in Germany due to increased vaccination coverage and improved measles surveillance in recent years, the potential for local outbreaks is still present, and measles control and vaccination awareness should be continued and improved at all levels.

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ORIGINAL ARTICLES

Outbreak report

A REGIONAL OUTBREAK OF *S. TYPHIMURIUM* IN DENMARK AND IDENTIFICATION OF THE SOURCE USING MLVA TYPING

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In Denmark, as part of the national laboratory-based surveillance system of human enteric infections, all *S. Typhimurium* isolates are currently sub-typed using phage typing, antibiogram typing, and pulsed-field gel electrophoresis (PFGE). However, the discriminatory ability of PFGE is not always high enough to discriminate within certain phage types, and it is not always possible to separate unrelated and related isolates. We have therefore applied multiple locus variable number of tandem repeats analysis (MLVA) for surveillance typing of *S. Typhimurium* since 2004. In May and June 2005, an outbreak with 26 cases of *S. Typhimurium* infection was identified by MLVA. The isolates were fully sensitive and had one of the most frequently occurring Danish phage types (DT12) and PFGE types. *S. Typhimurium* DT12 isolates from routine surveillance of animals and food were typed using MLVA and PFGE for comparison with the human isolates. The typing results revealed that an isolate from a pig herd and its corresponding slaughterhouse located in the same geographic region as the outbreak had the same PFGE and MLVA type as the human isolates. In contrast, all other DT12 isolates investigated, which had the same PFGE profile, had different MLVA types. The conclusion that the pig herd was the source of the human infections was supported by patient information, and pork from the herd stopped entering the market on 29 June. MLVA may contribute

significantly to both surveillance and outbreak investigations of *S. Typhimurium*, as without MLVA typing this outbreak would not have been found nor its origin traced.

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Introduction

In Denmark there is a large and coordinated surveillance of salmonella infections in food-production animals. *Salmonella enterica* subspecies *enterica* serotype Typhimurium (*S. Typhimurium*) is the second most frequent serotype causing infections in humans after *S. Enteritidis* [1].

Typing is an important tool for surveillance as well as for investigating outbreaks of human *S. Typhimurium* infections, and as part of surveillance in Denmark, all *S. Typhimurium* isolates are routinely typed for resistance, phage, and pulsed-field gel electrophoresis (PFGE). PFGE has been shown to be useful in investigations of *S. Typhimurium* outbreaks [2,3] and is widely used in local, national and international surveillance [1,4,5]. Unfortunately the discriminatory ability of both PFGE and phage typing is not always high enough within *S. Typhimurium* when trying to link outbreak isolates. The discriminatory ability of PFGE is particularly low within DT12 and DT104 (two of the most frequent phage types in Denmark) where 80%-90% of all human infections are caused by the same PFGE type. Multiple locus variable number of tandem repeats analysis (MLVA) is a new and promising typing method [6] that has been shown to have good discriminatory power within

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