



Measles vaccination – An underestimated prevention measure: Analyzing a fatal case in Hildesheim, Germany

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ABSTRACT

Measles and rubella are targeted for elimination in the WHO region Europe. To reach the elimination goal, vaccination coverage of 95% must be achieved and sustained, the genotype information has to be provided for 80% of all outbreaks and transmission chains of a certain variant must not be detected for >12 months. The latter information is collected at Germany's National Reference Center Measles, Mumps, Rubella (NRC MMR).

We describe here an outbreak of measles occurring in Hildesheim. The outbreak comprised 43 cases and lasted 14 weeks. Surprisingly, a high number of vaccination failures was observed since 11 cases had received two doses of the MMR vaccine and 4 additional cases were vaccinated once.

A 33-year-old woman passed away during the outbreak. She was the mother of 5 children between 4 and 16 years of age. Two schoolchildren contracted measles and passed it on to the rest of the family. Due to delivery bottlenecks, the vaccination of the mother was delayed. She developed measles-like symptoms 3 days after vaccination and was found dead on the morning of day 8 after vaccination. A post-mortem examination was done to identify the cause of death. Moreover, molecular characterization of the virus was performed to analyze whether she was infected by the wildtype virus circulating at that time in Hildesheim or whether the vaccine may have been a concomitant and aggravating feature of her death.

The result showed that the samples taken from her at the time of death and during necropsy contained the wildtype measles virus variant corresponding to MVs/Gir Somnath.IND/42.16 (WHO Seq-ID D8-4683) that fueled the Hildesheim outbreak and circulated in Germany from March 2018 to March 2020. The vaccine virus was not detected. Moreover, two aspects uncovered by the post-mortem examination were remarkable; the woman died from giant cell pneumonia, which is a complication seen in immune-suppressed individuals and she was actively using cannabis. THC is known to influence the immune system, but literature reports describing the effects are limited.

1. Introduction

Measles is a viral disease transmitted by droplets and aerosols. It is one of the most contagious infectious agents known. The basic reproduction number R_0 , indicating the number of secondary cases initiated in a susceptible population, has been assessed to 12–18 (Guerra et al., 2017). The fatality rate is about 1:1000. In 2019, 136,000 fatalities were

recorded globally (WHO Media Team, 2023). The development of measles vaccines in the 1960s led to a significant reduction in morbidity and mortality but to prevent outbreaks and achieve interruption of measles virus (MV) transmission, the vaccine must be administered to > 95% of a population. Despite huge efforts and a WHO global elimination goal for measles, MV elimination has yet been reached only in certain countries. The process is endangered immediately when vaccination

Abbreviations: ADEM, acute disseminated encephalomyelitis; COVID, Coronavirus Disease; HE, Hemalaun-eosin; STIKO, Standing committee on Vaccination, Germany; MV, measles virus; MMR, Measles, mumps, rubella; WHO, World Health Organization; THC, Tetrahydrocannabinol; NRC MMR, National Reference Center Measles, Mumps, Rubella; PVF, primary vaccination failure; SVF, secondary vaccination failure.

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rates are not kept up.

Germany has made good progress towards measles elimination: The number of cases declined from 926 in 2017 to 516 in 2019, despite that larger outbreaks in neighboring countries were observed. The 15 cases notified in 2020 presented an all-time-low as a response to the non-pharmaceutical measures initiated to control the COVID-19 pandemic. In late 2023, we saw a slight increase in the number of measles cases (58 cases in early December) but still on a low level.

In accordance with the German infection protection act, suspected measles cases as well as positive laboratory reports must be notified in Germany within 24 h via an electronic reporting system. Measles vaccination is based on the recommendations by the German Standing Committee on vaccination (STIKO) and includes two doses of MMR(V) for children at the age of 11 and 15 months respectively and one dose of MMR for adults born after 1970 (RKI, 2023). According to the German measles protection act, MMR vaccination is mandatory for visitors or employees of community services like day care units, refugee shelters, or health care institutions. Vaccination quotes are retrieved from the check-up for school beginners (RKI, 2022) and by health care insurance claims (Rieck et al., 2020). All instruments show that the vaccination coverage for MMR has not declined in Germany during the pandemic.

Molecular surveillance of measles and rubella virus is performed at the National Reference Center Measles, Mumps, Rubella (NRC MMR) at the Robert Koch-Institute in Berlin. During the last years, only two of the 24 MV genotypes were detected, B3 and D8, of which D8 was predominant in the years preceding the COVID pandemic. MV of the genotype D8 are endemic in India (Rota et al., 2011), the variant MVs/Gir Somnath.IND/42.16 (D8-4683) dominates the global MV circulation since 2018. D8-4683 was associated with the second largest measles outbreak reported globally in 2018 affecting The Ukraine with 115,000 reported cases from early 2017 to the end of 2019 (WHO, 2018, 2019, 2020).

In Germany, MV circulated endemically and outbreaks were seen until 2020. Activity tapered off due to the measures that were taken to control the SARS-CoV2 pandemic. Molecular surveillance revealed that MVs/Gir Somnath.IND/42.16 (D8-4683) circulated in Germany from March 2018 to March 2020. During that 25 months period, several larger outbreaks were observed in different regions of the country, one of them affecting Hildesheim, a city in Lower Saxony. This manuscript describes a fatal case of measles in a young woman. She was the mother of 5 children and died after she had contracted measles from her children. With exception of the eldest daughter, all family members were unvaccinated.

2. Materials and methods

2.1. Molecular characterization of MV performed at the NRC MMR

Detection of MV genome, phylogenetic analyses and genotype assignment were performed in the NRC MMR according to the WHO standard protocol as described before (Hummel et al., 2006; WHO, 2005). The 450 nt encoding the 150 C-terminal amino acids of the N protein (N-450 region) are a highly variable part of the MV genome and are therefore used for genotype assignment (Williams et al., 2022). According to the WHO nomenclature using the N-450 region, wild-type MV are divided into eight clades (A–H) and further subdivided into 24 genotypes. All sequences used for construction of the phylogenetic tree were deposited in MeaNS2, a WHO-hosted database for MV sequences (<https://who-gmrln.org/means2>).

2.2. Pathology

The autopsy was carried out according to the guidelines of the German Society for Forensic Medicine (AWMF, 2022). This also included the preservation of tissue samples for histological examinations of all internal organs, in this specific case also of lymph nodes and tissue samples of the skin as well as samples for chemical-toxicological and

clinical-chemical examinations. For histological diagnostics, conventionally histologically stained tissue sections (hemalaun-eosin staining, HE) were prepared. The clinical-chemical diagnostics to detect or rule out allergic reactions were carried out in the Clinic for Dermatology, Allergy and Venerology at the Hannover Medical School.

3. Results

3.1. Epidemiology of the Hildesheim outbreak

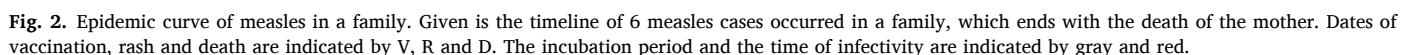
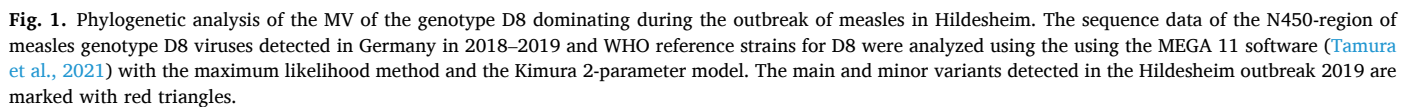
In early 2019, an outbreak of measles affected the district of Hildesheim. The first notified case was a 15-year-old schoolboy. Repeated visits of the emergency room of a hospital in Hildesheim 11–13 days prior to rash onset is seen as the putative setting of infection. The boy was vaccinated twice against measles in 2004 according to the recommendation of the STIKO. He developed the characteristic rash on 13 January 2019. In the following 14 weeks of the outbreak, 43 measles cases were notified; 31 residents of the city of Hildesheim and 12 living in the Hildesheim district. Of the 43 affected individuals, 23 were female and 20 male. The age span of the infected persons reached from < 1 year to 48 years with a median of 17 years. The majority of the cases were infected within their respective family setting (n = 14; 32.6%), 3 cases in a hospital (7%), and 2 cases in a community facility (4.6%). For 24 cases (56%) the place of infection was not ascertainable. The majority of the infected persons was not vaccinated against measles (n = 28; 65%). Unexpectedly, the number of vaccinated individuals with a measles diagnosis was high: 4 persons had been vaccinated once against measles and 11 individuals had received 2 doses of the MMR-vaccine. All measles infections were laboratory confirmed by a positive anti-MV IgM result and/or detection of MV by PCR. It was possible to analyze 4 of the 11 vaccination failures: The serum samples of the 4 cases showed high avidity of the anti-measles IgG indicative of a secondary vaccination failure due to waning of the anti-measles IgG-titer. A control visit of the doctor's office in which several of these patients had been vaccinated by the local health authority did not indicate improper storage or application of the vaccine.

3.2. Measures taken to contain the outbreak

Due to the high contagiousness of MV immediate action by the public health authority is an absolute priority when a suspected case of measles is reported, even more so when the case occurs in community facilities such as day-care centers or schools (Roggendorf et al., 2010). Consequently, the population was informed via the press about the beginning outbreak, the risk of infection and the protective effect of the vaccination. In the following weeks, the local health authority in Hildesheim checked the immunization status of > 2000 contact persons and post-exposure immunization was carried out. Infected or suspected cases were advised to stay at home and avoid contact with susceptible persons. Home visits were made to sample symptomatic patients, while counselling was conducted by phone. The local health authority excluded 81 susceptible persons after exposure from attending a community facility. Readmission of confirmed measles cases was possible earliest 5 days after appearance of rash. The consistency and the immense control effort plus the continuous information of the public paid off: no further cases of infection were observed in the day-care centres and schools, all subsequent cases arose within families.

3.3. Molecular characterization of the virus associated with the outbreak

From mid-January to early May, the NRC MMR received samples of 29 individuals affected by the outbreak in Hildesheim for genotyping. For the 26 successful reactions, 21 cases were associated with MVs/Gir Somnath.IND/42.16 (D8-4683) (Fig. 1). Two cases showed the variant D8-6031, which is closely related to D8-4683. Another patient was infected with MV B3-4299, which is completely unrelated to D8-4683.



Two individuals with a history of recent vaccination showed the vaccine virus genotype A. These findings indicate that the outbreak was driven comprehensively by MVs/Gir Somnath.IND/42.16 (D8–4683) and its descendant D8–6031. Moreover, the detection of B3–4299 demonstrates that even in an outbreak situation, unrelated importations can contribute to the transmission.

3.4. A fatal case in a 33-year-old woman

Tragically, a 33-year-old woman died. She was the mother of five children aged 4, 12, 13, 14 and 16. The eldest daughter (case 1) was vaccinated by her practitioner on March 1st, 2019 in ignorance of her pregnancy. She received the vaccine presumably 4 days after the incubation (Fig. 2), which was too late to prevent the infection. The girl developed a rash on March 12th 2019. Molecular characterization made evident that she had contracted the wt-virus (D8–4683). We suppose that although the infection was not prevented by the vaccine, the girl was less infectious, since only one of her siblings (case 2) was subsequently infected. Case 2 was a 12-year-old boy (unvaccinated), who developed a rash on March 26th 2019. Apparently, he infected the rest of the family (cases 3–6). Two other siblings developed a rash on April 6th 2019 (4-year-old boy, 14-year-old girl, both unvaccinated). The 13-year-old girl and her 33-year-old mother were counseled to take the vaccine as soon as possible. Due to delivery bottlenecks the application was postponed until 3rd April 2019. Both developed a maculo-papular rash on April 8th 2019. The mother had fever, headache, sore throat, flu-like symptoms and gastrointestinal complaints. She was found dead in the morning of 11th April 2019. The interval between vaccination and onset of symptoms was 5 days, while onset of symptoms and death were 3 days apart (Fig. 2). To investigate the cause of death of the young and otherwise not critically ill woman, a post-mortem examination was done in accordance with § 5 of the Lower Saxony Law on Mortuary, Burial and Cemetery Services (BestattG). Moreover, clinical samples were investigated for presence of the vaccine or MV wildtype (Table 1).

3.5. Post-mortem examination of the fatal case

The typical maculo-papular rash was seen (Fig. 3A), but no cause of death was found, when the organs were assessed macroscopically for size, shape, color, consistency and coherence and morphologically visible changes deviating from the norm.

While most measles-induced deaths are triggered by secondary bacterial infections in the context of infectious immunosuppression, neurological complications can also add to morbidity and mortality in measles patients. Measles-induced monophasic acute disseminated encephalomyelitis (ADEM) can develop during an acute measles infection (Morrison et al., 2020; Mutoh et al., 2021). ADEM is a post-infectious autoimmune event, in which T lymphocytes attack the myelin formed by oligodendrocytes, particularly in the perivenous space, so that a perivenous demyelination is typically found as a

morphological correlate. Furthermore, more T-lymphocytes than B-lymphocytes can be seen microscopically in the perivenous space, as well as myelin-clearing, resorbing macrophages, while MV detection in the brain is not a diagnostic hallmark of ADEM. In the present case, demyelination or of resorbing macrophages were not observed. ADEM with localized demyelination as well as a myocarditis or a bacterial superinfection were excluded.

The microbiological examinations of samples of heart blood, brain, lungs right and left, spleen, trachea, revealed physiologically occurring germs in the mouth, nasopharynx and skin, for which a post-mortem migration or contamination without disease value were assumed. The allergological immunological examination with of total IgE and tryptase on the basis of the femoral vein blood collected during the autopsy yielded no indication of an allergic shock that are very rare adverse events of an immunization. The chemical-toxicological investigation revealed that the deceased person was an active THC user with recent consumption. THC possess immuno-suppressive properties (Huemer et al., 2007; Milad et al., 2023), but whether the concentration detected contributed to the fatal development cannot be assessed with sufficient certainty.

The fine-tissue examination of the internal organs and lymph nodes revealed a profound effect in the lungs: massive mixed-cell (predominantly lymphocytic) inflammatory cell infiltrates with connective tissue thickened and cellular infiltrated septa were found. In the alveolar lungs, a giant cell infiltrate was observed (Fig. 3B), as well as edema to a lesser amount. The lung tissue also showed emphysematous and atelectatic areas. Signs of inflammation were detected in the skin and lung sampling sites. In particular, the lungs showed a severe inflammatory reaction (Fig. 3C), which must be regarded as the cause of death. The skin samples taken from an area with measles exanthema showed isolated coliocytic cells (Fig. 3D). These cells characterized by pallid nuclei surrounded by a reduced amount of cytoplasm are a hallmark of a viral infection. In addition, a perivascular round cell infiltrate was seen in the dermis.

3.6. Molecular characterization of the MV detected in the fatal case

The NRC MMR has received a set of 11 clinical samples from the deceased woman (trachea, lung, bronchus on the left, liver, spleen, heart blood and cerebrospinal fluid) from which RNA was extracted (Table 1). The RNA was subjected to two MV-specific PCR reaction. The diagnostic test detects all variants of MV, the second amplifies exclusively the MV vaccine strain (Roy et al., 2017). All materials were positive in the diagnostic test but negative in the vaccine-specific reaction. MV genotyping revealed MVs/Gir Somnath.IND/42.16 in every sample. This demonstrates clearly infection of the fatal case with the circulating MV wildtype.

4. Discussion

Vaccines are the most powerful tools to prevent infectious diseases but especially in high-income countries a bad reputation can be encountered. The vaccine paradox (Karafillakis and Larson, 2018) results from the fact, that vaccines relieve the population from a burden which is subsequently no longer perceived as a health threat. Consequently, maintaining awareness and high vaccination rates is difficult and vaccine skepticism has been nominated as one of the major health threats by WHO (Nuwarda et al., 2022). Reaching the elimination goal implies keeping up the vaccination rate, supporting an active and sensitive surveillance and molecular surveillance of circulating MV. Germany has made good progress towards the elimination goal and measles incidences were low from 2020 to 2023.

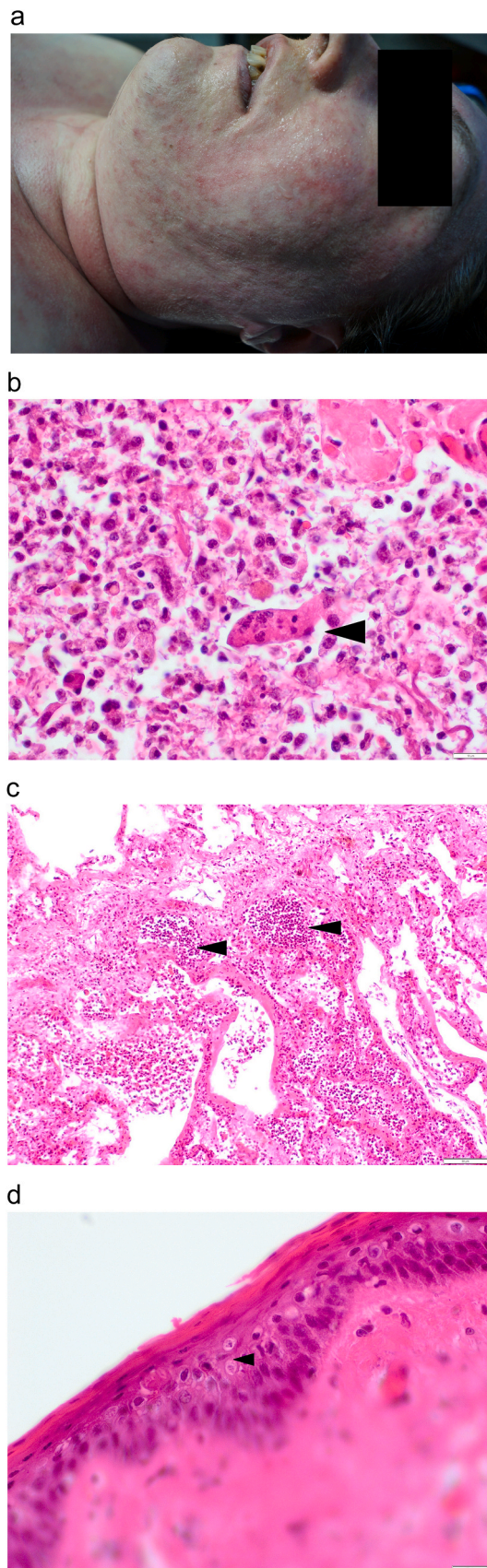
4.1. Vaccination failures observed during the outbreak

The high proportion of vaccination failures was surprising. Primary

Table 1

Materials of the fatal case investigated for presence of measles wildtype or vaccine virus.

	Clinical specimen	MeV PCR	Vaccine virus PCR	Genotype
1	Throat swab	pos	neg	D8-4683
2	Mouth swab	pos	neg	D8-4683
3	Liquor	pos	neg	D8-4683
4	Left lung	pos	neg	D8-4683
5	Right lung	pos	neg	D8-4683
6	Trachea	pos	neg	D8-4683
7	Left bronchus	pos	neg	D8-4683
8	Trachea swab	pos	neg	D8-4683
9	Spleen	pos	neg	D8-4683
10	Heart blood	pos	neg	D8-4683
11	Liver	pos	neg	D8-4683



(caption on next column)

Fig. 3. Macroscopic and histologic results from the post-mortem investigation 3 A: Macroscopic picture of the skin. The typical maculo-papular rash is seen. 3B: Histopathological characterization of lung tissue. Tissue from the lower lobe of the right lung was subjected to a HE staining. A multi-nucleated giant cell, the typical hallmark of giant-cell-pneumonia is indicated. 3 C: Tissue from the middle lobe of the lung. The tissue shows massive infiltration by lymphocytes (indicated by triangles) as a classical sign of inflammation. 3D: Histopathological characterization of the skin affected by rash. Indicated is the formation of two coilocytes as a hallmark of viral infection characterized by light nuclei and reduction of the cytoplasm.

vaccination failure (PVF) are often related to incorrect storage or application of the vaccine, while waning of the antibody titers are associated with a secondary vaccination failure (SVF). The type of vaccination failure can be discriminated by a serologic approach. High avidity IgG indicates a preformed immune response, while a freshly established infection or vaccination is reflected by an immature immune response, i.e. IgG of low avidity. The respective test for anti-measles IgG-avidity was performed in 4 of 11 cases. All 4 sera demonstrated high avidity indicating a SVF. A possible explanation for the high number of SVF could be the long absence of MV circulation in Hildesheim. The district has not recorded larger measles outbreaks since the infection protection act was implemented in 2001. Similar observations were made 2011 in Slovenia, where a high proportion (9 cases out of 14; 64%) of patients experienced a SVF after a longer absence of MV transmission (Santibanez et al., 2014). The lacking natural booster effect might explain the rather high number of MV infections in vaccinated here as well.

4.2. Evaluation of the measures taken/Lessons learned

Despite the 43 measles cases and the fatal case in a mother of 5 children could not be prevented, the outbreak management was positively evaluated: the risk-adapted protective measures not only prevented further spread especially in schools, but also the intensive public relations work resulted in an increase in the uptake of measles vaccine by 85% when the first quarters of 2019 and 2018 were compared.

4.3. Assessment of the fatal case

Our report describes a fatal case. The analysis of the tragic event was aggravated by the fact, that the 33-year-old mother had received a measles vaccination 3 days prior the onset of symptoms giving raise to the suspicion that the fatality was associated with a vaccine adverse reaction. The post-mortem investigation revealed a giant cell pneumonia as cause of death, which is a known complication for MV infection in immune-suppressed individuals (Griffin, 2020; Rahman et al., 1996). The other remarkable result was the detection of recent cannabis consumption by the toxicologic investigation. Cannabinoids have an impact on the immune system, they alter the signaling of the inflammasome (Suryavanshi et al., 2020) and suppress antitumor activity in T-cells by inhibiting the JAK/STAT pathway (Xiong et al., 2022). In virus infection, antiviral effects were described (van Breemen and Simchuk, 2023) as well as impairment of immune function to defeat virus infection (Maggirwar and Khalsa, 2021). Without further studies, it is not feasible to decide whether drug consumption had an influence on this fatal outcome.

5. Conclusion

A measles outbreak occurred in Hildesheim after more than 20 years absence of MV transmission. 43 cases were recorded, 11 of which were observed in individuals vaccinated earlier. Investigation of 4 of the 11 vaccinated cases indicated a SVF in 4 of 4 cases. The high proportion of SVF may be the result of a longer absence of MV circulation in the Hildesheim area.

The outbreak led to enhanced activity of the local health authority and timely vaccination was recommended for susceptible inhabitants. Strengthened communication raised awareness of the public and led to an increase in vaccination. The measures taken led to the cessation of the transmission chains after 14 weeks. After the implementation of the measures, most transmissions were observed in family settings and no longer in community services as schools or day care centers.

A family of 7 was affected by the outbreak and all 5 children and their mother contracted measles. The family was not vaccinated, three of them received a post-exposition prophylaxis. Due to a scarcity of the vaccine, the mother was vaccinated more than 2 weeks after the first case of measles was observed in the family. She developed rash and fever 3 days after the vaccination and was found dead on day 8 after vaccination. Molecular characterization of the virus demonstrated incubation with the outbreak virus MVs/Gir Somnath.IND/42.16; the vaccine was not detected. A post-mortem analysis indicated a giant cell pneumonia as consequence of the measles infection as cause of death. Active consumption of cannabis may have aggravated the symptoms.

Vaccination of the 5 children as well as the 33-year-old and otherwise healthy mother according to the STIKO recommendations may have prevented this tragic case.

CRedit authorship contribution statement

Hueppe Katharina: Investigation, Data curation. **Mankertz Annette:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Santibanez Sabine:** Investigation. **Gaußmann Hannah:** Investigation. **Ortmann Jan:** Investigation.

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