

# Outbreak-related mumps vaccine effectiveness among a cohort of children and of young adults in Germany 2011

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**Abbreviations:** AR, attack rate; VE, vaccine effectiveness; CI, confidence interval; Ig, immunoglobulin; MMR, measles-mumps-rubella; RR, relative risk; STIKO, German Standing Committee on Vaccination; US, United States of America; VC, vaccination card

Mumps outbreaks in populations with high 2-dose vaccination coverage and among young adults are increasingly reported. However, data on the duration of vaccine-induced protection conferred by mumps vaccines are scarce. As part of a supra-regional outbreak in Germany 2010/11, we conducted two retrospective cohort studies in a primary school and among adult ice hockey teams to determine mumps vaccine effectiveness (VE). Via questionnaires we collected information on demography, clinical manifestations, and reviewed vaccination cards. We estimated VE as 1-RR, RR being the rate ratio of disease among two-times or one-time mumps-vaccinated compared with unvaccinated persons. The response rate was 92.6% (100/108—children cohort) and 91.7% (44/48—adult cohort). Fourteen cases were identified in the children and 6 in the adult cohort. In the children cohort (mean age: 9 y), 2-dose VE was 91.9% (95% CI 81.0–96.5%). In the adult cohort (mean age: 26 y), no cases occurred among the 13 2-times vaccinated, while 1-dose VE was 50.0% (95% CI –9.4–87.1%). Average time since last vaccination showed no significant difference for cases and non-cases, but cases were younger at age of last mumps vaccination (children cohort: 2 vs. 3 y,  $P = 0.04$ ; adult cohort: 1 vs. 4 y,  $P = 0.03$ ). We did not observe signs of waning immunity in the children cohort. Due to the small sample size VE in the adult cohort should be interpreted with caution. Given the estimated VE, very high 2-dose vaccination coverage is required to prevent future outbreaks. Intervention efforts to increase coverage must especially target young adults who received <2 vaccinations during childhood.

## Introduction

Mumps is a viral disease that typically leads to uni- or bilateral swelling of the parotid glands. Approximately 30% of infections occur unapparent or sub-clinical. However, there is also a risk of developing complications like orchitis, meningitis, pancreatitis, oophoritis, or encephalitis, which increases with age. Before the introduction of mumps vaccines, infections predominantly affected the age group of 5- to 9-y-olds.<sup>1–4</sup>

In the previous decades, many industrialized countries have implemented a 2-dose measles-mumps-rubella (MMR) immunization schedule.<sup>5–7</sup> In Germany, 1-dose mumps vaccination was introduced in West Germany as part of the childhood immunization schedule in 1976, whereas East Germany did not routinely vaccinate against mumps. A 2-dose schedule throughout

the reunified Germany has been recommended by the German Standing Committee on Vaccination (STIKO) since 1991 with the first dose being administered in the second year and the second dose in the sixth year of life. In 2001, the recommended vaccination age was changed to 11–14 mo for the 1st and 15–23 mo for the second dose. The vast majority of vaccines licensed since 1974 in (West) Germany contained the Jeryl Lynn or the Jeryl Lynn-derived RIT 4385 strain.<sup>8</sup> In randomized controlled trials vaccine efficacy for the monovalent vaccine containing Jeryl Lynn was measured to be 95% and 96%, respectively.<sup>9,10</sup> However, vaccine effectiveness (VE) for this strain determined in outbreak settings ranged from 73% to 91% for 1 dose and was 92% for 2 doses<sup>11</sup>; a recent Cochrane review found VE for  $\geq 1$  dose of Jeryl Lynn containing MMR-vaccines to be 69–81%.<sup>12</sup>

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Several industrialized countries with long-standing 2-dose vaccination programs have recently reported larger-scale outbreaks, among them the United States (US),<sup>13–15</sup> the Netherlands,<sup>16,17</sup> the United Kingdom,<sup>4</sup> the Czech Republic,<sup>18</sup> Israel,<sup>19,20</sup> and Canada.<sup>21</sup> These outbreaks had in common that they predominantly affected adolescents and young adults, and that a high proportion of cases were 2-times vaccinated. Several theories have been discussed to explain the age shift and the high proportion of vaccinated cases, such as waning immunity, lack of boosting due to decreased wild virus circulation after vaccine introduction, and mismatch between wild and vaccine virus.<sup>1,11,13,19</sup> In Germany, a seroprevalence study including >13 000 children aged 0–17 y in 2003–06 identified significant waning of immunoglobulin (Ig) G antibodies over this age range<sup>22</sup>; however, it is still unclear if this observed waning of antibodies also results in a waning protection against mumps disease. Data on the vaccine-induced protection against clinical disease several decades after mumps vaccination are still lacking.

Because nationwide mandatory case-based notification of mumps has only recently been introduced in Germany, comprehensive data on the local epidemiology is not available. However, the “German Infection Protection Act” requires outbreaks occurring in institutional settings to be immediately reported to district health authorities. Based on this act, a mumps outbreak in the federal state of Bavaria was reported in 2010. The outbreak was supra-regional, lasted from July 2010 to May 2011, and affected mainly adolescents and young adults.<sup>23</sup> Based on temporarily-implemented voluntary surveillance, 295 cases were reported to the district health authorities. However, recent analysis of corresponding statutory health insurance claims data suggests that the outbreak affected more than 2000 persons.<sup>24</sup> Genotype G was identified as the causative strain in multiple isolates of cases.<sup>25</sup> Among the variety of institutions and groups affected by the mumps-outbreak was a primary school in the city of Nuremberg and two young adult ice hockey teams in the district of Erding. The aim of our study was (1) to epidemiologically describe the outbreak among the cohort of primary school students (children cohort) and the ice hockey players (adult cohort), and (2) to calculate outbreak-related mumps VE separately for both groups.

## Results

### Epidemiological description of the outbreak and cohorts

#### Children cohort

The primary school comprised of 354 students from first to fourth grade with 4 classes per grade. A total of 23 mumps cases (14 students, 3 teachers, 6 siblings/parents) occurred between March and May 2011 in the context of the affected school. The student cases belonged to 5 classes with a total of 108 students: 1 class with 7 cases, 1 class with 3 cases, 1 class with 2 cases, and 2 classes with 1 case.

Mean age of the 14 cases was 9 y (range 8–10). Two cases were laboratory-confirmed, and 12 cases had a clinical-epidemiological link. Two of the 6 male cases developed orchitis. Six cases had received 2 MMR doses, 3 1 dose and 5 were unvaccinated.

**Table 1.** Demographics, mumps vaccination status (based on vaccination card check), previous history of mumps, and attack rate (AR) by vaccination status among the primary school cohort, Nuremberg (Germany), 2011

	N (%)	AR in %
Total number	100 (100)	14
Age		
Mean in years	9	-
Range in years	8–12	-
Sex		
Males	51 (51)	-
Vaccination status		
2 doses	89 (89)	7
1 dose	4 (4)	75
Unvaccinated	6 (6)	83
Unknown status	1 (1)	-
Previous mumps history		
Yes	0 (0)	-

Response rate for the questionnaire and vaccination card (VC) presentation was 92.6% (n = 100/108). Cohort characteristics and attack rates (AR) are shown in Table 1. Of the 6 children unvaccinated, all parents stated that they had deliberately chosen not to vaccinate their child. All vaccinated children for whom the administered vaccine brand was known (first dose: 80/92 [87.0%]; second dose: 82/89 [92.1%]) had received a vaccine containing either the RIT 4385 or the Jeryl Lynn strain.

#### Adult cohort

The outbreak among the 2 ice-hockey teams (Team 1: 24 players and 3 staff members; Team 2: 21 players and 4 staff members) lasted for 9 weeks between January and March 2011. Over that time period, both teams participated each in 10 matches; Team 1 and Team 2 trained 3 and 2 times per week, respectively. In each of the 2 ice-hockey teams 3 mumps cases were identified. All 6 cases were male and on average 28 y old (range 20–46). Five cases were laboratory-confirmed, 1 case had a clinical-epidemiological link. Two cases developed orchitis; 1 of these 2 cases was in addition diagnosed with pancreatitis. Three cases had received no or one mumps vaccine dose. All cases reported that they had trained until 1 day before the onset of symptoms, resulting in continuous exposure for the other team members.

We excluded 4 team members from the cohort due to permanent absence from training during the outbreak period. The response rate of the remaining team members was 91.7% (n = 44/48). Of those, 5/44 (11%) reported that they had lost their VC but stated to have received one previous vaccination (n = 3) or being unvaccinated (n = 2). Cohort characteristics and AR are given in Table 2. Of the team members with no previous mumps history (n = 37), 13 (35.1%) had received 2 vaccinations. Mean age of the cohort stratified by vaccination status was 22 y (range 18–28 y) for those vaccinated twice, 27 y (range 20–35 y) for those vaccinated once, and 31 y (range 19–46 y) for the

**Table 2.** Demographics, mumps vaccination status, previous history of mumps, and attack rate (AR) by vaccination status among the ice hockey team cohort, Erding (Germany), 2011

	N (%)	AR in %
Total number	44 (100)	14
Age		
Mean in years	26	-
Range in years	18–46	-
Sex		
Males	41 (93)	-
Vaccination status		
VC* only		
2 doses	13 (30)	0
1 dose	13 (30)	23
Unvaccinated	6 (14)	50
VC* lost	5 (11)	0
VC* and oral history		
2 doses	13 (30)	0
1 dose	16 (36)	19
Unvaccinated	8 (18)	38
Previous mumps history		
Yes	7 (16)	-

non-vaccinated; mean age among cohort members with a previous history of mumps was 36 y (range 25–46 y). Differences in mean age were statistically significant for 2-times vaccinated compared with 1-time vaccinated ( $P < 0.005$ ), 2-times vaccinated to non-vaccinated ( $P = 0.05$ ), and 2-times vaccinated to persons with a previous history of mumps ( $P < 0.005$ ). For 7/44 (16%) the vaccine brand used was documented: all had received a vaccine containing either the RIT 4385 or the Jeryl Lynn strain.

In Team 1, end of January 2011 4 players received a single MMR vaccination after the 2nd mumps case had occurred in their team: 3 had a history of one previous mumps vaccination and 1 of 2 mumps vaccinations; none of them acquired mumps during the outbreak period.

#### Vaccine effectiveness, time since last vaccination, and age at last vaccination

##### Children cohort

VE for 2 doses was 91.9% (95% confidence interval [CI] 81.0–96.5). Mean time since last MMR vaccination was statistically not significantly different ( $P = 0.97$ ) between cases (5.9 y; 95% CI 5.2–6.5) and non-cases (5.3 y; 95% CI 4.8–5.8). Mean age at 2nd vaccination was 1.7 y (95% CI 1.1–2.2) for cases and 3.1 y (95% CI 2.7–3.6) for non-cases ( $P = 0.04$ ). We did not calculate 1-dose VE as only 3 cases and 2 non-cases in the cohort had been vaccinated once.

##### Adult cohort

One-dose VE was 53.8% (95% CI -65.1–87.1) for persons with documented vaccination and 50.0% (95% CI -9.4–87.1) when including also persons with an oral vaccination history. Mean time since MMR vaccination was 22.0 y (95% CI -16.1–60.1)

for cases and 23.0 y (95% CI 19.9–26.1) for non-cases ( $P = 0.75$ ). Mean age at vaccination was 1.3 y (95% CI 0.9–1.7) for cases and 4.4 y (95% CI 2.3–6.6) for non-cases; the difference was statistically significant ( $P = 0.03$ ).

Two-dose VE was 88.0% (95% CI -11.7–100) for persons with a documented vaccination and 84.0% (95% CI -48.9–100) when including also persons with an oral vaccination history. As no cases occurred among 2-times vaccinated, no comparison could be conducted for mean time since last vaccination and age at last vaccination between cases and non-cases.

## Discussion

During the supra-regional mumps outbreak in Bavaria we were able to identify a pediatric and a young adult cohort suitable to estimate VE. In the children cohort, VE 5–6 y after the 2nd vaccine dose was high with 91.9%. This finding is compatible with the outbreak-related VE of 92.4% and 86.4% seen 5–6 y after the 2nd dose given at school entry among 9- to 10- and 11- to 12-y-olds in England.<sup>26</sup> Our results are also similar to the 2-dose VE of 91.6% calculated during a summer camp outbreak in the US;<sup>27</sup> however, mean time since last dose was not determined, and the cohort consisted of both younger campers (mean age: 12 y) and older staff (21 y). Though response rates were high in the adult cohort, cohort sizes for 1-dose and 2-dose vaccinated were small. Interpretation of the VE results is therefore limited. However, to our knowledge there are no reports available so far on VE assessments in a population that has been vaccinated on average more than 20 y ago. This data are therefore helpful for the interpretation of recently observed mumps outbreaks affecting a large proportion of young adults.

Our analysis revealed that vaccination coverage among the children cohort was high, and that nearly all children had received 2 mumps vaccinations as it has been recommended by STIKO. The 2-dose coverage in our study population was identical with the 88.6% seen at school entry exams in Bavaria in 2010.<sup>28</sup> However, given a VE of 90% and a basic reproductive number of 4, 6, or 8, respectively, Deeks and colleagues estimated that coverage needs to exceed 83.3%, 92.6%, or 97.2% to provide herd immunity and prevent mumps outbreaks.<sup>29</sup> In contrast, in the adult cohort the number of received doses varied according to age, and only about a third had received 2 vaccinations. Coverage in the now adult age groups had historically been low in Germany and only increased in the recent decade: a cross-sectional study in 1988 examining ~86 100 VCs of 10- to 12-y-old children in Bavaria yielded a mumps vaccination coverage of only 55%.<sup>30</sup> In 2010, STIKO recommended one MMR vaccination for all persons born after 1970 with less than 2 measles vaccinations in their childhood or unclear vaccination status.<sup>31</sup> Nevertheless, we did not see any recent MMR vaccinations based on this recommendation. This might be due to a general lack of concerted catch-up campaigns in Germany as well as the short time span between the new recommendation and the Bavarian outbreak.

Mean time since last vaccination did not statistically differ for cases and non-cases in both cohorts, but the results for the adult cohort are limited due to the small sample size. However, both cohorts showed statistically significant differences regarding

age at last vaccination: cases had been younger than non-cases. Davidkin et al. suggested that giving the second MMR dose before the age of 2 years may induce shorter protection against mumps,<sup>32</sup> and Eriksen et al. had observed in their study analyzing mumps-seroepidemiology in Europe in regard to countries' vaccination programs and recent outbreaks that longer intervals between the first and the second dose were associated with a reduced risk of mumps outbreaks.<sup>5</sup> Germany recommends an early second MMR vaccination (second year of life),<sup>31</sup> motivated by the primary aim to prevent measles cases by increasing 2-dose coverage: the early second vaccination provides better access to young children due to routine well-baby check-ups and also allows for a timely catch-up of children with primary vaccine failure following the first dose. In contrast, a number of European countries recommend the second MMR dose at school entry or up to an age of 13 y.<sup>5</sup> With the re-occurrence of mumps outbreaks and hints of waning immunity as a potentially contributing factor, optimal age at second dose for long-lasting immunity as well as a routine booster or outbreak-related administration of a third dose are increasingly discussed in the international community.<sup>13,19,32-34</sup> The administration of a third dose as an outbreak intervention was recently applied during a mumps outbreak in the US and proved successful to stop further spread.<sup>35</sup> Nevertheless, evidence was not yet considered sufficient by the Centers for Disease Control and Prevention to routinely recommend the administration of a third dose in outbreaks.<sup>36</sup>

Our study had mainly 2 limitations. Though response rate was very high in both cohorts, sample size in the adult cohort was too small to calculate a precise VE estimate, which resulted in wide confidence intervals. However, as obtaining closed cohorts among adults poses a challenge and as they are at center of discussion regarding recent outbreaks, results even of small outbreak investigations could be an important contribution to future meta-analysis studies. Furthermore, 4 ice hockey players were vaccinated during the outbreak. Yet all of them had previously received  $\geq 1$  vaccination, and the vaccination occurred during the incubation period of the last case in the team. We therefore refrained from using a person-time approach.

In conclusion, we did not observe signs of waning immunity or vaccine failure in the cohort of primary school children 5–6 y after last vaccination. Even though our analysis for the adult cohort is limited by the small sample size, the point estimates suggest that VE 2 decades after the 2nd dose is still at an acceptable level but that VE after 1 dose has dropped considerably. However, due to the imprecision of the VE point estimate we cannot fully rule out that waning immunity also might play a role in 2-times vaccinated adults. Since previous surveys suggest that a substantial proportion of young adults living in the Western federal states of Germany has  $< 2$  mumps vaccinations, thereby forming a relevant pool of susceptibles for further outbreaks, it seems plausible that from a public health point of view priority should be given to close these vaccination gaps. Given the current mumps vaccine, two-dose coverage rates should exceed 95%<sup>29</sup> in all age groups born after vaccine introduction into the routine schedule to prevent future outbreaks. Therefore, in Germany interventions are needed that are specifically

targeted at adolescents and young adults who have received  $< 2$  vaccine doses during their childhood or have an unknown vaccination status.

## Material and Methods

We performed 2 retrospective cohort studies in (1) 1 primary school and (2) 2 ice hockey teams that had  $\geq 1$  mumps case attending class/training during his/her infectious period. The collected information was supplemented by results of previously conducted active and passive case finding (including mode of diagnosis, mumps-related symptoms, and mumps vaccination status) conducted by the responsible local health authority during the outbreak period.

### Definitions

A mumps case was defined as a primary school student (children cohort) or a player or staff member of one of the 2 ice hockey teams (adult cohort) who was diagnosed by a physician with acute mumps disease (defined as  $\geq 2$  d of 1- or 2-sided parotid swelling without any other apparent cause and/or laboratory detection [IgM detection or significant increase of IgG between 2 specimens] and/or a clinical-epidemiological link) between March 12th and May 9th, 2011 (children cohort) or January 7th and March 20th, 2011 (adult cohort), respectively. Vaccination status was determined by number of received vaccinations up to 18 d prior to disease onset in the index case of the respective cohort.

### Study population and design

#### *Children cohort*

All students of classes with  $\geq 1$  mumps case were included in the retrospective cohort study. The cohort was limited to affected classes because students of the same class stay in the same classroom for instruction, mixing with other grades is usually limited, and instruction only lasts until noon before students walk/cycle home for lunch. A voluntary parent-administered questionnaire was handed out to the students collecting information on demography and mumps-related symptoms and complications. Additionally, parents were asked to return the questionnaire with the child's VC or a copy of the VC to retrieve documented number of mumps vaccinations, vaccine brand, and date of administration. Given parents' written consent, we contacted the student's physician in case of missing or ambiguous information.

#### *Adult cohort*

Members of the 2 ice hockey teams were merged into a single cohort, as both teams had mumps cases, trained at the same stadium, and comprised of the same age-group. We excluded team members not regularly present at training during the outbreak period (e.g., because of injury). Team members were asked to fill out a voluntary self-administered questionnaire and present their VC to the ice hockey team physician for extraction of vaccine brand and number/date of administered dose(s). Team members with missing information were again contacted face-to-face, via telephone, email, or facebook®. Copies or photos of the VC were also sent per email or mobile phone. Given written consent, we contacted the player's or staff member's physician in case of missing or ambiguous information.

## Epidemiological description of the outbreak and outbreak cohorts

We described the time-course of the outbreak as well as demographics, AR, number of complications and vaccination coverage among the children cohort and adult cohort, respectively.

## Calculation of VE, time since last vaccination, and age at last vaccination

We calculated VE for 1 or 2 mumps-vaccine doses(s) compared with no dose. VE was hereby estimated as  $(1-RR) \times 100$  with 95% CI, RR being the rate ratio between AR in one or 2-times vaccinated cohort members, respectively, and the AR in unvaccinated cohort members.<sup>37</sup> Non-cases with a previous history of mumps were excluded for VE calculation. Persons vaccinated during the outbreak period were classified according to their pre-outbreak vaccination status. In case of a lost VC or unclear vaccination status, if possible we verified the stated information by contacting the respective physician or parent. Calculations of time since last vaccination and age at last vaccination were based on birthdates, documented date of last vaccination, and last day of the defined outbreak period.

## Ethical considerations

In accordance with Article 25 paragraph 1 of the “German Infection Protection Act” a formal ethical review process and approval was not required for these outbreak investigations. Study participation was voluntary and based on informed consent.

## Statistical analysis

Wilcoxon rank sum and Fisher’s exact test were used to compare means and proportions, respectively; Fisher’s exact test was

also applied to calculate RR and corresponding 95% CI for the VE in the children cohort and 1-dose VE in the adult cohort; Exact Poisson regression was only used to calculate RR and corresponding 95% CI for 2-dose VE in the adult cohort. Statistical analysis was performed by using Stata® version 12.1.

## Disclosure of Potential Conflicts of Interest

All authors report no potential conflict of interest.

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