

ORIGINAL STUDIES

Marked Underreporting of Pertussis Requiring Hospitalization in Infants as Estimated by Capture–Recapture Methodology, Germany, 2013–2015

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Background: In Germany, pertussis became notifiable in eastern federal states in 2002 and nationwide in March 2013. Infants are at greatest risk for severe disease, with a high proportion requiring hospitalization. We implemented enhanced hospital-based surveillance to estimate the incidence of pertussis requiring hospitalization among infants in Germany and to determine the proportion of infants hospitalized with pertussis too young to have been vaccinated.

Methods: Enhanced surveillance was implemented within a nationwide hospital surveillance network (ESPED). We defined cases as children less than 1 year of age hospitalized due to laboratory-confirmed pertussis with disease onset from 01/07/2013–30/06/2015. We matched cases to those ascertained in the national statutory notification system, and estimated incidence using capture–recapture methodology.

Results: The estimated annual incidence of pertussis requiring hospitalization in infants was 52/100,000 infants (95% confidence interval [CI] 48–57/100,000), with 39% under-reporting to the national notification system. During the two epidemiologic years under-reporting decreased from 46% to 32% and was lower in eastern than western federal states (21% vs. 40%). Within ESPED, 154 of 240 infants (64%) were younger than or still at the age recommended for the first vaccine dose; 55 (23%) could have received one or more vaccine doses. Median length of hospitalization was 9 days (IQR 5–13 days) and 18% required intensive care treatment.

Conclusions: Our study revealed a high burden of pertussis in infants with marked under-reporting, especially in western federal states where notification was only recently established. Strategies for the prevention of severe pertussis.

Key Words: pertussis, incidence, infants, hospitalization, capture–recapture (*Pediatr Infect Dis J* 2018;37:119–125)

Whooping cough, also referred to as pertussis, is a highly contagious respiratory disease primarily caused by the bacterium *Bordetella pertussis* and more rarely by *Bordetella parapertussis*, which generally causes milder disease.^{1,2} Only the former is vaccine preventable. The disease is most severe in unvaccinated or incompletely vaccinated infants, who may develop apnea, seizures secondary to hypoxia, pulmonary hypertension, pneumonia or otitis media.²

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Cyclical increases in pertussis incidence continue to be described every 3 to 5 years in most developed countries despite high vaccination coverage. This is explained largely by waning immunity both after vaccination and after natural infection.^{3–6} There is evidence for more rapid waning of immunity after vaccination with acellular compared with whole cell pertussis vaccines.^{7,8} In Germany, acellular vaccines were introduced in 1995 and rapidly replaced whole cell vaccines. Infection of previously vaccinated persons may be asymptomatic or cause significantly milder illness⁹ and may, thus, go undiagnosed but may nonetheless result in transmission of pertussis to infants.^{9–11}

The German Standing Committee on Vaccination (STIKO) recommends primary pertussis vaccination with vaccines containing high concentrations of pertussis antigens at age 2, 3 and 4 months followed by a booster at 11–14 months. Further boosters are recommended at school entry, in adolescence and in adults using vaccines containing lower concentrations of pertussis antigens. To further protect infants, especially those too young to be vaccinated, a cocoon strategy that recommends vaccination of women planning pregnancy, as well as household contacts and caregivers of infants, was adopted in 2004.¹²

Notification of pertussis was obligatory in the 5 eastern federal states of Germany according to a uniform case definition since 2002, but nationwide notification according to the Protection Against Infection Act was not implemented until March 29, 2013.¹³ Approximately half of all infants notified with pertussis are reported to have been hospitalized,¹⁴ which we consider an indicator of severe disease.

Knowledge of disease burden in infants, including the proportion of cases too young for vaccination, is essential for evaluation and possible adaptation of the current pertussis vaccination strategy. To estimate the true burden of severe pertussis in infants and to quantify the degree of underreporting in the national statutory reporting system in Germany, we conducted prospective hospital-based enhanced surveillance over 2 years and applied capture–recapture methodology.^{15,16}

MATERIALS AND METHODS

Data Sources for Capture–Recapture Analysis National Statutory Notification System (SurvNet)

Physicians and laboratories are required to report suspected and confirmed cases of pertussis to local health authorities (LHA). Only data from cases fulfilling the laboratory criteria of the national surveillance case definition¹⁷ are then electronically forwarded via the state health departments to the Robert Koch Institute.

Nationwide Hospital Network for the Surveillance of Rare Pediatric Diseases

All pediatric hospitals were invited to participate in this network from 1992 onwards.¹⁸ Each month, hospitals receive a reporting form asking for the number of cases hospitalized because of one of up to 12 different diseases according to the respective study case definition. From July 1, 2013 to June 30, 2015, this included

pertussis in infants. Cases were defined as infants under 1 year of age hospitalized because of an acute *B. pertussis* infection confirmed by polymerase chain reaction, culture or serologic testing for pertussis toxin antibodies. For each reported case, the attending physician was asked to complete a standardized questionnaire and return it to the ESPED study office, which forwarded it to the Robert Koch Institute.

Matching of Cases

Data on month and year of birth, as well as sex of the child, district and federal state of residence, dates of disease onset and hospitalization, vaccination status, clinical findings and results of laboratory testing were available from both data sources, although more detail was available for the latter 2 from the active surveillance in the hospital network. If either the date of hospitalization or illness onset was missing in cases captured by ESPED, we estimated these as follows: we calculated the median interval between these 2 dates for all cases without missing data. We then estimated the date of hospitalization as the date of illness onset plus this median interval or the date of illness onset as the date of hospitalization minus this median interval. For cases captured by the national surveillance system with missing dates of disease onset or hospitalization, these were calculated analogously based on the median time between date of notification and either date of illness onset or date of hospitalization.

SurvNet and ESPED records were matched if the following criteria were fulfilled:

1. Month and year of birth
AND
2. Sex
AND
3. District of residence (if missing, district of hospital)
AND
- 4a. Date of hospitalization (± 7 days; if missing, estimated date of hospitalization)
OR
- 4b. Disease onset (± 14 days; if missing, estimated disease onset)

For the following analysis, we included cases from both data sources if they were younger than 1 year of age and hospitalized because of a laboratory-confirmed acute *B. pertussis* infection with disease onset from July 1, 2013 to June 30, 2015.

Statistical Analysis

We performed a descriptive analysis of the notified infants with pertussis according to age, sex, vaccination status, clinical manifestations and complications, length of hospital stay and treatment. As only month and year of birth were available to comply with data protection requirements, calculation of age in months was imprecise. We assumed the day of birth to be the 15th of the month, meaning our age estimates could deviate by ± 1 month.

We applied capture–recapture calculation (CRC) to estimate the total number of cases (Fig. 1) and their 95% confidence intervals (CI) using Chapman's Nearly Unbiased Estimator.^{19,20} Incidences were calculated using official population data for Germany, 2014, from the Federal Statistical Office. We defined underreporting as the percentage difference between the CRC estimate and the incidence calculated based on the number of cases captured by the statutory or hospital-based surveillance systems, respectively.

We investigated whether validating the hospitalization status of cases reported to the national surveillance system influenced our

$$n = \frac{(L1 + 1) \times (L2 + 1)}{d + 1} - 1$$

Abbreviation	Number of cases:
L1	from data source 1
L2	from data source 2
d	from both sources
m	not found in any data source
n	estimated as Nearly Unbiased Estimator [Chapman, 1951]

FIGURE 1. Formula used for capture–recapture calculations.

CRC estimates as follows: we asked LHA staff to perform a retrospective validation of the hospitalization status in SurvNet for cases notified in 2013 and 2014 if the current hospitalization status was classified as “missing” or “not hospitalized”. We then compared results of capture–recapture analysis performed using validated and unvalidated data. In addition, we stratified our CRC analysis by study year, region (eastern vs. western states) and age (<3 months vs. 3–11 months) to evaluate the consistency of estimates (variable catchability) by comparing crude estimates with the sum of the respective stratum estimates as recommended by Hook and Regal.²¹

Ethics

The study was approved by the local Ethics Committee of Charité Medical University, Berlin (EA2/080/13).

RESULTS

Description of Cases and Comparison of the Two Data Sets

SurvNet

In the study period, 439 cases of pertussis in infants requiring hospitalization were reported to the national surveillance system, described in detail in Table 1. Briefly, the median age in months of the infants with plausible data ($n=437$) was 3 months (interquartile range: 2–5 months). The proportion of infants with a calculated age under 3 months, and, thus, younger than or still at the age recommended for the first vaccine dose, was 38% ($n=165$). The majority of the pertussis cases were laboratory confirmed by polymerase chain reaction. Median length of the reported hospital stay was 5 days. The most commonly reported symptom was cough, with paroxysmal attacks in about half and inspiratory stridor and apnea in about a quarter of the cases. No infant death was reported.

Nationwide Hospital Network for the Surveillance of Rare Pediatric Diseases

According to the Association of Pediatric Hospitals and Pediatric Hospital Departments, there were 360 (2013) and 356 (2014) pediatric hospitals or pediatric hospital departments in Germany (Personal communication, GKInD, 2016). Data for 2015 were not available at the time of writing. A total of 346 hospitals/hospital departments participated in ESPED during the study period (>95%). Response was received from 97% of participating hospitals/hospital departments for at least one of the months.

Over the study period, the participating hospitals reported a total of 247 pertussis cases to ESPED. Physicians completed the questionnaire for 240 (97%) of these, which were, thus, included in the analysis and are described in Table 1. Briefly, median age was 2 months (interquartile range: 1–3 months), and the proportion of infants with a calculated age under 3 months, that is,

TABLE 1. Characteristics of Infants Hospitalized Due to Pertussis Captured by the Data Sources SurvNet and ESPED and of the Cases for Which Matching Was Possible

Characteristics	SurvNet			ESPED			Matched Cases		
	N	%	Median	N	%	Median	N	%	Median
Number of cases in total	439			240			147		
Age (months)	437		3 months (IQR 2–5)	239		2 months (IQR 1–3)	147		2 months (IQR 1–3)
Infants under 2 months of age	85	19%		100	42%		65	44%	
Infants 2 months of age	80	18%		54	23%		31	21%	
Infants probably too young for vaccination (under 3 months)	165	38%		154	64%		96	65%	
Proportion of girls	218	50%		116	48%		75	51%	
Reported from hospitals in western states	385	88%		217	90%		129	88%	
Duration of hospital stay (days)	100		5 days (IQR 3–9; range 1–29)	235		9 days (IQR 5–13; range 1–44)	144		9 days (IQR 5–13; range 1–44)
PCR	335	76%		228	95%		143	97%	
Serology	42*	10%		10†	4%		3	2%	
Culture	12	3%		2	1%		1	1%	
No specification of laboratory method	50	11%							
Cough	370	84%		238	99%		146	99%	
With paroxysmal attacks	185	50%		181	76%		110	75%	
With inspiratory stridor	77	21%		35	15%		21	14%	
Apnea	105	24%		79	33%		47	32%	
Time (days) between first and last apnea episode			NA	53		10 days (IQR 4–14; range 0–32)	32		10 days (IQR 6–15; range 0–31)
Pneumonia		NA		30	13%		16	11%	
Intensive care		NA		42	18%		23	16%	
Deaths		0			0			0	

*Twenty-two cases were confirmed with only a single elevated pertussis toxin antibody measurement; of these, 3 had received 1 dose of aP vaccine.

†Eight cases were confirmed with only a single elevated pertussis toxin antibody measurement; of these, 2 had received 1 dose of aP vaccine.

aP indicates pertussis antigen; ESPED, Nationwide Hospital Network for the Surveillance of Rare Pediatric Diseases; IQR, interquartile range; NA, data not available; PCR, polymerase chain reaction.

younger than or still at the age recommended for the first vaccine dose, was 64% (n=154) and, thus, higher than among the statutorily notified cases. Median length of the hospital stay was 9 days (interquartile range: 5–13 days; range: 1–44 days; n=235). The predominant symptom was cough in 99% (n=238). Of infants with cough, 76% (n=181) had paroxysmal attacks typical for whooping cough and 15% (n=35) inspiratory stridor. Apnea was observed in one third of the infants (n=79) with a median duration of 10 days. Pneumonia was reported in 13% (n=30), and 18% (n=42) required intensive care treatment. An additional 12% (n=29) required cardiorespiratory monitoring. Additional symptoms were reported for 58% (n=140) of the infants. These were mainly other respiratory symptoms (85%, n=120) such as dyspnea, tachypnea, cyanosis, low oxygen saturation and posttussive vomiting or general symptoms (24%, n=33) such as somnolence, fever, loss of appetite and refusal to drink. No child developed otitis media, seizures, hypoxic encephalitis or died. Standard treatment was erythromycin (68%; n=162).

Of the 240 infants, 180 (75%) had never been vaccinated against pertussis (Table 2). At least 55 infants with known age (47 unvaccinated and 8 vaccinated with fewer doses than recommended for age) could have received at least one (further) vaccine dose (23% of infants with known age; Table 2).

Matching of Cases

We were able to match 147 ESPED cases to SurvNet cases. Based on our predefined matching criteria, 133 matches were entirely unambiguous. Case pairs that did not fulfill the matching criteria, but for which matching appeared probable (n=18), were individually assessed, and 14 were judged to match. Characteristics of matched cases were very similar to those of all ESPED cases (Table 1).

Estimated Incidences

By CRC, we estimated a crude annual incidence of 50 pertussis cases per 100,000 infants (95% CI: 46–54/100,000; Table 3).

The estimated nationwide incidence changed only slightly over time. In the first observed epidemiologic year (mid-2013 to mid-2014), incidence was estimated at 52 cases/100,000 infants (95% CI: 46–59/100,000 infants), decreasing to 49 (95% CI: 44–54) in the second epidemiologic year (mid-2014 to mid-2015). In contrast, our statutory surveillance system indicated an increasing incidence during the same time period (28 to 33/100,000 infants; Fig. 2). This was because of an increase in the number of notified cases in western (from 28 to 34 cases/100,000 infants) but not in eastern states, where incidence actually decreased from 28 to 24/100,000.

We requested LHA to verify the hospitalization status for cases in 2013 and 2014 if hospitalization status was reported as “no” or “missing” (n=341). LHA confirmed validation for 103 cases (93 originally reported as not hospitalized, 10 originally reported with missing hospitalization status). In 24 of the 103 cases, hospitalization status changed, in 19 cases to “hospitalized”, thus fulfilling our case definition only after validation. Hospitalization status changed for a lower proportion of cases in 2014 (18%; 10/56) than in 2013 (30%; 14/47). However, our CRC estimates based on the data set with validated hospitalization status changed minimally compared with using the unvalidated hospitalization status (49/100,000 [validated] vs. 50/100,000 [unvalidated]).

Estimated Underreporting

Underreporting to the national notification system was 39% overall and was lower in eastern than in western federal states (21% vs. 40%). It decreased from 46% in the first epidemiologic year to 32% in the second (Fig. 2). Despite greater underreporting in western federal states with improvement from the first to

TABLE 2. Vaccination Status of the Cases Captured by ESPED According to the STIKO Recommendation

Age Group (Months)	STIKO Recommendation for the Age Group	Number of Infants per Age Group	Unvaccinated	Vaccinated 1 Dose	Vaccinated 2 Doses	Vaccinated 3 Doses	Unknown Number of Doses
0–1	No vaccination	100	90*	0*	0*	0*	10*
2	1 dose possible	54	43†	5†	0	0	6‡
3	At least 1 dose	31	16§	10†	2†	0	3‡
4	At least 2 doses	21	14§	3§	2†	0†	2‡
5	Three doses	13	10§	1§	0§	0†	2‡
6+	Three doses	20	7§	3§	1§	3†	6‡
Unknown age	Not possible	1	0‡	0‡	0‡	0‡	1‡
Sum		240	180	22	5	3	30

*Number of infants too young to be vaccinated (n=100).

†Number of infants vaccinated according to the STIKO recommendation for the age group (n=65).

‡Number of infants for whom vaccination status could not be assessed (n=20).

§Number of infants NOT vaccinated according to the STIKO recommendation for the age group (n=55).

ESPED indicates Nationwide Hospital Network for the Surveillance of Rare Pediatric Diseases; STIKO, German Standing Committee on Vaccination.

the second study year, in stratified analyses according to time and region, the sum of the CRC estimates in the strata was similar to the crude CRC estimate. However, when we stratified for age (under 3 months vs. 3–11 months of age), the sum of the CRC estimates in the strata was higher compared with the crude estimate (Table 3).

DISCUSSION

Using a 2-source capture–recapture approach, we estimated a high incidence of severe pertussis in infants in Germany, higher in western than in eastern federal states. This is in line with hospital discharge statistics showing higher pertussis incidence in infants in western compared with those in eastern German states.²² A higher pertussis disease burden would be in keeping with observed lower vaccination coverage in western states, most marked in adolescents.^{23–25} Our results thus indicate that the lower incidences in most western compared with most eastern states as based on national statutory surveillance data available since 2013¹⁴ are due to underreporting and possibly under-ascertainment related to the only recent implementation of statutory notification in western Germany. Indeed, the degree of underreporting was markedly higher in western than in eastern states, although this improved over the course of the study.

The incidence of pertussis in infants based on cases notified to the statutory surveillance system in eastern states (not corrected for underreporting) was 2- to 3-fold lower during our study period (annual incidence 2013–2015: 31 cases/100,000 infants)

than during the last cyclic peak in 2011–2012, when the incidence in infants peaked at 95 cases/100,000 infants.²² Thus, taking this and the estimated underreporting into account, an incidence well over 100 hospitalizations/100,000 infants would be expected in epidemic years.

We hypothesize that underreporting and under-ascertainment in older age groups with typically milder disease may be even higher because these patients are less likely to seek medical care and, even when they do, may not be tested for pertussis.

The severity of pertussis in infants, reflected in prolonged hospitalization and requirement for intensive care in a high proportion of affected infants, together with the high incidence estimated in our study during an interepidemic period call for the implementation of further preventive measures. A high proportion of our cases was younger than or still at the age recommended for the first pertussis vaccine dose, that is, <3 months of age. In the United Kingdom, maternal vaccination introduced in response to an increase in infant deaths because of pertussis in 2012 was shown to have an effectiveness of 91% for preventing pertussis in infants under 3 months of age.²⁶ In addition, a recent study from the United States found a relative effectiveness of 85% for maternal vaccination in pregnancy versus postpartum maternal vaccination.²⁷ A number of countries have introduced maternal vaccination during pregnancy into their vaccination programs.^{26,28–32} While maternal antibodies of mothers who received vaccination antenatally may interfere with the immune response to routine vaccination of their infants, this effect appears to be small^{33,34} and was no longer significant after

TABLE 3. Incidence Estimates and Underreporting Based on CRC Stratified by Time, Region and Age Group

	Cases in SurvNet	Cases in ESPED	Matching Cases	CRC Case Estimate	Total	Annual CRC Case Estimate	Annual CRC Incidence Estimate per 100,000 (95% CI)	Underreporting to SurvNet	Underreporting to ESPED
Crude	439	240	147	715		358	50 (46–54)	39%	66%
Stratified by time									
July 2013 to June 2014	203	126	68	374	722*	374	52 (46–59)	46%	66%
July 2014 to June 2015	236	114	77	348		348	49 (44–54)	32%	67%
Stratified by region									
Eastern states	54	23	18	68	714†	34	33 (28–39)	21%	66%
Western states	385	217	129	646		323	53 (48–57)	40%	66%
Stratified by age									
0–2 months	209	154	87	369	777‡	184	103 (92–114)	43%	58%
3–11 months	227	85	47	408		204	38 (32–44)	44%	79%

Point estimates for the annual incidence based on the sum of the respective strata (column “Total”):

*50;

†50;

‡54 cases/100,000 inhabitants.

ESPED indicates Nationwide Hospital Network for the Surveillance of Rare Pediatric Diseases.

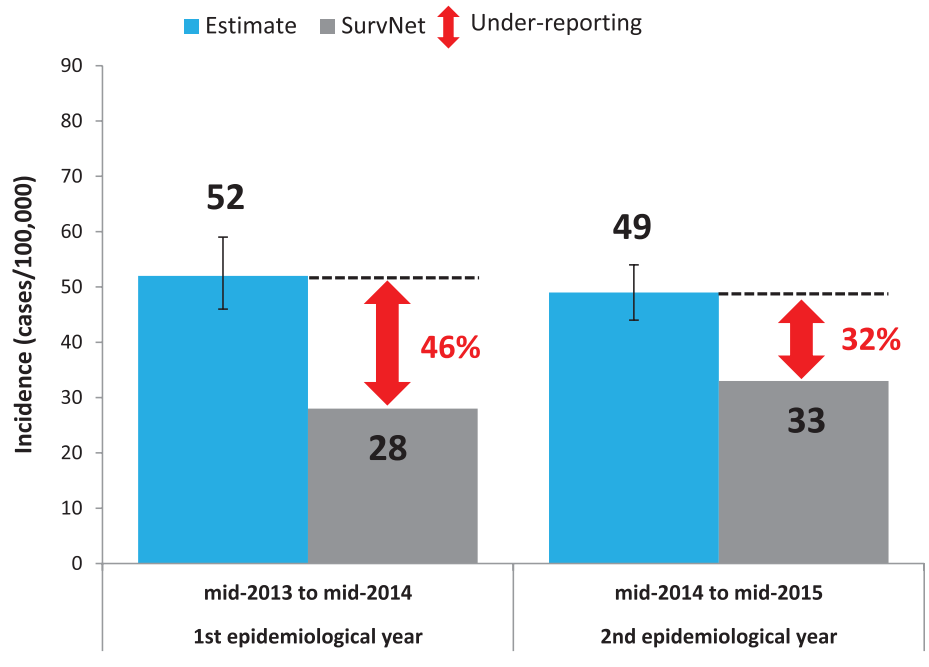


FIGURE 2. Comparison of incidences of pertussis hospitalizations in infants estimated using capture–recapture methodology and based on SurvNet data in the 2 epidemiologic years 2013–2014 and 2014–2015 in Germany. Underreporting is highlighted by the red arrow. [full color online](#)

a booster dose at ≈1 year of age.^{33,35–37} In addition, there is early evidence that this might be overcome by using different vaccine preparations for the child and the mother.³⁸

About one quarter of our cases could have received their first or a subsequent vaccine dose and, thus, possibly been protected because significant protection against pertussis is already achieved after the first vaccine dose.^{39–41} Indeed, modeling by Pesco et al.⁴² suggests that decreasing delays in primary vaccination doses can have a significant impact on pertussis incidence. Thus, awareness for timely vaccination should be increased among parents and physicians. In addition, several studies suggest that infants are often infected by household contacts, particularly mothers and older siblings,^{11,43–45} and this is the rationale underlying the cocoon strategy with pertussis vaccination of close infant contacts. However, this strategy is only moderately effective⁴¹ and can only have an impact if vaccination coverage among the target group is high, which is not the case in Germany⁴⁶: In a representative population-based telephone survey in 2012/2013, only 22% of participants from households with children <1 year of age reported having received pertussis vaccination in the preceding 10 years.⁴⁷ In addition, there is evidence that cocoon strategies are relatively inefficient at incidence levels comparable to Germany.^{48–50} Finally, acellular vaccines may not prevent asymptomatic transmission.^{10,51}

Our study is limited by use of 2-source CRC, which requires fulfillment of some key prerequisites¹⁶ not entirely met in our study setting. While the requirement of a closed population is rarely completely fulfilled, both mortality and migration in infants are low in Germany. In particular, it is unlikely that infants would travel in or out of Germany during a disease episode. Although complicated by lack of unique identifiers, the prerequisite of matchability of individuals from the 2 data sources was largely fulfilled. We were able to define clear criteria for matching based on available variables in the 2 systems that resulted in a very low number of cases with ambiguous matching. However, it is likely that our 2 sources were not independent because the same clinicians are required to report a case to both systems. Use of a third data source permits adjusting for source dependence,⁵² but an additional case-based data source was not available in Germany. If in fact clinicians were reporting conscientiously to both surveillance systems (positive dependency),

we may have underestimated incidence. The high degree of under-reporting to ESPED suggests that this was not the case. Overestimation would result if reporting to one system made reporting to the other less likely (negative dependency). However, as not only clinicians, but also laboratories are required to notify cases to SurvNet, and laboratory notification is largely automated, this scenario also seems unlikely. Finally, the prerequisite of homogenous capture probabilities across all individuals in the population was not always met in our study. Although cases from the 2 parts of Germany were equally likely to be reported to ESPED, we observed a lower reporting probability to the statutory surveillance system from western states, where notification only recently became mandatory. We also found a higher degree of underreporting to ESPED for cases ≥3 months of age than for younger cases. Nonetheless, in our analyses stratified by region and study year, the incidence estimates based on the sum of stratified estimates differed only marginally from the crude estimate (Table 3). Results of our stratified analysis by age, however, suggest that our crude estimate may be an underestimate, with a point estimate for annual pertussis incidence for infants based on the sum of the cases in the strata of 54 hospitalizations/100,000 (Table 3). Thus, overall, we believe the results of our CRC analysis provide a conservative estimate of pertussis requiring hospitalization in infancy in Germany. Our estimated crude incidence of 50 hospitalizations/100,000 infants was also higher than the incidence of hospitalizations for pertussis in infants calculated based on official aggregated hospital discharge statistics⁵³—a mean of 300 pertussis hospitalizations annually from 2013 to 2015 or 42 hospitalizations/100,000 infants. However, the difference was less than that compared with incidence based on statutory surveillance data (Fig. 2). In any case, available aggregate hospital discharge data do not provide important information required for a comprehensive understanding of disease burden in infants, such as age in months, diagnostic confirmation, vaccination status or disease severity.

One final limitation of our study involves infants diagnosed with only a single measurement of elevated PT antibodies.^{54,55} However, because polymerase chain reaction or cultural confirmation of pertussis are preferred in infants, this applies only for a small proportion of infants. High levels of maternal antibodies are only

rarely seen in infants whose mothers did not receive a pertussis antigen vaccine during pregnancy,^{56,57} and only 3 of the serologically confirmed cases had been vaccinated (Table 1).

In conclusion, we found a high incidence of pertussis requiring hospitalization in infants during an interepidemic period of the pertussis cycle. A high proportion of cases was too young to have been protected through pertussis vaccination recommended from 2 months of age. In view of the poor implementation of the cocoon strategy in Germany and the observed effectiveness of maternal vaccination in other countries, these findings suggest that maternal vaccination would be an effective strategy to prevent pertussis in young infants in Germany and should, therefore, be assessed by STIKO. In addition, about a quarter of the affected infants were old enough to have received at least their first pertussis vaccine dose, highlighting the importance of timely vaccination in infancy. Finally, this study should be repeated in a few years to confirm the anticipated further improvement in case ascertainment in western federal states.

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