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Severe underestimation of pertussis related hospitalizations and deaths in the Netherlands: A capture-recapture analysis

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ABSTRACT

Ojective: Despite vaccination, pertussis has remained endemic, sometimes leading to severe disease. We aimed to quantify the completeness of reporting (CoR) of pertussis hospitalizations and deaths in the Netherlands.

Study design: CoR was estimated using capture-recapture analyses. Hospitalizations (2007–2014) from the National Registration Hospital Care (hospital data) were matched to the notifiable Infectious Disease case registry (notifications) providing (month and) year of birth, gender and postal code. Deaths (1996–2014) from Statistics Netherlands (death registry) were matched to notifications using gender, age, year of death and notification date. Cases <2 years (y) and ≥2y were analysed separately. Chao's estimator estimated the total population, which was used to calculate CoR.

Results: Using strict matching criteria, we found 461 matches among 876 (hospital data) and 757 (notifications) hospitalizations <2y. The population estimate of hospitalized infants was 1446, resulting in CoR between 52% and 61%. For hospitalizations ≥2y (246; hospital data and 264; notifications) 43 matches were found, with a population estimate of 1512 and CoR between 16.5% and 22%.

Among thirteen (death registry) and eight (notifications) deaths <2y, seven cases overlapped. The population estimate was 16. CoR of the two sources was 50–81%. With two (death registry) and eight (notifications) deaths ≥2y without overlap, the population estimate was 26 and CoR 8–31%.

Conclusion: Results showed substantial underestimation of pertussis hospitalizations and deaths. This has to be taken into account in evaluation of current and future immunization programs.

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1. Introduction

Pertussis is a respiratory tract infection, commonly caused by *Bordetella pertussis* [1]. Typical pertussis illness including paroxysmal coughing mainly affects young children who are not (fully) vaccinated, who are also at the highest risk for severe morbidity and mortality. Still, pertussis can also occur as a milder infection or even asymptomatic in older children, adolescents and adults.

To prevent severe disease and mortality, routine vaccination against pertussis was introduced in the National Immunization Program of the Netherlands in 1957 [2]. Up to 2005, a whole cell pertussis combination vaccine was used [3], but at present, an acellular pertussis combination vaccine, targeting diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* type b, and Hepatitis B (DTaP-IPV-Hib-HBV) at 2, 3, 4 and 11 months of age is offered, with vaccination coverage above 95% [4]. Since 2001, the National Immunization Program also includes an acellular pertussis booster for 4-year-olds because of the observed high incidence of pertussis in this age group [5]. The vaccination coverage of the booster amounts to approximately 92% [4].

Despite these changes and uninterrupted high vaccine coverage from 1980 onwards, an increase of pertussis is observed, not only in the Netherlands, but also worldwide [6,7]. This increase occurs in all ages, with epidemic peaks every 2 to 3 years [3]. Surveillance data also show that infants, too young to be (fully) vaccinated, show increasing pertussis incidence rates from 2005 onwards with 64 (2013) and 222 (2014) notifications per 100,000.

To evaluate the potential impact of vaccination strategies, adequate data on morbidity of severe pertussis infection and mortality caused by pertussis are essential. However, different sources to assess severe morbidity and mortality vary in their completeness of reporting [8,9]. Therefore, the aim of this study is to quantify the completeness of reporting (CoR) of hospitalization and death caused by pertussis in the Netherlands by means of capture-recapture analyses.

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2. Methods

2.1. Setting

Reports of pertussis were derived from three databases with national coverage.

Data of the National Registration Hospital Care (hospital data) and of the 'Online System for Infectious diseases Reporting within the Infectious diseases Surveillance System' (notifications) were used in the analysis of hospitalizations. CoR was studied over the period from 2007 up to 2014, during which all pertussis vaccines within the National Immunization Program were acellular and date of birth was available in hospital data.

Data of notifications and of Statistics Netherlands (death registry) were used in the analysis of deaths. CoR was studied between 1996 and 2014. The case definition for pertussis has remained the same since 1996 [8].

No medical ethical approval was needed because only routinely collected data were used and people were not imposed to specific deed.

2.2. Data sources

2.2.1. National registration hospital care data (hospital data)

Hospital data is collected by Dutch Hospital Data. This database registers medical and administrative information from hospitalized patients in the Netherlands [10]. From 2007 onwards, the rate of nationally participating hospitals fluctuated around 90% [11]. Main diagnosis as well as date of birth, four digits of the zip code, gender, and date of hospital admission is registered. Cases within the hospital data were included for analysis when a patient was diagnosed with whooping cough according to the International Classification of Diseases (ICD) codes, i.e. ICD-9 0330 or ICD-10 A370 (caused by *B. pertussis*), ICD-9 0331 or ICD-10 A371 (*B. parapertussis*), ICD-9 0338 or ICD-10 A378 (other specified organism) or ICD-9 0339 or ICD-10 A379 (other unspecified organism).

2.2.2. Notification data

Notification data is part of the national surveillance system for notifiable infectious diseases in the Netherlands. Information on reported cases in the system includes year of birth, four digits of the zip code, gender, date of disease onset and vaccination status. Month of birth is only provided in cases < 2y of age. Furthermore, information on hospitalizations or death of the reported case is registered if known. Cases were included when a patient was notified for pertussis. Criteria for notification are 1. Clinical symptoms of pertussis (i.e. coughing for at least two weeks or either paroxysmal coughing, inspiratory whooping or vomiting after coughing) and 2. Laboratory confirmation using culture, PCR or serology or 3. Close contact to a laboratory confirmed case in the previous three weeks. Only patients which were hospitalized or death according to the notification system, were included in the respective analyses.

2.2.3. Data of Statistics Netherlands (death registry)

Statistics Netherlands collects and presents data and national statistics on societal and demographic aspects for scientific and political purposes [12]. Information on deceased individuals includes cause of death, gender, year of death, and age or age category at death. Cases were included for analyses when pertussis was reported as the cause of death (ICD-10 code A37).

2.3. Linkage procedure

2.3.1. Hospitalized cases

Prior to the actual linking procedure, the database of hospitalizations was checked for double entries of the same individual based on date of birth, gender, four digits of the zip code, date of hospitalization, date of discharge, and hospital code. Only first hospitalizations were included.

Furthermore, about 25% of notifications were supplemented with an imputed day of disease onset because this was missing. Here, the median interval between disease onset and notification from the records with a known day of disease onset (i.e. 43 days) was subtracted from the notification date.

For infants <2y, matching variables were four digits of the zip code, gender, and month and year of birth. For cases ≥2y, matching variables were identical, though without the month of birth. Matched hospitalized cases were classified as certain, likely, probable and unlikely matches (Table 1). Cases with identical matching variables and a maximum of 30 days (d) between a known day of disease onset and hospitalization were classified as certain matches. Cases with identical matching variables and an imputed day of disease onset were classified as likely matches if the interval between disease onset and hospitalization was 30d at most. Cases with an interval of 31–45d were classified as probable matches if all matching variables were identical irrespective of a known or imputed day of disease onset.

Furthermore, if there was one logical deviation in matching variables, e.g. typing errors like zip code 8013 instead of 8031, and the interval between disease onset and hospitalization was 45d at most, likelihood of matching was lowered by one category. Likewise, in case of two deviations the likelihood decreased by two categories.

First, certain matches were matched using the statistical software. Remaining cases were categorized according to matching criteria manually by two researchers independently (JH and NvdM). For these manually matched records, the Kappa statistic for observer agreement was calculated and conflicting cases were discussed until agreement was reached [13]. Analyses were performed using the number of matched cases after full agreement.

2.3.2. Deceased cases

Deceased cases were linked manually across the notifications and the death registry using the variables gender, year of death (available in death registry), date of notification (available in notifications), and age. Cases were linked when the date of notification was within the year of death, and all other variables were identical.

2.4. Statistical analyses

Descriptive statistics were performed regarding age and gender of included cases. Capture-recapture analyses were performed using Chao's lower bound estimator for total population size [14,15]. The total population size (N) including the unreported cases, is estimated by identifying the number of unique cases in each source and the number of overlapping cases [14,16]. The applied formula and corresponding 95% confidence interval (95% CI) are defined by:

Table 1
Combinations of criteria per matching category.

	0 deviations	1 deviation	2 deviations
Known disease onset, <31 days from hospitalization	Certain match	Likely match	Probable match
Imputed disease onset, <31 days from hospitalization	Likely match	Probable match	Unlikely match
Known disease onset, 31–45 days from hospitalization	Probable match	Unlikely match	No match
Imputed disease onset, 31–45 days from hospitalization	Probable match	Unlikely match	No match

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