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# Pertussis epidemiology including direct and indirect effects of the childhood pertussis booster vaccinations, Norway, 1998–2019

Elina Seppälä [a,b,*], Anja Bråthen Kristoffersen [a], Håkon Bøås [a], Didrik Frimann Vestrheim [a], Margrethe Greve-Isdahl [a], Birgitte Freiesleben De Blasio [a], Anneke Steens [a,1]

[a] Norwegian Institute of Public Health, Lovisenberggata 6 & 8, 0456 Oslo, Norway
[b] European Program for Intervention Epidemiology Training, European Centre for Disease Prevention and Control, Gustav III:s Boulevard 40, 169 73 Solna, Sweden

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ABSTRACT

*Background:* The acellular pertussis vaccine has been used in the Norwegian national immunisation program since 1998. Following an increase in pertussis incidence in all age groups, booster doses were introduced for 7–8-year-olds in 2006, and for 15–16-year-olds in 2013. We assessed the effects of the booster doses on pertussis incidence in different age groups to inform potential changes in vaccination policy.
*Methods:* We included all pertussis cases notified to the Norwegian Surveillance System for Communicable Diseases in 1998–2019. We calculated annual incidence rates (IR, per 100,000 inhabitants) by age group. We estimated average annual changes in IRs (incidence rate ratios, IRR) for each age group for 2006–2012 and 2013–2019 using Poisson regression.
*Results:* In 1998–2019, 74,675 cases of pertussis were notified. Coinciding with booster introduction, between 2006 and 2012 the IR decreased among 8–15-year-olds (from 433 to 199/100,000, IRR 0.89 [95% confidence interval 0.88–0.90]). A similar decrease was seen between 2013 and 2019 among 16–19-year-olds (from 171 to 77/100,000, IRR 0.84 [0.82–0.86]). There was no significant change in IRs among children < 1 year of age between 2006 and 2012 (IRR 0.99 [0.95–1.04]) or 2013–2019 (IRR 0.96 [0.91–1.02]). The IR decreased in both periods among adults aged 20–39 and 40+ (IRR 0.94 [0.93–0.95] and 0.92 [0.91–0.92] in 2006–2012; IRR 0.97 [0.96–0.99] and 0.97 [0.96–0.99] in 2013–2019, respectively). Despite steady, high vaccination coverage, in 2013–2019, there was an increase in the IR among children aged 1–7 (63 to 86/100,000, IRR 1.05 [1.03–1.07]) and 8–15 years (88 to 122/100,000, IRR 1.08 [1.06–1.10]).
*Conclusions:* Pertussis booster doses have offered direct protection in the targeted age groups. Our findings suggest indirect protection in adults, while the incidence in infants hasn't changed. The recent increase in IRs among 1–15-year-olds warrants close monitoring and further evaluation of the vaccination schedule.


## 1. Introduction

Pertussis (whooping cough) is a highly transmissible respiratory infection caused by the bacterium *Bordetella pertussis*. The disease is endemic worldwide and continues to be a public health concern despite established pertussis immunisation programs with high coverage. Infants and young children are at highest risk of severe disease and death, especially during their first months of life [1].

Many countries, including Norway, have reported an increase in pertussis incidence during the past two decades [2,3]. Furthermore, in recent years, Norway and some other high-income countries have reported a shift in the age distribution of pertussis towards older age groups, namely adolescents and young adults [1,3]. The observed age shift may be partly explained by increased recognition of the less typical clinical manifestations among older subjects, improved sensitivity of laboratory diagnostics and improved sensitivity of surveillance. Additionally, waning of vaccine-derived immunity and reduced natural boosting of immunity by circulating *B. pertussis* are likely to increase the susceptibility of adolescents and adults [1,4]. The observation is worrisome, as a shift of the peak in incidence to child-bearing age may increase the risk of infection among new-borns [5].

* Corresponding author at: Norwegian Institute of Public Health, Lovisenberggata 6 & 8, 0456 Oslo, Norway.
*E-mail address:* elina.seppala@fhi.no (E. Seppälä).
[1] Present address: National Institute for Public Health and the Environment, Antonie van Leeuwenhoeklaan 9, 3721 BA Bilthoven, The Netherlands.

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As the disease is most severe in infants and young children, the main aim of the pertussis vaccination program is to prevent disease in this age group. In Norway, a whole cell pertussis (wP) vaccine was used from 1952 to 1997. In 1998, it was replaced by an acellular (aP) vaccine consisting of purified components of *B. pertussis*. The primary series includes three doses given at the age of 3, 5 and 12 months. Following a national outbreak of pertussis in 2004 that affected especially adolescents as well as younger children and infants, which lead to two infant deaths, all birth cohorts primed with the aP vaccine have been offered booster doses. A school-age booster dose at 7–8 years was introduced in 2006. Despite a decrease in incidence in the targeted age group, the introduction of the booster dose did not have a significant protective herd effect on infants and the incidence of pertussis also continued to be high among teenagers, with biannual peaks [3]. Since school year 2013/14, an adolescent booster dose at the age of 15–16 years has been added to the program. Lavine et al. predicted that the second booster would offer only short-lived immunity to adolescents and no indirect protection to infants and young children [3]. Furthermore, they found that the seasonality in school-aged children was different from the seasonality in pre-school children, and indirect protection was seen only within an age-cohort and not between age-cohorts [3].

The aim of this study is to assess the effect of adding the boosters to the childhood immunisation program on the pertussis epidemiology in Norway in 1998–2019. We assessed changes in incidence rate (IR), presence of indirect protection, shifts in age-profile and transmission between age groups. The results will be used to inform potential changes in vaccination policy.

## 2. Methods

### 2.1. Study population and data sources

In this study, we included all cases of pertussis reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) between 1 January 1998 and 31 December 2019. MSIS contains mandatory case-based notifications of pertussis from physicians and laboratories for all age groups since 1993, with incomplete reporting during the first few years. A pertussis case is defined as a person with a clinical picture compatible with pertussis, and microbiologically confirmed pertussis infection by detection of *B. pertussis* by isolation or nucleic acid examination or serological evidence of infection, or an epidemiological link to a laboratory confirmed case [6]. We retrieved data on demographic characteristics (including age and year of birth), diagnostics (including month and year of sampling), and disease severity for each case. For those persons who were reported to MSIS more than once, we defined true reinfection as an episode occurring > 12 months later than the previous infection. We considered all true reinfections as independent cases. Episodes reported within one year after the previous episode were excluded.

We retrieved aggregated population data by year and age from the National Population Register, provided by Statistics Norway [7]. We also obtained annual vaccination coverage data for 2-, 9- and 16-year-olds, reflecting the coverage of the primary series, first and second boosters, for years 2002–2019, from publicly available reports on the childhood immunisation program [8].

### 2.2. Data analysis

We described cases in terms of age, sex, month, and year of diagnosis, testing method, and disease severity as defined by hospitalisation and/or death. We calculated incidence per 100,000 inhabitants by year of testing, both overall and by age groups 0, 1–7, 8–15, 16–19, 20–39 and 40 + years, which were defined based on the vaccination schedule. To assess direct and indirect effects of vaccination, we estimated average annual changes in IR (incidence rate ratios, IRR) with 95% confidence intervals (95% CI) for each age group for the periods before booster introduction (1998–2005), after introduction of the school-age booster (2006–2012) and after introduction of the adolescent booster (2013–2019) using Poisson regression. As infants and young children have highest risk of severe disease, we calculated hospitalisation rates, defined as the number of hospitalised pertussis cases per 100,000 inhabitants, and estimated average annual changes for the aforementioned periods among < 1-year-olds and 1–4-year-olds. To assess changes in age distribution, we calculated the mean number of cases per year by age for the three periods. As proxy for transmission between age groups, we used the distribution of cases over a year (proportion per month) per age group and determined the correlation between the age groups using Pearson's correlation. We ran this analysis for the entire study period as well as the periods 1998–2005, 2006–2012 and 2013–2019.

We conducted the analyses in StataSE 16 and R-4.0.4 [9]. Ethical approval was granted by Regional Committees for Medical and Health Research Ethics South East (reference number 47332). The need for informed consent was waived.

## 3. Results

From January 1998 to December 2019, altogether 74,675 cases of pertussis were notified to MSIS. A median of 2,759 cases (min–max 922–6,599) were reported annually. The median age at time of infection was 19 years (lower–upper quartile 12–45 years), and 54% of all cases were female (Table 1).

### 3.1. Age-specific incidence rates and age distribution

The IR differed by age group and changed over time (Fig. 1A), with sudden trend changes seen in the cumulative incidence coinciding with booster introductions (Fig. 1B). The IR among the 8–15-year-olds increased over time to 433 cases/100,000 in 2006 but decreased significantly to 199/100,000 in 2012 (IRR per year for 2006–2021: 0.89 [95 %CI 0.88–0.90]) (Fig. 2) coinciding with the booster introduction in the 7–8-year-olds. A similar decrease was seen between 2013 and 2019 among the 16–19-year-olds (from 196 to 86/100,000, IRR 0.83 [95 %CI 0.81–0.85]), coinciding with the booster introduction in the 15–16-year-olds. There was no significant change in IRs among children < 1 year of age between 2006 and 2012 (IRR 0.99 [95 %CI 0.95–1.04]) or 2013–2019 (IRR 0.96 [95 %CI 0.91–1.02]). The IR decreased in both periods among adults aged 20–39 and 40+ (Fig. 2). During the period 2013–2019, the IR among children aged 1–7 years increased from 63 to 86/100,000 (IRR 1.05 [95 %CI 1.03–1.07]) and for 8–15-year-olds from 88 to 122/100,000 (IRR 1.08 [95 %CI 1.06–1.10]). At the same time, the vaccination coverage in the population was stable at around 93–95% for the primary series and 91–95% for the school-age booster.

The age distribution of cases changed over time (Fig. 3). After the introduction of the school-age booster, there was a more prominent shift towards adolescents, with an increase in the mean annual number of cases especially in those aged between 13 and 18 years (Fig. 3B). The introduction of the adolescent booster was followed by a decrease in the mean annual number of cases among adolescents, resulting in a more even age distribution, with less prominent peaks among young children, adolescents, and young adults (Fig. 3C). In this period and especially in 2016–2019, the highest annual numbers of cases were reported among children and adolescents approaching the age of booster vaccination (Supplementary figure S2).

**Table 1**
Characteristics of the cases of pertussis reported to the Norwegian Surveillance System for Communicable diseases (N = 74,675), Norway, 1998–2019.

| | 1998–2005 | | 2006–2012 | | 2013–2019 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| **Age group** | | | | | | | | |
| 0 | 535 | 2 | 426 | 1 | 260 | 2 | **1,221** | **2** |
| 1–7 | 2,802 | 12 | 2,462 | 7 | 2,391 | 14 | **7,655** | **10** |
| 8–15 | 8,215 | 34 | 9,601 | 29 | 3,547 | 21 | **21,363** | **29** |
| 16–19 | 1,774 | 7 | 4,235 | 13 | 2,359 | 14 | **8,368** | **11** |
| 20–39 | 3,711 | 15 | 5,611 | 17 | 3,309 | 19 | **12,631** | **17** |
| 40+ | 7,124 | 29 | 11,067 | 33 | 5,246 | 31 | **23,437** | **31** |
| Total | 24,161 | 100 | 33,402 | 100 | 17,112 | 100 | **74,675** | **100** |
| **Sex** | | | | | | | | |
| Male | 10,917 | 45 | 15,481 | 46 | 7,782 | 45 | **34,180** | **46** |
| Female | 13,244 | 55 | 17,921 | 54 | 9,330 | 55 | **40,495** | **54** |
| Total | 24,161 | 100 | 33,402 | 100 | 17,112 | 100 | **74,675** | **100** |
| **Diagnostic method**[1] | | | | | | | | |
| Culture | 554 | 4 | 65 | 0 | 0 | 0 | **619** | **1** |
| Serology | 11,382 | 88 | 12,948 | 61 | 3,675 | 22 | **28,005** | **55** |
| PCR | 1,030 | 8 | 8,368 | 39 | 13,072 | 78 | **22,470** | **44** |
| PCR and serology | 0 | 0 | 0 | 0 | 3 | 0 | **3** | **0** |
| No/negative test | 8 | 0 | 4 | 0 | 9 | 0 | **21** | **0** |
| Total | 12,974 | 100 | 21,385 | 100 | 16,759 | 100 | **51,118** | **100** |
| **Hospitalisation**[2] | | | | | | | | |
| Yes | 406 | 32 | 221 | 18 | 164 | 14 | **791** | **21** |
| No | 862 | 68 | 1,038 | 82 | 1,023 | 86 | **2,923** | **79** |
| Total | 1,268 | 100 | 1,259 | 100 | 1,187 | 100 | **3,714** | **100** |

[1] See supplementary figure S1 for more information on the changes in testing methods and completeness of data. Note that reporting of the variable was not complete; 32% was missing.
[2] Includes *only 0–4-year-olds.*

### 3.2. Hospitalisations and deaths

For children aged 0–4 years, data on hospitalisation was available for 97% (n = 3,714) (Table 1). Of them, 21% (n = 791) were hospitalised (Fig. 4). Fifty-three percent (n = 635) of the cases under 1 year of age were hospitalised, accounting for 80% of all hospitalised cases among the 0–4-year-olds (Fig. 4). The hospitalisation rate among children < 1 year varied between 114 and 51/100,000 in the years 1998–2005 and decreased subsequently to 24/100,000 in 2019, whereas the rate among 1–4-year-olds was lower and remained more stable, varying between 6.2/100,000 recorded in 1998 and 0.8/100,000 in 2013 (Fig. 4). Apart from an annual decrease in hospitalisation rate among children < 1 year in 2006–2012 (IRR 0.93 [95 %CI 0.86–1.00]), the annual changes in hospitalisation rates in the three periods were not statistically significant in either age group (data not shown). The proportion of hospitalised cases among children < 1 year decreased from a high of 74% in 1998 to a low of 33% in 2016, after which it varied between 35% and 48% in 2017–2019 (Fig. 4). The proportion hospitalised among 1–4-year-olds was at its highest in 2002 with 6%, after which it varied between 1% and 5% during the rest of the study period.

Data on survival was available for 66% of the 0–4-year-olds; of them, 0.1% (n = 2) died because of pertussis. Both deaths occurred among children < 1 year of age before the introduction of the boosters. One additional pertussis-associated death was reported in a case ≥ 40 years of age.

### 3.3. Correlation of the distribution of cases throughout the year between age groups

The distribution of cases throughout each year, assessed as the proportion of cases diagnosed per month, was significantly correlated between different age groups (Fig. 5; see Supplementary figure S3 for more detailed information). The strongest correlation was observed between 20 and 39-year-olds and ≥ 40-year-olds (Pearson correlation coefficient 0.76, 95 %CI 0.70–0.81), 1–7-year-olds and 8–15-year-olds (0.73, 95 %CI 0.66–0.78), and 8–15-year-olds and ≥ 40-year-olds (0.65, 95 %CI 0.57–0.71) indicating that these pairs of age groups likely transmit pertussis to each other. The correlation between children < 1 year and other age groups was weak: it was somewhat stronger between children < 1 year and 1–7-year-olds (0.45, 95 %CI 0.34–0.54) and 8–15-year-olds (0.40, 95 %CI 0.29–0.50), and it was weakest with the 16–19-year-olds (0.19, 95 %CI 0.07–0.30). The correlations between different age group pairs were strongest in the period 2006–2012, whereas they became weaker in 2013–2019 (Fig. 5).

## 4. Discussion

The childhood immunisation program against pertussis and the pertussis epidemiology in Norway have changed during the past two decades. In this study, we found a decrease in the IRs after the introduction of the aP booster doses in the targeted age groups, i.e., the 8–15-year-olds in 2006–2012, and the 16–19-year-olds in 2013–2019, suggesting direct protection. When looking at indirect protection, we found a decrease in IRs among adults but not among infants, the primary target group of the childhood immunisation program. The lack of indirect protection from the boosters to infants may be explained by the weak correlation in seasonality between adolescents and infants, suggesting limited transmission between those age groups.

Our findings on the direct effect of the school-age and adolescent booster vaccinations on the pertussis incidence are in line with previous studies, which have demonstrated the effectiveness of the aP booster doses in different countries [10–15]. The indirect effects among non-targeted age groups are heterogenous. It should be noted, though, that the population itself is heterogenous concerning pertussis immunity; it consists of those who have been offered the aP vaccine (born in 1998 and onwards), those who were immunised with the wP vaccine (born between 1952 and 1997) and those who lived in the pre-pertussis vaccination era when

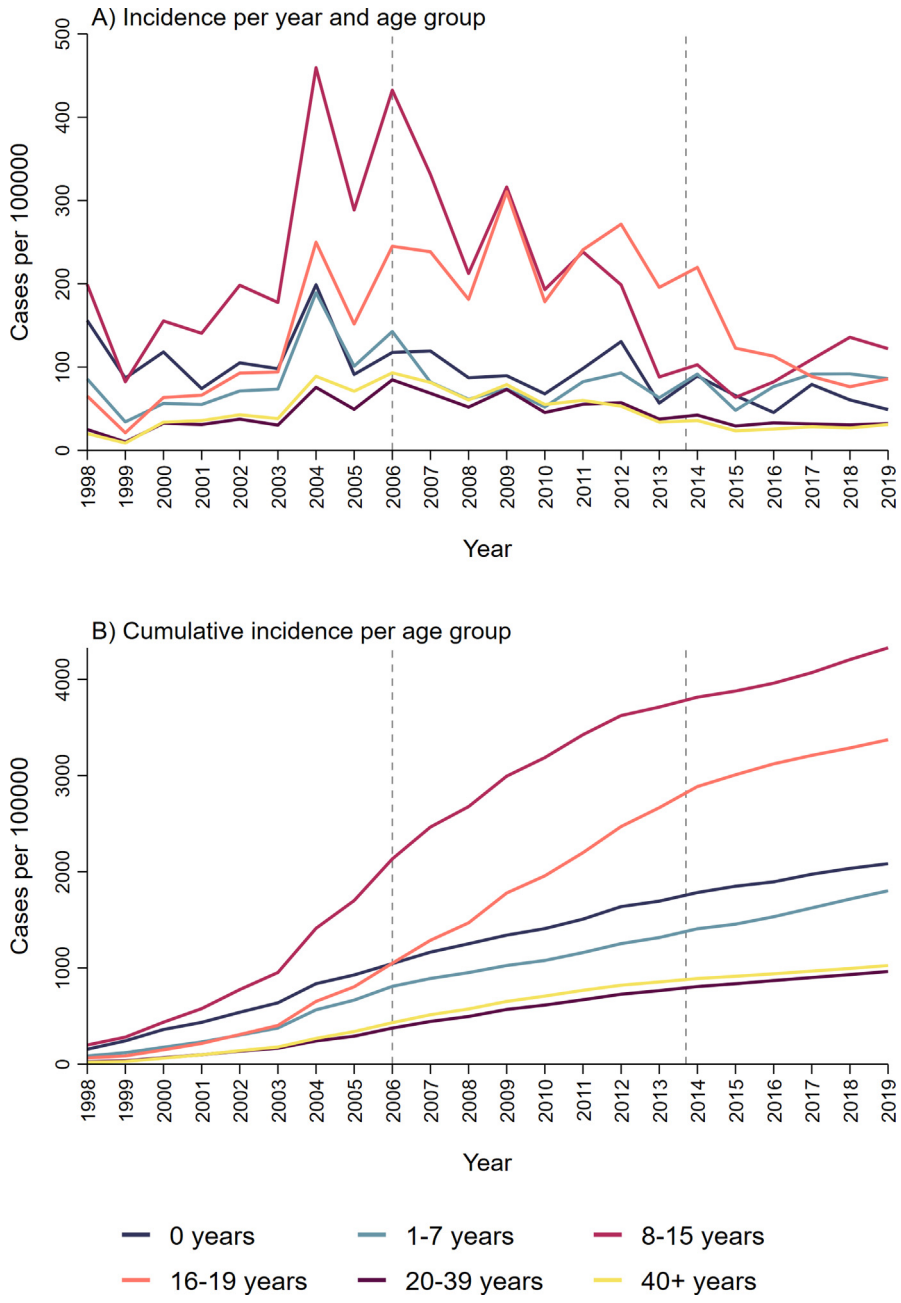


**Fig. 1.** Annual (A) and cumulative (B) incidence rate of pertussis by age group, Norway, 1998–2019. The vertical dashed lines indicate the introduction of the booster doses in 7–8-year-olds (2006) and in 15–16-year-olds (school year 2013/2014).

exposure to natural infection happened frequently (born before 1952). The IRs among infants were stable over time, suggesting that no indirect protection took place, which is in agreement with other studies [4,16,17]. Among 1–7- and 8–15-year-olds, we observed an increase in IRs towards the end of the study period even though the vaccination coverage of the primary series and the school-age booster remained high. While we are not aware of any obvious reasons for this increase, such as localized outbreaks, this increase is not completely unexpected either. In addition to the shorter duration of immunity induced by aP vaccines, these vaccines are thought to have limited ability to reduce the circulation of pertussis even in highly vaccinated populations as aP vaccines do not induce a valid mucosal immune response in the way that wP vaccines or natural infection do [4,16,17]. More circulation in these age groups may therefore lead to more symptomatic infections. Furthermore, as shown in many countries [18–21], a shift in allelic profiles of the *B. pertussis* population has taken place over time [22]. Recently circulating clones of *B. pertussis* harbour allelic profiles of antigens that mismatch with components of the aP vaccines. Whether this switch contributes to the recent increase in pertussis incidence in the age groups 1–7 and 8–15 is not yet known. It can thus be expected that cases of pertussis will continue to occur in the population, also among (aP) vaccinated individuals. Contradictory to the recent increases in the 1–7- and 8–15-year-olds, the IRs of the age-groups 20–39 and 40 + years, including those of child-bearing age, decreased after booster introductions. We also observed significant correlations in the monthly distribution of cases between adults and the age groups targeted by the

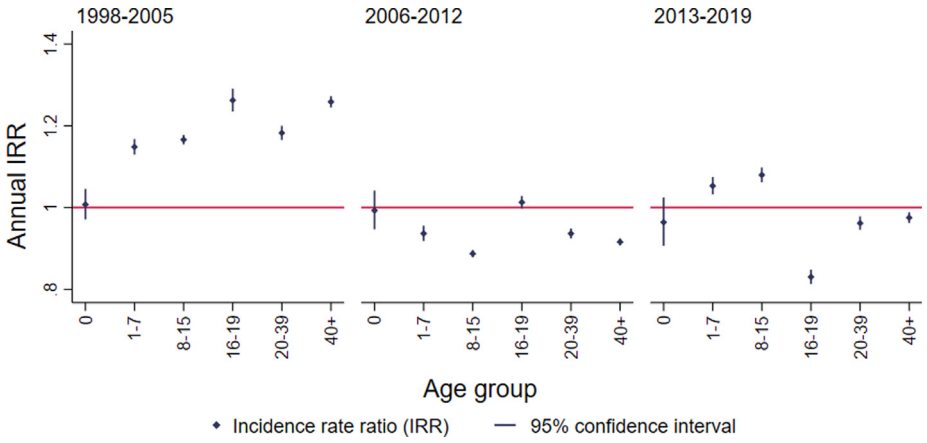


**Fig. 2.** Incidence rate ratio (IRR) per year (dots) and their 95% confidence intervals (lines) of pertussis by age group and period (before boosters, after the school-age booster and after the adolescent booster), Norway, 1998–2019. The red horizontal line indicates an IRR of 1, i.e., no change in incidence rate.

boosters, suggesting pertussis transmission between these age groups. The adults may therefore have profited from indirect protection from the booster vaccinations. However, the fact that these age groups have been vaccinated with wP vaccines or were already living in the pre-immunisation era with higher exposure, may also play a role; with their different immunological background, increased circulation may result in natural boosting. Alternatively, some adults may have been vaccinated themselves, as a booster dose of pertussis-containing vaccine has been recommended for adults every ten years since 2014. Reliable vaccination coverage data for adults is not available, since registration of adult vaccinations to the Norwegian Immunisation Registry required informed consent up to the year 2020. However, seroprevalence studies among 20–39- and 40–59-year-olds have indicated that at least 4–25% of them had recently been exposed and/or immunised [23,24]. Thus, we cannot conclude that the decrease in incidence among adults in 2006–2019 was just the result of indirect protection from the boosters; boosted immunity due to vaccinations and/or natural boosting may (also) play a role.

The Norwegian study by Lavine et al. found no change in the IR of pertussis among infants following the introduction of the school-age booster and predicted that the adolescent booster would not offer any indirect protection to infants either [3]. Our findings on the unchanged IRs among infants as well as the findings of studies conducted in Israel and the United States [10,14,25] support this prediction. Nevertheless, we observed a significant decrease in the hospitalisation rates among infants after the introduction of the school-age booster. While no recommendation was in place for maternal vaccination against pertussis during the study period, guidelines on prophylactic administration of antibiotics to unvaccinated or partly vaccinated children who are household contacts of pertussis cases were updated after the 2003–2004 outbreak, which may have contributed to the decrease in hospitalisation rates among infants. Furthermore, the proportion of hospitalised cases among all cases in this age group also decreased. While this may be a consequence of increased testing of milder cases due to increased awareness of pertussis after the 2003–2004 outbreak, we cannot rule out that the change in hospitalisation rate may also reflect changes in hospitalisation practices, and not purely the effect of the immunisation program. Other studies have, however, reported similar findings of decreased hospitalisation rates among infants after the introduction of pre-school age boosters [12,26]. We observed no further decrease in hospitalisation rates among infants after the introduction of the adolescent booster. This might be explained by a lower rate of transmission between infants and 16–19-year-olds, as suggested both by our findings on the weak correlation of monthly distribution of pertussis cases between infants and 16–19-year-olds. It is possible, though, that infants are more likely to be diagnosed with pertussis throughout the year while smaller outbreaks among adolescents with atypical clinical pictures may be undetected, leading to differences in the monthly distribution of cases between these two age groups. Findings from the United Kingdom, however, suggest low contact rates between these age groups [27].

One limitation of our study is that it is based on passive notifications of pertussis, and that information on hospitalisation is usually recorded at the time of testing, meaning that the number of hospitalisations may also have been underestimated. Even though testing for pertussis has been free of charge in Norway since 1995 [28], the extent of underestimation of the true incidence of pertussis and hospitalisation rates may have differed between different time periods and age groups. The changes in laboratory diagnostics may also have introduced bias into our study. The use of diagnostic methods changed at a different pace among different age groups, and different laboratories and hospitals. Serological methods were predominantly used in the 1990 s until the early 2000 s. In 2011, the cut-off value for positivity was increased from 80 to 100 IU to enhance the specificity of the test (Audun Aase, personal communication). The use of PCR gradually increased since 2002, first among the youngest age groups, and since 2012 the majority of laboratory confirmed pertussis cases have been diagnosed by PCR. Several factors made it difficult to assess the possible effects of changes in testing methods on our results. The data on diagnostic methods for cases > 15 years of age were incomplete especially in 2004–2008, when pertussis incidence was high. In addition, it is recommended that the diagnostic method should be chosen based on the duration of symptoms [29–31]. The data on the time between symptom onset and sampling was highly incomplete and we lacked data on negative test results altogether. Furthermore, the World Health Organization recommends that serology should not be used during the first year after pertussis vaccination [31,32]. Since we did not have data on immunization history for the cases, we could not assess the possibility of false positive serological results.

In conclusion, our findings indicate that the pertussis booster doses have offered direct protection in the targeted age groups. Yet we observed an increase in incidence among 8–15-year-olds towards the end of our study period. Our results do not show indirect protection of young children, and the incidence in 1–7-year-olds increased towards the end of the study period. Importantly,

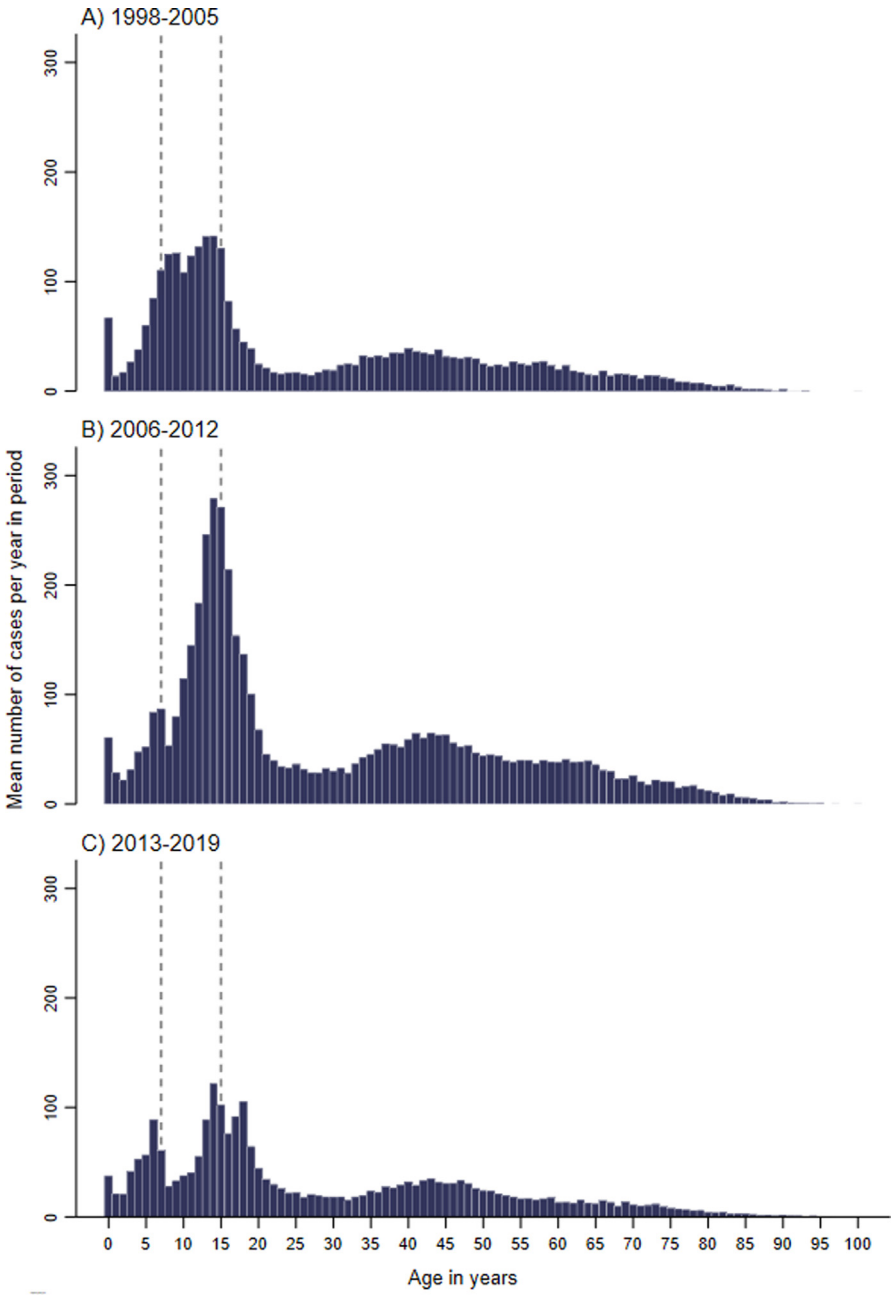


**Fig. 3.** Mean number of pertussis cases by age in years, Norway, 1998–2005 (A), 2006–2012 (B; after introduction of the school-age pertussis booster dose at 7–8 years of age in 2006) and 2013–2019 (C; after introduction of the adolescent pertussis booster dose at 15–16 years of age in 2013). The dashed lines indicate the ages of 7 and 15 years.

we did not observe any negative effects in infants after the introduction of the boosters. Adults may have profited from indirect protection from the boosters. Nevertheless, the second booster dose was introduced only 6 years before the end of our study period, meaning that the full effect of the second booster on the young adults of childbearing age, and thereby also infants, remains to be seen. Further monitoring and research are required to gain an understanding of the duration of protection of aP booster doses, and to further evaluate the vaccination schedule in Norway.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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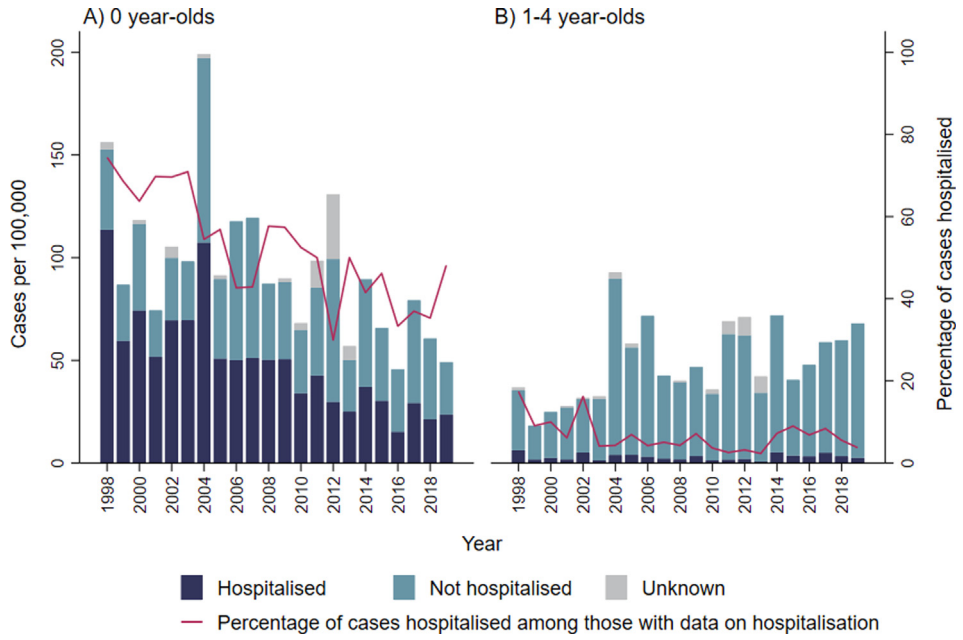


**Fig. 4.** Pertussis cases per 100,000 inhabitants by hospitalisation status (bars), and the percentage of all cases hospitalised (red line) by year of sampling, Norway, 1998–2019, among A: 0-year-olds and B: 1–4-year-olds.

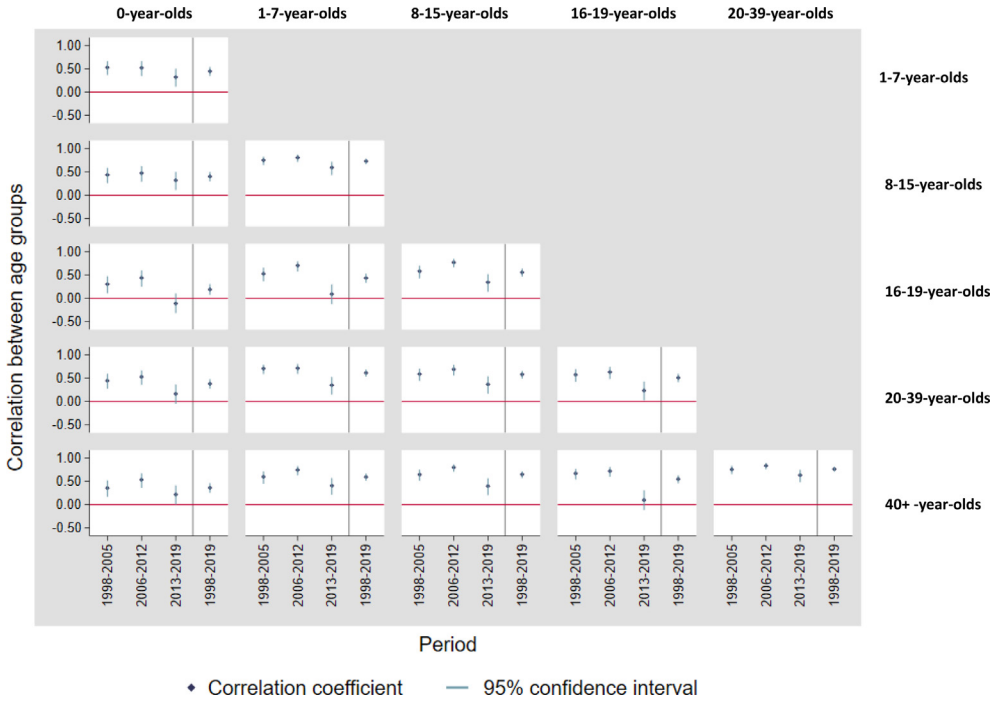


**Fig. 5.** Correlation between pairs of age groups in proportion of pertussis cases diagnosed per month in each year, Norway, 1998–2019. The dots represent the Pearson correlation coefficient, and the lines represent its 95% confidence intervals. The red horizontal line indicates no correlation.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.04.038.

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