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Review

Pertussis immunisation strategies to optimise infant pertussis control: A narrative systematic review

Elise Tessier [a,*], Daniel Newport [b,c], Anh Tran [a], Sophie G. Nash [a], Anna A. Mensah [a], Tian Yun Wang [a], Saran Shantikumar [b], Helen Campbell [a], Gayatri Amirthalingam [a,1], Daniel Todkill [a,b,1]

[a] UK Health Security Agency, London, UK
[b] Warwick Medical School, University of Warwick, Coventry, UK
[c] University Hospitals of Birmingham NHS Trust, Birmingham, UK

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ABSTRACT

Objective: Countries routinely offering acellular pertussis vaccine, where long-term protection is not sustained, have the challenge of selecting an optimal schedule to minimise disease among young infants. We conducted a narrative systematic review and synthesis of information to evaluate different pertussis immunisation strategies at controlling pertussis disease, hospitalisation, deaths, and vaccine effectiveness among young infants.

Methods: We conducted a review of the literature on studies about the primary, booster, and/or maternal vaccination series and synthesised findings narratively. Countries offering the first three doses of vaccine within six-months of life and a booster on or before the second year or life were defined as accelerated primary and booster schedules, respectively. Countries offering primary and booster doses later were defined as extended primary and booster schedules. All search results were screened, and articles reviewed and reconciled, by two authors. The Risk of Bias in Non-randomised Studies of Intervention tool was used to evaluate the risk of bias.

Findings: A total of 98 studies were included in the analyses and the following recurring themes were described: timing of vaccination, vaccine coverage, waning immunity/vaccine effectiveness, direct and indirect effectiveness, switching from an accelerated to extended schedule, impact of changes in testing. The risk of bias was generally low to moderate for most studies.

Conclusion: Comparing schedules is challenging and there was insufficient evidence to that one schedule was superior to another. Countries must select a schedule that maintains high vaccine coverage and reduced the risk of delaying the delivery vaccines to protect infants.

1. Introduction

Over 40 countries have replaced whole-cell pertussis vaccine (wP) with a less reactogenic highly purified acellular vaccine (aP) based on 1–5 pertussis antigens. Although aP vaccines are highly efficacious at protecting against severe disease, aP derived immunity wanes more rapidly compared with wP vaccination and is less effective at preventing infection and transmission. The World Health Organization (WHO) recommends that replacing wP with aP primary vaccination should only be considered where maternal or additional booster doses could be sustained and countries using wP should continue to do so for the primary programmes [1]. Infants too young for pertussis vaccination remain the most vulnerable population at risk of severe pertussis and death.

Over decades there has been debate on the optimal timing for primary pertussis immunisation to protect infants. The WHO recommends offering first dose of vaccine as early as six-weeks-old and no later than eight-weeks-old [1]. Most countries, have an accelerated schedule offering three doses of pertussis-containing vaccine within the first six months of life. Others use an extended schedule offering three doses within the first year of life [2–8].

This systematic review synthesises information on the impact of different primary and booster aP schedules on pertussis disease, hospitalisations, deaths, and vaccine effectiveness on infants and young

* Corresponding author at: UK Health Security Agency, 61 Colindale Avenue, London NW9 5EQ, UK.
E-mail address: Elise.Tessier@ukhsa.gov.uk (E. Tessier).
[1] Authors contributed equally.

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children. This review was registered on PROSPERO (record ID: 346609) [9].

2. Methods

2.1. Literature search

The systematic literature search was conducted using the databases Embase, Medline, Web of Science, Scopus, and Trip medical database up to April 27, 2023. The search strategy included thesaural and free text terms and synonyms for *Bordetella pertussis,* primary acellular pertussis vaccination, cases, hospitalisation, mortality, and vaccine effectiveness (Supplementary Table 1).

2.2. Eligibility criteria

No language filter was applied, however, only studies in English were included. Eligible studies for inclusion were observational studies, vaccine effectiveness and mathematical modelling studies. We excluded studies that evaluated solely maternal, adolescent, adult, or cocooning vaccinations and that did not adjust for primary immunisations. Studies that evaluated only wP, or that switched schedules while transitioning from wP to aP were excluded. We also excluded vaccine-efficacy, animal andlaboratory studies (i.e., serological studies), and studies that focused solely on antibody concentrations.

2.2.1. Accelerated versus extended schedules

For this study, we allocated infants as either having an accelerated or extended primary and booster series as follows:

- Accelerated primary schedule: First three doses of pertussis vaccine offered within the first six months of life.
- Extended primary schedule: First three doses of pertussis vaccine offered within the first 11–12 months of life.
- Booster doses offered on or before the second year of life
- Booster doses offered after the second year of life

2.3. Study selection

Titles, abstract and full-texts were sequentially screened for eligibility by two reviewers independently, with one author being a reviewer for all records to maintain consistency (ET; the other reviewers were DN, SN, SW and AM). Conflicts were resolved through mutual discussion (Fig. 1). EPPI Reviewer software was used [10].

2.4. Quality assessment

Risk of bias was assessed by two authors independently (ET for all; DN, SN, SQ or AM as second reviewer) using the Risk of Bias in Non-randomised Studies of Intervention (ROBINS-I) tool [11]. Conflicts were agreed through discussion with a third reviewer.

2.5. Data extraction

Data on incidence rates and vaccine effectiveness were extracted (by ET) from the full text studies using the coding function in EPPI Reviewer and a data extraction template [10]. A second author reviewer and validated the extraction (DN, SN, SW, or AM).

2.6. Data synthesis

Due to heterogeneity of methods used to diagnose pertussis and variation in vaccine coverage, a meta-analysis was precluded. We summarized the results narratively and commented on the quality of the available evidence. Where possible, we extracted information on pertussis incidence and vaccine effectiveness estimates to compare accelerated versus extended schedules.

3. Results

3.1. Study characteristics

Of the 98 selected studies (Fig. 1), 65 were observational, 19 were vaccine effectiveness, seven were mathematical modelling, five were both observational and vaccine effectiveness, and two were both

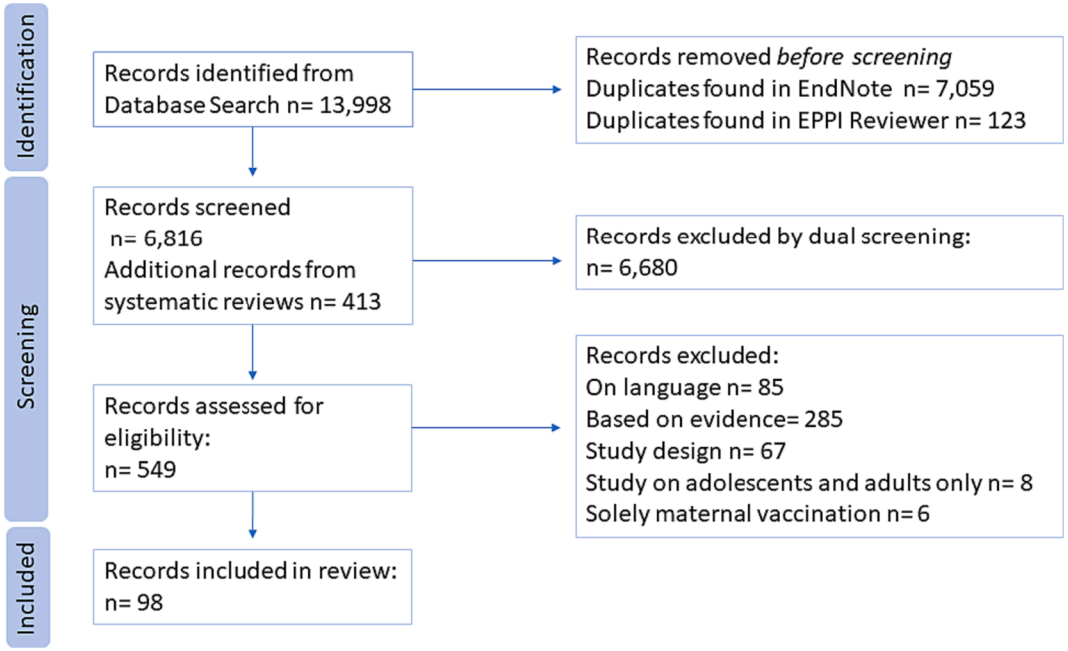

Fig. 1. Study-flow diagram of papers obtained from database searches, double screened on title and abstract, full text, and selected for inclusion according to PRISMA Guidelines y [12].

observational and mathematical modelling analyses. Studies from 24 different countries were included (Table 1).

3.2. Risk of bias in included studies

Most studies were observational studies using vaccination registers and surveillance systems to report on pertussis notifications or lab confirmed cases (Supplementary Table 2) [112]. The scale of bias due to missing data and misclassification was often unknown, though expected to be low within each study and to vary between studies due to differences in defining cases. Infants and children who are unvaccinated, under-vaccinated, or who delayed vaccination, may be inherently different to those who adhere to the recommended schedule. However, pertussis vaccination is well established, and most countries report high vaccine coverage.

3.3. The impact of primary immunisation schedules on infant disease

3.3.1. Observational studies on moving from a primary accelerated schedule to a primary extended schedule

Two studies analysed switching from an accelerated to an extended primary schedule [7,13]. A study in Switzerland between 2013 and 2020 did not observe any change in infant hospitalisations after implementing the extended schedule in March 2019, but the COVID-19 pandemic likely impacted the results [7]. Another study in France evaluated pertussis disease in the three years after switching from an extended to an accelerated series and found no increase in infant cases. But the authors used data solely from a GP surveillance system, and the COVID-19 pandemic impacted the data [13].

Table 1
Total number of studies included in the narrative systematic literature review by country and by an accelerated or extended primary aP vaccination series.

Country	Studies with an Accelerated schedule	Studies with an Extended schedule	Studies that switched from accelerated to extended	Total number of studies
Australia	17	0	0	17
Bulgaria	1	0	0	1
Canada	6	0	0	6
China	1	0	0	1
Costa Rica	1	0	0	1
Czech Republic, Ireland, Italy, and Spain	*	*	0	1
Denmark	0	3	0	3
Denmark, Sweden, Norway, and Finland	0	1	0	1
England	1	0	0	1
England and Wales	2	0	0	2
France	1	1	1	3
Germany	2	0	0	2
Italy	0	5	0	5
Japan	0	3	0	3
Israel	1	0	0	1
Netherlands	1	0	0	1
New Zealand	4	0	0	4
Norway	0	2	0	2
Singapore	1	0	0	1
Slovenia	1	0	0	1
South Korea	1	0	0	1
Spain	6	0	0	6
Sweden	0	7	0	7
Switzerland	2	0	1	3
United States of America	24	0	0	24
Total	**73**	**22**	**2**	**98**

*The study conducted in Czech Republic, Ireland, Italy, and Spain had a series of different vaccination schedules.
Czech Republic primary series: 3, 5, 11–13 months (switched in 2018 from 2, 3, 4 and 10 months).
Ireland primary series: 2, 4, 6 months.
Italy primary series: 3, 5, 11 months.
Spain primary series: 2, 4, 11 months and switched in 2016 from 2, 4, 6 months.

3.3.2. Mathematical modelling predictions of switching schedules

In France, a mathematical modelling study evaluated the switch from a primary series at two, three and four months, and a booster between 16 and 18-months to two and four months and a booster at 11-months in 2013 [14]. The authors estimated an increase in cases among children ages two-to-five-years-old following the switch due to the lowered antibody response during the 11-month booster in the extended schedule versus the previous accelerated schedule [14]. Furthermore, a mathematical modelling study in Australia predicted that switching from a primary series at two, four, and six-months to two, four and 12-months would reduce the incidence among children 18-months to four-years-old by 2 %, though increase pertussis in children younger than one-year-old by 6 % [15].

3.3.3. Studies on the timing of primary vaccinations

Numerous studies highlighted the importance of maintaining timely delivery of vaccines for high vaccine coverage [16–21]. 24.5 % (24/98) of the studies commented on the timeliness of delivering vaccines, of which 87.5 % (21/24) had an accelerated schedule and 12.5 % (3/24) had an extended schedule.

3.3.4. Primary first dose

Six studies discussed the timeliness of the first dose, though all were conducted before the introduction of maternal vaccination. One study with an extended schedule offering first dose at three-months stated that further evidence is needed before bringing forward the first dose [6]. Five studies with accelerated schedules offering the first dose at two-months highlighted earlier protection and/or the positive impact of offering the first dose at six weeks on reducing notifications, hospitalisations, and deaths among infant groups [5,22–25].

3.3.5. Primary third dose

A total of 10 (10.6 %) studies mentioned the role of the third dose; eight with an accelerated schedule [3,4,24,26–30] and two with an extended schedule [31,32]. Of the studies with an accelerated schedule, three indicated a plateauing or drop in odds, effectiveness, and incidence after the third dose, respectively [3,26,27], though two [3,26] had small sample sizes or non-significant results. Three studies found that three accelerated doses were associated with higher vaccine effectiveness against disease among 12–39-month-olds and 6–14-month-olds [4,28] and hospitalisations among infants less than two-years-old [29] compared to those with fewer or zero aP doses. Of the two studies with an extended schedule, one found reduced pertussis incidence following the third dose [31], while the second found higher effectiveness against reported duration of cough [32]. Although the second study had a high risk of bias due to the selection of participants and missing data [32].

3.3.6. Delayed and incomplete primary immunisations

Many studies evaluated pertussis in infants and children who delayed vaccination (did not receive a pertussis vaccination within the recommended vaccination period) or had incomplete or under-vaccination (did not have the correct number of doses by a certain age) [3,25,30,33–36].

Rane et al., concluded that delaying the vaccination series initiation was not associated with an increased risk of pertussis, however led to under-vaccination that resulted in a 3.5-fold increased risk of pertussis in infants up to one-years-old [37].

Four studies evaluated hospitalisations when delaying one or more

doses in the primary series. Two studies, one in Australia in 2001 among infants [38] and the other in Spain between 2003 and 2009 on anyone older than two-months-old [39], found 37 % and 38.7 % of hospitalised cases were appropriately vaccinated, respectively, meaning approximately 60 % of hospitalised cases were not appropriately vaccinated. Similar results were found in Switzerland, during their accelerated era, and in Japan [40,41].

3.3.7. Summary of primary immunisation schedule impact on infant disease

In summary, of the few observational studies evaluating the switch from an accelerated to an extended vaccination schedule, none saw an increase in infant cases, though note that the COVID-19 pandemic may have impacted the results. Two modelling studies did indicate a potential onward impact delaying doses resulting in an increase in pertussis cases in young children and infants. The timeliness of delivering vaccines is key. The first dose is important in reducing pertussis cases and hospitalisations in infants, regardless of the schedule. Some evidence suggests that delivering the first dose earlier is associated with fewer cases, particularly if no maternal vaccine is offered. Some evidence suggests that the third dose in an accelerated schedule results in a plateau or slight drop in incidence, however there are inconclusive results on whether delaying the third dose in an accelerated schedule reduces incidence [3,4,26–29]. Finally, regardless of the schedule, incomplete or delayed vaccinations result in disproportionately more cases and hospitalisations.

3.4. The impact of booster immunisation schedules on infants

3.4.1. Accelerated and extended booster doses

Seventeen studies evaluated the effectiveness of accelerated boosters [42–58]. Five studies concluded that effectiveness from an accelerated schedule and booster dose on or before the second year of life wanes from around four years to eight years since the last dose administered [54,56,59,50–52]. Despite waning, protection remains in vaccinated children compared with their unvaccinated counterparts [44], with an estimated increase in the odds of pertussis of 1.44 (95 % CI 1.03–2.02) each year following the 18-month booster dose found in Australia [57].

Similarly, four studies examined the effectiveness of extended boosters [60–63] and found vaccine effectiveness to last a few years before waning. This resulted in the introduction of a preschool booster because of waning in the primary series was in Sweden [60,62].

3.4.2. The impact of booster vaccines on infant cases

Three studies in Australia with an accelerated primary schedule focused on evaluating vaccine effectiveness following the replacement of the 18-month booster with an 11-year-old booster from 2003 to 2016. Hale et al., compared two epidemic eras where the second era had no 18-month booster. Despite accounting for the differences in case ascertainment due to changes in testing practices and some wP delivered in the earlier era, removing the 18-month booster resulted in an increase in hospitalisations among fully vaccinated children between six-months and three-years-old [45]. A mathematical modelling study concluded that removing the 18-month booster would decrease immunity among children 19–47-months-old, resulting in a 13 % rise in pertussis cases among this age by 2050 [47]. Finally, a protective effect was observed after reintroducing the 18-month booster in Australia [57].

Like Australia, New Zealand discontinued a 15-month booster in 2015. Whilst Radke et al., found a small decrease in vaccine effectiveness in the two to four years, after the last dose of vaccination offered at five-months of age, protection was sustained through the child's fourth birthday [50].

3.4.3. Impact of maternal boosters on infant cases

Many studies agree that maternal vaccination effectively protects infants [26,64–69]. Though not included in this systematic review, laboratory antibody studies indicate that maternal vaccinations are associated a lower immune response following primary immunisation. [70–72] When reviewing whether the lowering of antibodies translates to epidemiological observational findings, three studies found a possible plateauing or dropping of incidence and effectiveness following two or three dose of an accelerated schedule with infants primed with maternal vaccination [27,73,74]. A study in Australia found no significant difference, while a study in England showed some declines in effectiveness following maternal and primary vaccinations, but there were few observations in both studies [26,67].

3.4.4. Summary of the impact of booster immunisation schedules on infant disease

The first series of booster doses delivered to children wane at a similar rate both in accelerated (before the second year of life) and extended schedules (after the second year of life), which has led to preschool or school boosters being added to many schedules. Delaying booster doses to pre-adolescence may result in increased pertussis cases among infants and children when an accelerated schedule is offered because of decreasing immunity over time. Maternal vaccination has resulted in a significant reduction in infant pertussis cases, though there is mixed evidence of whether it impacts the effectiveness of the second and third dose in an accelerated schedule.

3.4.5. Direct and indirect effects of pertussis vaccination

With waning immunity following aP there has been a shift in pertussis among older age groups and more booster doses have been offered throughout the life-course to try to reduce cases directly among targeted age groups and indirectly through herd immunity to the youngest and most vulnerable.

3.4.6. Primary vaccinations

It is well known that there is a positive direct impact of vaccinating young infants against pertussis. However, McNamara et al., in the United States found no overall protection against posttussive vomiting and severe disease between age appropriately vaccinated versus non-age appropriately vaccinated infants younger than six-months-old [35].

One study in the United States showed posible indirect herd effects protecting against pertussis [112]. A study in Sweden with an extended schedule found that the primary series reduced pertussis among infants younger than three-months-old, but the data was compared with that of a pre-vaccination era, and the incidence still remained greater than 200 cases per 100,000 population in infants younger than four-months-old [75].

3.4.7. Booster vaccinations

Four studies concluded that booster doses following both accelerated [49,76] and extended [77,78] schedules did not indirectly protect younger infants. One Swedish study suggested possible indirect protection of the seven-year-old booster among infants [79], though it showed no concrete evidence. This ambiguity was reflected in another Swedish study concluding that the observed decrease may have been due to vaccination or natural variation in pertussis [80]. In Australia, Pillsbury et al. suggested that cases among young children were due to the direct effect of a prolonged period between the six-month dose and four-year booster, when the 18-month booster had been replaced with an adolescent booster [81].

Vaccinating older children and adolescents provided direct protection though it did not indirectly protect infants [4,55,82–92]. One study suggested that higher infant pertussis incidence in Denmark may be due to not having adolescent boosting, however it provided no data on adolescent cases [93].

Seven studies discuss booster doses shifting the burden of pertussis disease to older age groups [75,78,79,85,90,91,94]. One study suggested the adolescent dose plays a protective role against pertussis among those aged 15 to 30-year-olds, and subsequently infants [15]. Other studies suggested that boosting older children and adolescents

could shift the burden of pertussis to adults, who may serve as a reservoir for young infants [33,85] and that high vaccine coverage would need to be sustained to protect both adults and children [95].

3.4.8. Effects of parents and siblings

Parents and siblings are a likely direct source of infection among infants [14,25,96–98]. After switching from an accelerated to extended schedule in France, Paireau et al. found increased cases in two to five-years-old and suspected a possible increase in infant cases coming from older siblings, though the study did not provide any data [14].

3.4.9. Summary of the direct and indirect effects of pertussis vaccination

In summary there is some evidence that primary vaccination and little evidence that pertussis boosters indirectly protect the youngest infants not yet eligible for vaccination. There is concern that vaccinating adolescents may increase the risk of pertussis when they become adults, particularly women of childbearing age. Parents and siblings are a source of infection among infants and it is possible that switching from an accelerated to extended schedule may result in increased infant cases coming from older siblings, though further evidence is needed.

3.5. Impact of changes in testing

In summary, methods for testing and notification of pertussis disease vary [69,99]. Studies in Spain, Italy and Germany highlight the differences in notification, sentinel surveillance, and hospitalisation data [100,101]. Finally, the aP era has coincided with improved surveillance systems and the introduction of PCR testing, which could in part explain observed increases in cases [45,54,85,102–106]. A WHO report indicated that in 2011–2012 only data from five out of 19 countries showed a true resurgence of pertussis, whereas in other countries increases in cases were attributed to cyclic patterns of disease and improved diagnostics [107].

3.6. Data synthesis

Supplementary Table 4 summarises all studies included in the systematic review, with information on the study location and period, the study design, vaccination schedule delivered and the overall findings in relation to the vaccination schedule.

Twenty-two studies reported pertussis incidence data in infants. These data were extracted and plotted to compare pertussis incidence in cases younger than three-months-old, and cases and hospitalisation incidence among children younger than one-year-old (Supplementary Figs. 2 and 3). The results are inconclusive due to fluctuation of incidence after the introduction of aP in some countries, the natural cyclical variation in pertussis and using average estimates for pertussis incidence over several years. In addition, the COVID-19 pandemic has resulted in a drop in pertussis worldwide.

Likewise, vaccine effectiveness from 16 different studies was difficult to compare due to the aforementioned reasons, as well as the different methods of estimating vaccine effectiveness (Supplementary Table 3).

4. Discussion

The primary objective of any pertussis immunisation strategy is to optimise protection for infants who are at highest risk of severe disease. Countries offering aP have the challenge that repeat booster vaccines don't offer sustained long-term protection.

There is a lack of clear evidence from the published literature on the comparative effectiveness of different primary schedules. However, it is evident that regardless of the schedule, the first dose should be administered in a timely way to reduce pertussis among young infants. Whilst completion of the schedule on time is critical for both primary and booster doses, infants with delayed doses are likely to have suboptimal protection at the age they are most susceptible to severe pertussis disease. Countries that recently switched to an extended schedule should continue to evaluate the impact of the vaccine schedule on pertussis disease among young infants as we emerge from the pandemic to provide more robust evidence. For many countries, the pandemic control measures induced a sudden drop in pertussis incidence, with a reduction in natural boosting from pertussis exposure and fall in vaccine coverage, leading to higher susceptibility in the population [108–111]. All countries should therefore review pertussis immunisation to ensure optimal infant pertussis control.

Maternal vaccination is key to protecting young infants from pertussis disease, though there is no clear evidence of whether the choice of an accelerated or extended vaccination schedule among infants of vaccinated mothers leads to any difference in cases, hospitalisations, deaths or vaccine effectiveness. Primary vaccine effectiveness wanes within approximately four years of vaccination, so booster vaccination amongst young children is important. There is also some evidence that accelerated booster doses may indirectly protect young infants, though further studies in different countries would be helpful. Vaccinating adolescents, however, doesn't indirectly protect infants. Parents and siblings are a source of pertussis transmission, and vaccinating adolescents could shift the burden of disease to adults of childbearing age, inadvertently increasing the risk of pertussis among young infants.

The limitations of this review include the inability to analyse non-English-language studies. Evaluating the risk of bias was generally low to moderate because most studies were observational, using national surveillance data. However, comparisons across studies proved challenging due to different surveillance methods and the impact of the COVID-19 pandemic.

While this study evaluates the impact of vaccination schedules on pertussis disease in infants, further research is needed to consider the impact of schedules on other diseases protected through the primary schedule. Countries must choose an optimal schedule that is easy to adhere to and high vaccine coverage must be sustained to protect infants too young for direct protection through vaccination.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The UK Health Security Agency (UKHSA) has provided vaccine manufacturers with post-marketing surveillance reports which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy, and a cost recovery charge is made for these reports.

Data availability

The search strategy is available in the supplementary materials. A copy of the data extraction form may be available upon request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.08.073.

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