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MINI-REVIEW

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Available evidence on the co-administration of the four-component meningococcal B vaccine (4CMenB) with three vaccines at the same visit among pediatric individuals

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ABSTRACT

Vaccine co-administration is a useful strategy for improving vaccine coverage and adherence. In Italy, an update to the national immunization program (NIP) in 2023 included recommendations for co-administration of pediatric vaccines, including the four-component vaccine for meningococcus B (4CMenB), pneumococcal conjugate vaccine (PCV), hexavalent vaccines, and oral rotavirus vaccines. Safety is a major concern when considering vaccine co-administration; therefore, a literature review of the available evidence on 4CMenB co-administration with PCV, hexavalent/pentavalent, and rotavirus vaccines was performed. Of 763 publications screened, two studies were reviewed that reported safety data on 4CMenB co-administration with PCV, hexavalent/pentavalent, and rotavirus vaccines in infants aged 0–24 months. Overall, these studies supported that there were no significant safety signals when co-administering 4CMenB with PCV, hexavalent/pentavalent, and rotavirus vaccines, compared with individual vaccination. This review provides key insights for healthcare professionals on the tolerability of co-administering 4CMenB with routine vaccines.

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Introduction

Vaccine co-administration describes the process in which two or more vaccines are administered during the same appointment or session. Vaccine co-administration has been identified as a useful strategy to improve vaccine coverage rates and compliance with national immunization programs (NIPs) by reducing the number of vaccination sessions needed,[1,2] thereby reducing the resource utilization of vaccination services in addition to potential stress imposed on children and parents.[2–4] Furthermore, co-administration may also reduce the number of missed opportunities for vaccination, a key contributor to incomplete immunization.[2,5]

The burden of infectious diseases such as invasive meningococcal disease (IMD) and rotavirus (RV) disease, which mainly affect infants and toddlers within 2 y of age, has substantially reduced following the introduction of respective vaccines.[6,7] In Italy, recent studies have indicated that earlier immunization of infants with the four component vaccine for meningococcus B (4CMenB) and RV vaccines may provide a greater level of protection against their respective diseases.[8–10] In particular, initiating the 4CMenB vaccination schedule at 2 months versus 7 months of age led to more than a 2-fold decrease in the incidence of IMD when comparing discrete data from two different regions,[8] consistent with a peak in IMD reported in infants aged 4–8 months old.[11] Therefore, optimizing immunization calendars is important to ensure maximum coverage and protection against disease.

In Italy, the immunization schedule for infants aged less than 24 months includes both mandatory vaccines (e.g., hexavalent vaccines), which are compulsory by national law, and recommended vaccines (e.g., 4CMenB, RV and pneumococcus vaccines). This can lead to variable rates of adherence between vaccines. According to data from the Italian Ministry of Health, coverage rates of mandatory vaccines, are generally higher than for recommended vaccines (Figure 1).[12] This is potentially due to crowded immunization schedules,[13] particularly among infants less than 24 months old, which could impact adherence or delay scheduled vaccination timings. It is also interesting to note that pneumococcus vaccination, which is historically co-administered with hexavalent vaccines, reached high coverage rates, similar to those of mandatory vaccines, despite being recommended and not mandatory (Figure 1). The National Vaccine Prevention Plan (NVPP) in Italy was recently updated in 2023 (version: 2023– 2025),[14] recommending that, whenever possible, vaccines should be offered in co-administration, including pediatric vaccines. Although the impact on immunogenicity must be considered when co-administering vaccines, the combination of pediatric vaccines typically has no significant impact on immunogenicity profiles, and is seen as common practice in many countries.[2] A survey conducted in Calabria, Italy, in 2022, reported that the majority of healthcare professionals (HCPs) supported vaccine co-administration as an effective strategy to improve immunization calendars, as it can provide a range of benefits to healthcare systems and patients.[15] However, concerns were raised regarding the lack of readily available information on

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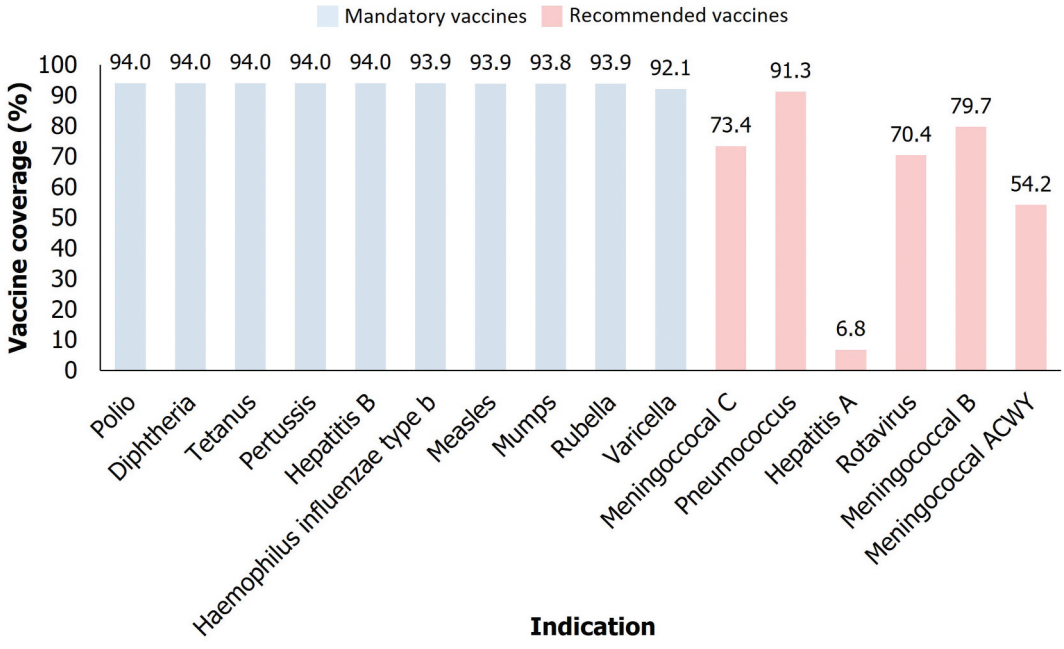

Figure 1. Vaccination coverage of mandatory and recommended vaccines in Italy, 2019.[12]

the safety of concomitant administration of multiple vaccines in pediatric populations, which could limit the implementation of coadministration strategies.[15] In particular, HCPs noted that limited safety data on co-administration of vaccines was often perceived as a key barrier, limiting its use in clinical practice.[15] Similar findings were also reported in 2022, in a survey carried out among Public Health Nurses.[16] An earlier study among HCPs had also reported hesitancy toward 4CMenB co-administration, owing to a lack of explicit guidance and information on the co-administration of pediatric vaccines.[17]

Given the importance of available information on the safety of vaccine co-administration, highlighted in surveys of HCPs,[15,16] the objective of this narrative review was to assess the available literature reporting on the safety profile of co-administering 4CMenB with three vaccines (pneumococcal conjugate vaccine [PCV], hexavalent, and RV vaccines) at the same visit in pediatric populations aged 0–24 months.

Methods

Search strategy

A targeted literature search was performed in July 2023 to identify the available evidence on the co-administration of 4CMenB with PCV, hexavalent vaccines (diphtheria, tetanus, acellular pertussis [DTaP], *Haemophilus influenzae* type b [Hib], poliovirus and hepatitis B [DTaP-Hib-IPV-HepB]), and oral RV vaccines, in infants aged 0–24 months.

The search strategy main string comprised: (4CMenB OR Bexsero OR pneumococcal vaccine OR rotavirus vaccine OR hexavalent vaccines) AND (co-administ* OR concomitant* administ* OR simultan* administ* OR coadministr*) AND (safety drug-related side effects OR adverse reactions OR adverse effects OR complications OR safety OR tolerability).

Articles that specifically reported data in infants aged 0–24 months related to the incidence of adverse events following immunization (AEFIs) and other safety signals for 4CMenB vaccination, co-administered with PCV, DTaP-Hib-IPV-HepB, and RV vaccines, were included. Studies that reported safety data for pentavalent vaccines (DTaP-IPV-Hib) co-administered with 4CMenB were also included, due to the similarity in safety profiles compared to hexavalent vaccines.[18] No geographical or language restrictions were applied in the literature search.

Articles that did not report safety data for 4CMenB coadministration with all specified vaccines of interest (PCV, DTaP-Hib-IPV-HepB [or DTaP-IPV-Hib], and RV) were excluded. To focus the literature search on recent findings, articles published before 2018 were excluded, since the United Kingdom (UK) was the only country to have implemented a 4CMenB infant vaccination program prior to 2018.

Results

Overview of included studies

A total of 763 articles in PubMed and 599 in Embase were identified. After screening, 167 articles (PubMed: $n = 86$; Embase: $n = 81$) published since 2018 were considered for eligibility.

Of the 167 articles considered, two studies included data for all primary vaccines included in the search strategy;[19,20] relevant findings from these studies are presented in the results. The remaining 165 articles were excluded from this section, owing to the strict nature of the inclusion criteria, in that co-administration data must be present for all three targeted vaccines in this review. Insights from this selection of studies that reported on the safety of 4CMenB co-administration, but reported on similar vaccine pairings with 4CMenB, are considered in the discussion.

Of the two included studies, both had originated from the UK. Summaries of the study designs and key outcomes are shown in Table 1.

Table 1. Summary of studies investigating 4CMenB co-administration with two or more vaccines.

	Reference	
	Bryan et al.[20]	Bauwens et al.[19]
N	1.29 m	46,532[a]
Age range	2–18 months	0–18 years
Vaccines co-administered	• 4CMenB + DTaP-IPV-Hib + PCV + RV • 4CMenB + Hib-MenC + PCV + MMR	• 4CMenB + DTaP-IPV-Hib + PCV • 4CMenB + DTaP-IPV-Hib + MenC + RV • 4CMenB + MenC + MMR + PCV
Comparators	• Expected number of adverse events according to background incidence and number of children vaccinated	Separate immunization with: • 4CMenB • DTap-IPV-Hib PCV • RV • Hib-MenC • MMR
Primary/secondary safety endpoint	• Frequency of AEFIs	• Incidence rate of AEFIs 0–42 d post-vaccine administration (high-risk period)
Most common AEFIs reported	• Injection site or local skin reactions (366/902 [41%] suspected AEs) • Fever (364/902 [40%] suspected AEs)	• Not stated for 4CMenB vaccine combinations
Key safety outcomes	• **No new safety signals reported for co-administration** • **High compliance for all vaccines**	• **No significant differences in the safety of 4CMenB co-administration vs individual vaccine administrations**

[a]Number of vaccine co-administrations. 4CMenB: four component meningococcal B; AE: adverse event; AEFI: adverse event following immunization; d: days; DTaP: diphtheria, tetanus, acellular pertussis; Hib: Haemophilus influenzae type b; IPV: inactivated polio vaccine; m: million; MenC: meningococcal C; MMR: measles, mumps, and rubella; PCV: pneumococcal conjugate vaccine; RV: rotavirus.

Vaccine co-administration safety outcomes

The safety of 4CMenB has been evaluated across 17 studies, which included 10 randomized controlled trials whereby participants received at least one dose of 4CMenB.[21] Among infants and children, the most commonly reported adverse events associated with 4CMenB administration include fever (≥38°C), irritability and tenderness and erythema at the injection site.[21]

In this targeted literature review, one article identified was a large prospective surveillance study in the UK, which evaluated approximately 1.29 million infants aged 2–18 months.[20] In total, the study population had received an estimated 3 million doses of 4CMenB co-administered with two injectable vaccines (DTaP-IPV-Hib and PCV) plus the oral RV vaccine, or with three injectable vaccines (Hib-meningococcal C [MenC], PCV, and measles, mumps, and rubella [MMR]) during routine vaccination campaigns (Table 1).[20] No safety issues were reported when comparing concomitant vaccine administration with the same vaccines administered without 4CMenB.[20] The most common AEFIs reported were local reactions (41%) and fever (40%). The introduction of 4CMenB co-administration had no reported impact on compliance with other routine vaccinations.[20]

The second article by Bauwens et al.[19] assessed AEFIs from 5,993,290 vaccine doses administered to 958,591 infants, of which 46,532 doses of 4CMenB were co-administered with two injectable vaccines (DTaP-IPV-Hib and PCV [$n = 42,154$]; or DTaP-IPV-Hib and MenC [$n = 2,748$]) or three injectable vaccines (MenC, MMR, and PCV [$n = 1,630$]). Similar to the UK prospective surveillance study,[20] there were no significant changes in the rate of AEFIs (including fever) in infants who received 4CMenB co-administrations when compared to the same vaccines administered without 4CMenB (Table 1).[19]

Discussion

This narrative review aimed to summarize available evidence on the rates of AEFIs following co-administration of 4CMenB with two injectable vaccines (PCV and hexavalent/pentavalent vaccines) and one oral vaccine (RV) in a single session.

Overall, there was a lack of studies evaluating the co-administration of 4CMenB with PCV and hexavalent/pentavalent and RV vaccines. Despite this, the limited evidence available suggests that co-administration of 4CMenB with PCV, hexavalent or pentavalent, and RV vaccines does not increase the risk or severity of AEFIs compared with individual administration.[19,20,22] In support of this, a review of the 4CmenB safety profile when co-administered with routine childhood and adulthood vaccines reported no significant safety concerns.[23] Relevant to this article, the authors also concluded no safety concerns with DtaP-Hib-IPV -HepB, PCV7 or PCV13, and RV vaccines co-administered with 4CmenB.[23]

The safety data reported here were also consistent with the clinical development program of 4CMenB, which included phase 2 and phase 3 trials in infants who received 4CMenB co-administered with a hexavalent vaccine and PCV.[24–26] In these trials, 4CMenB was well tolerated when administered alone or concomitantly with other injectable vaccines, and no differences in immunological responses were observed.[24] A subset of participants also concomitantly received an oral RV vaccine with 4CMenB and other routine vaccines. Rates of fever in the group receiving concomitant RV vaccination were similar to those who did not receive RV vaccination (2.2% [3/135] vs 2.6% [37/1,435]).[24] Overall rates of systemic reaction were 80.5% in the group who received concomitant RV vaccination versus 75.3% in the group not receiving concomitant RV vaccination.[24] However, given that only two studies were identified in this targeted review, further evaluation of the safety of simultaneous 4CMenB co-administration with PCV and hexavalent/pentavalent and RV vaccines would be beneficial.

Real-world, historic data from the UK further support the strategy of co-administering 4CMenB with PCV, DTaP-IPV-Hib, and the oral RV vaccine, as no notable reductions in vaccine efficacy, and no impact on the overall safety and tolerability of these vaccines were observed when co-administered in the NIP.[20,27] However, the UK has since updated the PCV immunization program so that 4CMenB is no longer co-administered with PCV, DTaP-IPV-Hib, and the oral RV vaccine.[28]

Another UK-based trial, excluded from the search results because of a lack of RV vaccination data and a non-concomitant control, investigated differences in immunogenicity and reactogenicity of 4CMenB co-administration with two licensed hexavalent vaccines, Hex-V (MCM Vaccines, Leiden, Netherlands) and Hex-IH (GlaxoSmithKline, Rixensart, Belgium).[29] Comparable rates of AEFIs were reported between Hex-IH or Hex-V co-administration with 4CMenB, with only one serious adverse event (fever) considered related to vaccination; the participant developed a fever, tachycardia, and tachypnea following vaccination.[29] However, it was not stated whether prophylactic paracetamol following MenB vaccination was enacted in this study, as recommended in the UK.[30] The immunogenicity of 4CMenB co-administration with hexavalent vaccines is not expected to be impaired, since high levels of *Haemophilus influenza* type b polysaccharide antigen, anti-polyribosylribitol phosphate immunoglobulin G, were observed post-vaccination.[29] However, there was a lack of data on the immunogenicity profiles of 4CMenB and the co-administered vaccines in the articles examined in this review.

An additional study, evaluating the occurrence of AEFIs related to 4CMenB co-administration with routine vaccines in three European randomized controlled trials (NCT00657709, NCT00847145, NCT00721396), was also not included in the search results due to a lack of data on RV vaccination.[22] However, this study provides further insight on the safety of 4CMenB co-administration. Of 5,026 healthy infants aged 2–15 months, the incidence of fever (≥38°C) reduced from 86% to 75% in infants who received concomitant administration of 4CMenB with routine vaccines compared with the cumulative incidence of AEFIs when vaccines were administered separately (1-month intervals).[22] Substantial reductions in the co-administration group versus separate vaccination were also reported for other AEFIs, including diarrhea, crying, and change in eating habits; however, a slight increase in the occurrence of tenderness at the site of injection was reported in infants who received concomitant versus separate vaccinations (66% vs 55%).[22] Overall, co-administration of 4CMenB reduced the cumulative risk of AEFIs by 4–49%, and the severity of AEFIs was not increased by co-administration of 4CMenB with routine vaccines, compared with separate vaccination.[22]

Co-administration of 4CMenB with DTaP-Hib-IPV-HepB and PCV is currently in use in Portugal,[31] and in regional vaccination calendars across Spain.[32,33] The value of vaccine co-administration is further highlighted by the Italian experience of concomitant MenC vaccination with two injectable vaccines (DTaP-Hib-IPV-HepB and PCV) in infants aged <12 months.[34] Following one year of implementation, Pellegrino et al.[34] reported a significant increase in vaccine coverage, from 46.9% to 64.8%, following co-administration of PCV, hexavalent, and MenC vaccines. MenC vaccination was however later re-scheduled to occur in children aged 2 y (one dose).[35]

In Italy, the NIP was updated in 2023 (NVPP 2023–2025),[14] introducing the option to co-administer 4CMenB, DTaP-Hib-IPV-HepB, PCV, and RV vaccines at 3 months and 5 months of age, thus halving the number of vaccination sessions required (a third session may occur at 4 months of age, should the 3-dose schedule for the RV vaccine be utilized). Supportive of this recommendation, the regional immunization calendar for Calabria was updated in 2022, ahead of the NIP update, introducing the option to also co-administer the measles-mumps-rubella-varicella vaccine (MMRV) with 4CMenB and MenC or meningococcal A, C, W, and Y (MenACWY) conjugated polysaccharide vaccines at 13–15 months of age.[36] Furthermore, the Centers for Disease Control and Prevention state that all vaccines have the possibility to be co-administered, unless there is a documented contraindication,[37] and the World Health Organization recommends the co-administration of many vaccines throughout the early stages of infancy.[38]

The potential benefits of full co-administration of pediatric vaccines in the Italian context have been underlined by Poscia et al.[39] By using the 2019 birth cohort in Italy, and assuming that 10 regions use the two-dose RV vaccine and 10 regions use the three-dose RV vaccine, with a target coverage of 95%, it was estimated that 950,190 vaccination appointments would be saved per year, leading to a forecast of 190,038 working hours per year that could be reinvested in other vaccination activities.[39] The feasibility of full co-administration of pediatric vaccines, as recommended by the NVPP 2023–2025,[14] was documented in the Local Health Unit of Reggio Calabria at an Italian Continued Medical Education seminar in April 2023.[40] Following the introduction of the option for full co-administration in the Calabria Immunization Calendar in April 2022,[15] the proportion of patients who had chosen for their child to receive full co-administration increased from 37.33% in May 2022 to 86.17% in March 2023.[40] Despite this, two surveys carried out among HCPs in Italy highlighted that the lack of information on vaccine co-administration provided in relevant data sheets is perceived as a key barrier to implementation,[15,16] although this may have been overcome by the subsequent updated NVPP 2023–2025 recommendations.[14] Coupled with public perceptions that administering multiple vaccines at once may burden the immune system, impact vaccine efficacy, or increase the frequency of AEFIs,[41] wider communication of safety profiles for vaccine co-administration is imperative.

Despite the few studies identified, the findings and discussion presented in this review highlight the lack of safety signals and new AEFIs when co-administering 4CMenB with two or more vaccines versus separate immunization. In some cases, vaccine co-administration resulted in lower overall AEFIs and increased vaccine coverage compared with separate vaccination. This is also pertinent with the recommendation in 2024 by the German Standing Committee on Vaccination (STIKO) for the co-administration of 4CMenB with PCV, hexavalent and RV vaccines, as discussed in this review.[42] However, there were limitations to this review. First, the literature searches and selection of studies were performed by one researcher, and no quality assessments of the included studies were conducted. Only two studies were included as results, of which all reported data solely from the UK. In addition, there was a lack of safety data in this context for hexavalent versus pentavalent vaccines. Taken together, this may highlight a need for analyses of pooled safety data on 4CMenB co-administration with hexavalent vaccines, and PCV and RV vaccines. Current data may also lack global representation.

Conclusions

Co-administration of multiple vaccines, compared with independent vaccination, can provide many benefits to healthcare systems, parents, and individuals receiving the vaccine, such as a reduced number of vaccination sessions. However, confidence on the safety profile of vaccines when co-administered in infants is necessary to support use in practice, both from the perspective of HCPs, caregivers, and vaccinated individuals.

This review highlighted that within the context of co-administering 4CMenB with two injectable vaccines and one oral vaccine, overall rates of AEFIs were similar or reduced in some instances. The ongoing experience of the Calabria region in Italy, that recently introduced the option to co-administer vaccines at 3 months, 5 months, and 13–15 months,[36] and the similar co-administration opportunity offered by the updated NIP in Italy,[14] are expected to provide further insight on the impact of 4CMenB co-administration. Vaccine co-administration safety/tolerability data reported in the literature do not show an increased risk of AEFIs compared to vaccines administered individually.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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