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The immunogenicity and safety of Group B Streptococcal maternal vaccines: A systematic review

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ABSTRACT

Purpose: To systematically review immunogenicity and safety data of maternal group B streptococcal (GBS) vaccines in published clinical trials until July 2023.
Methods: EMBASE, MEDLINE, Cochrane Library and clinicaltrial.gov. databases were searched for clinical studies that reported immunogenicity and/or safety of GBS vaccine in non-pregnant adults, pregnant women and infants between 1st of January 1996 to 31st of July 2023. Pairs of reviewers independently selected, data extracted, and assessed the risk of bias of the studies. Discrepancies were resolved by consensus. (PROSPERO CRD42020185213).
Results: We retrieved 1472 records from the literature search; 20 studies and 6 sub-studies were included, involving 4440 non-pregnant participants and 1325 pregnant women with their newborns. There was a significantly higher IgG Geometric Mean Concentration (GMC) and IgG placental transfer ratios in vaccinated compared to placebo groups, with peak response 4–8 weeks after vaccination. Placental transfer ratio varied from 0.4 to 1.4 across five studies. The different clinical trials used different assays that limited direct comparison. There were no significant differences in the risk of serious adverse events (adjusted OR 0.73; 95 % CI 0.49–1.07), serious adverse events leading to withdrawal (adjusted OR 0.44; 95 % CI 0.13–1.51), and systemic illness or fever (adjusted OR 1.05; 95 % CI 0.26–4.19) between the vaccine and placebo groups.
Conclusions: The published clinical trials show significant IgG GMC response in subjects receiving the conjugated capsular polysaccharide and surface subunit protein vaccines compared to placebo. In current clinical trials of experimental GBS maternal vaccines, there have been no observed serious adverse events of special interest directly linked to vaccination.

1. Introduction

Group B streptococcus (GBS) or *Streptococcus agalactiae* is widely recognized as the primary cause of severe bacterial infections in newborns during the initial weeks following birth [1–3]. Every year, it is estimated that around 200,000 newborns worldwide are affected by early-onset GBS disease and approximately 160,000 newborns affected by late-onset GBS disease. Maternal and infant GBS disease is also associated with approximately 2 million stillbirths, nearly 0.5 million preterm births, at least 91,900 deaths in children, and over 37,000 cases of moderate to severe neurodevelopmental impairment in children who survive invasive GBS infections [4].

Research on GBS vaccines started almost five decades ago by demonstrating a correlation between level of GBS antibodies and risk of neonatal infection [5–8]. Several GBS virulence factors have been identified as potential vaccine candidates, including the GBS capsular polysaccharides (CPS) and key surface subunit proteins. All 10 CPS-serotypes of GBS can cause disease [9], but the prevalence of the different CPS-serotypes varies worldwide [10,11]. The six CPS-serotypes Ia, Ib, II, III, IV and V are responsible for the majority of invasive infections and are included in the current vaccines in development [1,3,12]. GBS surface subunit proteins, such as Alp family proteins,

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serine-rich repeat proteins, C5a peptidase, and pilus islands, are also associated with invasiveness of GBS strains and are included in vaccines in various stages of clinical development [13–16].

Maternal vaccination leads to increased placental transfer of maternal antibodies [17]. This approach is employed to safeguard infants against many infections e.g. pertussis [18,19], tetanus [20], coronavirus 2 (SARS-CoV-2) [21], and influenza [22]. The development of a successful maternal GBS vaccine has great potential to alleviate the global burden of invasive GBS infections and to reduce antibiotic use in labour [1,3,10]. The purpose of this review is to systematically review and evaluate immunogenicity and safety data of maternal GBS vaccines in published clinical trials until July 2023.

2. Methods

This review follows the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses [23] and is registered in the international prospective register of systematic reviews; PROSPERO ID: CRD42020185213.

2.1. Search strategy and selection criteria

We identified articles by searching electronic databases EMBASE, MEDLINE, Cochrane Library and clinicaltrial.gov. from 1st of January 1996 up to the 31st of July 2023, with the search terms in the following combinations: “Streptococcus agalactiae” OR “Streptococcus Group B” OR “GBS6″ OR ”GBS“ AND ”Vaccine“ OR ”Streptococcal vaccine“ OR ”Maternal vaccine“ OR ” Maternal immunization“ OR ”Maternal immunization“ OR ”Active immunization“ OR ”Active immunization“ OR ”conjugate“ OR ”trivalent“ OR ”second dose“ OR ”immunogenicity“. Identified studies were collated and duplicates/triplicates were manually removed. All English-language published clinical trials (randomised and non-randomised) were eligible if they included an experimental GBS vaccine and reported on immunogenicity of the vaccine in human participants. The exclusion criteria were animal studies, studies dealing with screening and epidemiology, cost-effectiveness and attitudes towards a potential GBS vaccine. We also excluded studies reporting data solely on non-conjugated CPS vaccines, as non-conjugated CPS vaccines have been shown to be clearly inferior to conjugated CPS vaccines [24]. Full-text was read for studies eligible for inclusion to verify its suitability for inclusion. Reference lists of included studies and recent reviews were examined to identify additional studies. We did not conduct searches in the “grey literature”, i.e. unpublished studies, non-peer reviewed studies, conference abstracts and studies not indexed in high-quality databases.

2.2. Data extraction

Two reviewers (A.U.B. and S.R.) screened titles and abstracts independently according to predetermined inclusion and exclusion criteria, with disagreements between the reviewers being resolved through consensus with the third author (C.K.). We extracted the following variables: paper identification (title, first author and publication year), study design, inclusion and exclusion criteria, characteristics of the population (pregnant or non-pregnant adult, adult or infant, average age/gestation and week/day after delivery), study site for clinical trials, characteristics of the vaccines, characteristics of analytical assays, antibody response after vaccination, placental transfer ratio of GBS antibodies and adverse events after vaccination.

2.3. Data synthesis and analysis

The main outcomes assessed were immunogenicity defined as vaccine-elicited geometric mean antibody concentration (GMC), and vaccine efficacy if possible. Immunogenicity data were not possible to *meta*-analyse, and are therefore presented descriptively for each study. As secondary outcomes, we evaluated other immunological responses (e.g. opsonophagocytosis, geometric mean fold rise of GBS antibodies), placental transfer ratio and adverse events (AEs). We evaluated the reported AEs in all studies comparing participants that received a conjugated CPS or surface subunit protein-based vaccine versus those who received placebo. If studies reported data on AEs separately for adjuvanted or non-adjuvanted vaccines, we selected the data on AEs from adjuvanted vaccines. Many studies reported on AEs at different vaccine doses, but we collated these together when analysing the number of AEs in the vaccine group. AEs were reported differently in studies performed more than 15–20 years ago compared to more contemporary studies. Some of the more recent trials [25–33] have used the extensive MedDRA system to present AE data [34]. Three authors (A.U.B, C.K and R.M) assessed AEs independently and compared the findings. In order to obtain similar and comparable AE data across both older and more recent vaccine trials we report rates of the following AEs; serious AEs, AEs leading to withdrawal from the vaccine study, fever/systemic illness in relation to vaccine administration and vaccine-related death. Disagreements were discussed and resolved by consensus. AE data were *meta*-analysed using the online platform recommended for Cochrane intervention reviews (RevMan Web). We calculated risk rations (RRs) with 95 % confidence intervals (CI) for the AEs. We present the effect-estimates by using the random-effect model due to assumption of clinical and methodological diversity among the studies, subsequently often leading to statistical heterogeneity. Reactogenicity data were not possible to *meta*-analyse and therefore presented descriptively for each study.

2.4. Risk of bias of included studies

We used version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), with five domains of bias, to assess study quality [35]. The clinical studies were assessed by the adherence to the intervention (the “per-protocol” effect) and we evaluated the failures in implementing the intervention that could have affected the outcomes.

3. Results

3.1. Study selection

We retrieved 1472 records from databases and an additional 5 records from citations of reference lists. From these 1477, 48 studies were eligible for full-text review. The majority of excluded studies were published protocols, animal studies and preclinical studies. After full-text review we ended up including 26 publications of which 20 reported data from a main study [25–33,36–46] and six reported data from a sub-study of the main study [47–52]. Fig. 1 demonstrates the selection process of the included main studies and sub-studies.

3.2. Characteristics of the included studies

The 20 main clinical studies included a total of 5765 participants, of which 1325 were pregnant women. The characteristics of included studies and the main findings are summarized in Table 1. All studies were either Phase 1 or 2 trials. Nine of the included studies were double-blind randomized controlled trials (RCT) [33,36–43], eight were observer-blind randomized trials [25–28,30–32,46] and three were non-randomized open label trials [29,44,45]. All studies reported data on the elicited GBS-IgG response, except for one study that focus on vaginal GBS colonization [28]. Nine studies evaluated the GBS type-specific opsonophagocytic killing in adult study participants [36–38,41–44,50,51] and one study evaluated this only in sera from infants [40].

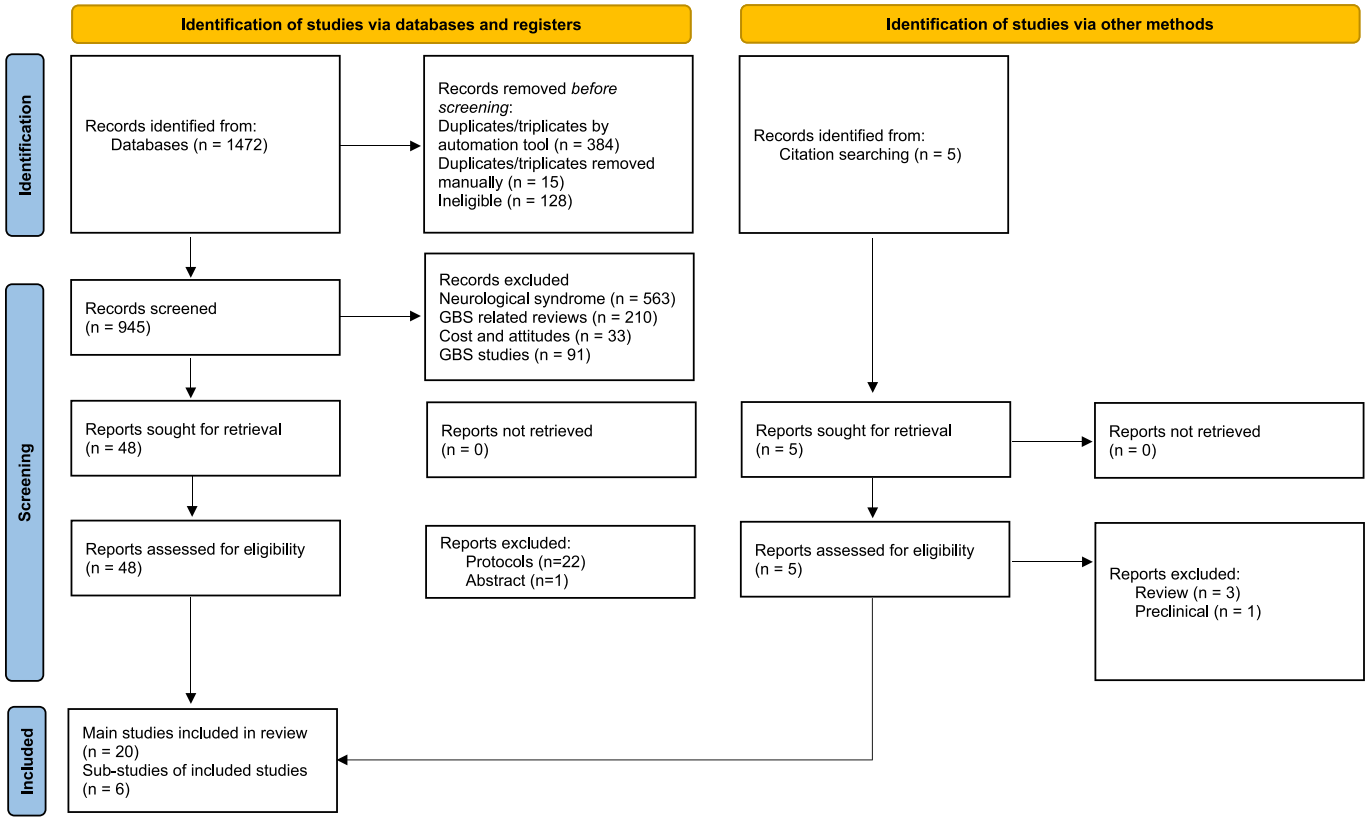

Fig. 1. PRISMA overview of systematic search results.

3.3. Risk of bias

Fig. 2 shows a summary of findings from the risk of bias assessment of the primary outcome immunogenicity. The overall risk of bias was rated as low for immunogenicity data in 12 of the 20 main studies [25–33,44–46]. Eight studies were downgraded to "some concerns" because they had insufficient information about whether the data was analyzed according to a predetermined analysis plan before unblinded outcome data became available for analysis [36–43]. Despite two studies [44,45] being open label and having a high risk of bias, and one study [29] being partially non-randomized and scoring "some concerns" in "Domain 1″, it was unanimously agreed that the open-label nature of these studies would not impact the immunogenicity data based on the judgement of the other domains.

3.4. Immunogenicity

Most studies showed that the GBS antibody GMC response peaked around 4–8 weeks after vaccine administration in healthy adults and pregnant women [31,32,36–43,45]. However, among pregnant women who received vaccinations, three studies reported that the levels of antibodies continued to increase for a minimum of 3 months after childbirth [25,26,31]. The GMC response remained markedly elevated compared to placebo up to 6–12 months after vaccination in both healthy adults and pregnant women [26–28,32,36–39,41–44,46]. Three studies evaluated antibody levels in infant serum during the first 3–6 months after birth [25,31,45]. One of these studies showed a GBS antibody half-life of 42 days in infants without HIV infection [45]. The other two studies found that infant antibody levels were 22–25 % of birth levels three months after birth [25], and while IgG GMCs in vaccinated infants declined with age, they remained 3–9 times higher than in the placebo group at day 90 [31]. One study found that breast milk sIgA GMCs were significantly higher in the Ia/Ib/III-vaccine group compared to the placebo group [31]. In five studies, including the surface subunit protein vaccine, the GMC response was dose-dependent [33,37,38,50] and correlated with *in vitro* opsonophagocytic activity [37,38,43,50]. In four other CPS vaccine dose–response studies there were no significant differences when increasing the dosage [26,27,32,44]. However, while the hexavalent CPS vaccine did not demonstrate a significant difference in testing various doses in non-pregnant adults [32], the interim descriptive analysis of the recent vaccine study in pregnant women suggests that the immune response in pregnant women was dose dependent [46].

The conjugated vaccines included in this review utilized diphtheria (D) toxoid, tetanus (T) toxoid or CRM197 (a non-toxic variant of diphtheria toxin) as conjugates. In the trials comparing a non-conjugated versus a conjugated GBS type-specific CPS vaccine there was a significant higher increase in the IgG GMC response in recipients of the conjugated vaccines versus the unconjugated vaccines [36–38,44]. The response for the conjugated CPS vaccine showed lower levels of IgG GMC in the HIV-infected pregnant women and their infants, compared to the HIV-uninfected pregnant women and their infants (44). A clinical trial investigating the surface subunit protein vaccine in immunocompromised women (NCT04596878) has been completed, but the results are not yet published.

A variety of adjuvants were used in many of the trials including aluminium salts [27,39] or oil-in-water emulsion adjuvant (e.g. MF59 ®) [27]. For the CPS vaccine studies, these adjuvants did not clearly increase immunogenicity [27,39]. In contrast, the surface subunit protein vaccine adjuvanted with aluminium hydroxide elicited a significantly higher GMC response compared to the same vaccine without adjuvant [33]. One study compared the effect of a fully liquid versus a lyophilized formulation of a trivalent (serotypes Ia, Ib and III) GBS vaccine, and found no differences in IgG GMCs 30 days after receiving the single-dose administration of each vaccine formulation in healthy non-pregnant women [30]. A detailed summary of the immunogenicity

Table 1
Included clinical studies om maternal GBS vaccines, immunogenicity data and placental transfer ratio.

Ref. nr.	Main study First author, year, country	Sub-study	Vaccine antigens and dose	Population	N	Intervention	**1.** Geometric mean concentrations (GMC) of GBS-IgG in μg/mL (95 % CI) **2.** Geometric mean fold rise (GMFR) of GBS-IgG Placental transfer ratio
[36]	Kasper 1996 USA	Guttormsen 2002	CPS III (monovalent) Dose: 3.6, 14.5 or 58 μg	Healthy non-pregnant adults	100	III-TT vs III-non-conjugated	**(1)** Four weeks after first dose: GMC against serotype III was 1.0 (0.3–3.6), 2.5 (1.9–7.3) and 4.2 (1.8–9.9), for three different doses, respectively. **(2)** Promoted GBS type-specific OPK up to 4 weeks post vaccination.
[37]	Baker 1999 USA	Brigtsen 2002 Edwards 2012	CPS Ia and Ib (monovalent) Dose Ia-TT: 3.75, 15 or 60 μg Dose Ib-TT: 3.94, 15.75 or 63 μg	Healthy non-pregnant adults	190	Ia-TT vs Ia-non-conjugated vs Placebo Ib-TT vs Ib-non-conjugated vs Placebo	**(1)** Four weeks after first dose: GMC against serotype Ia was 1.5 (0.6–4.3), 13.1 (4.3–39.8) and 25.5 (12.6–51.4), for three different doses, respectively. **(2)** Four weeks after first dose: GMC against serotype Ib was 2.9 (1.1–7.1), 10.7 (3.2–35.7) and 14.2 (5.8–35.0), for three different doses, respectively. **(3)** No cross-immunization. **(4)** Promoted GBS type-specific OPK up to 24 months.
[38]	Baker 2000 USA	–	CPS II (monovalent) Dose: 3.6 or 14.3 or 57 μg	Healthy non-pregnant adults	75	II-TT vs II-non conjugated vs Placebo	**(1)** Four weeks after first dose: GMC against serotype II was 12.7 (6.9–23.2), 39.4 (17.9–86.4) and 39.2 (21.5–71.2), for three different doses, respectively. **(2)** Promoted GBS type-specific OPK up to 4 weeks post vaccination.
[39]	Paoletti 2001 USA	–	CPS III (monovalent) Dose: 12.5 μg	Healthy non-pregnant adults	96	III-TT vs III-TT with $AlPO_4$ 2nd dose of III-TT (without adjuvant)	**(1)** Four weeks after first dose: GMC against serotype III was 3.6 (1.1–12.3). **(2)** Four weeks after 2nd dose: Only a booster effect, with a GMFR of 4, was observed after initial immunization in the eight participants who had undetectable III CPS-specific IgG before the first dose.
[40]	Baker 2003 USA	–	CPS III (monovalent) Dose: 12.5 μg	Healthy pregnant adults, 30–32 w GA	30	III-TT vs Placebo	**(1)** Four weeks after vaccination 95 % of recipients had a GMC $>$ 1.0 **(2)** Four weeks after vaccination the GMFR was $>$ 50-fold increased, and it persisted at delivery and 2 months postpartum. **(3)** Placental transfer ratio 1.4. **(4)** Promoted GBS type-specific OPK in infant sera 2 months after birth.
[41]	Baker 2003 USA	–	CPS II and/or III (mono- or bivalent) Dose: 3.6 μg or 12.5 μg or combined 3.6/12.5 μg	Healthy non-pregnant adults	75	II-TT and III-TT vs. bivalent II/III-TT	**(1)** Four weeks after first dose of 3.6 μg: GMC against serotype II was 6.7 (3.3–13.5). **(2)** Four weeks after first dose of 12.5 μg: GMC against serotype III was 2.0 (0.7–5.8). **(3)** Four weeks after first dose of 3.6/12.5 μg: GMC against serotype II/III was 13.8 (5.8–32.8). **(4)** Promoted GBS type-specific OPK up to 4 weeks post vaccination.
[42]	Baker 2004 USA	Edwards 2012	CPS V (monovalent) Dose: 50 μg	Healthy non-pregnant adults	35	V-TT vs V-CRM_{197}	**(1)** Four weeks after first dose V-TT: GMC against serotype V was 8.9 (3.5–22.4). **(2)** Four weeks after first dose V-CRM_{197}: GMC against serotype V was 6.5 (2.7–16.0). **(3)** Promoted GBS type-specific OPK up to 24 months.
[43]	Palazzi 2004 USA	–	CPS V (monovalent) Dose: 38.5 μg	Healthy non-pregnant adults	32	V-TT vs V-Td	**(1)** Four weeks after first dose V-TT: GMC against serotype V was 2.2 (0.7–6.8). **(2)** Promoted GBS type-specific OPK up to 4 weeks post vaccination.
[44]	Baker 2007 USA	–	CPS V (monovalent) Dose: 38.5 μg	Healthy non-pregnant adults	60	V-TT vs V-non-conjugated	**(1)** Four weeks after first dose V-TT: GMC against serotype V was 11.8 (3.7–37.2). **(2)** Promoted GBS type-specific OPK up to 4 weeks post vaccination.

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Table 1 (*continued*)

Ref. nr.	Main study First author, year, country	Sub-study	Vaccine antigens and dose	Population	N	Intervention	**1.** Geometric mean concentrations (GMC) of GBS-IgG in μg/mL (95 % CI) **2.** Geometric mean fold rise (GMFR) of GBS-IgG Placental transfer ratio
[25]	Donders 2016 Belgium and Canada	Fabbrini 2018	CPS Ia/Ib/III (trivalent) Dose: 5 μg	Healthy pregnant adults, 24–35 w GA	172	Ia/Ib/III-CRM_{197} vs placebo	**(1)** Maternal GMCs at delivery, were against serotypes Ia 5.2 (3.4–8.1), serotype Ib 2.4 (1.5–3.9) and serotype III 1.9 (1.2–3.1). **(2)** Infant GMC at birth, were against serotypes Ia 0.3 (0.2–0.3), serotype Ib 0.2 (0.2–0.3) and III 0.3 (0.2–0.3). **(3)** No interference with diphtheria vaccine. **(4)** Promoted GBS type-specific OPK at delivery. **(5)** Placental transfer ratio 0.7–0.8.
[45]	Heyderman 2016 Malawi and South-Africa	–	CPS Ia/Ib/III (trivalent)	Pregnant women with/ without HIV and newborns	536	Ia/Ib/III -CRM_{197}	**(1)** Four weeks after vaccination of HIV-uninfected participants GMCs against serotypes were for Ia 6.6 (4.4–10), Ib 5.4 (3.6–7.9) and III 5.4 (3.7–7.8). **(2)** Four weeks after vaccination of HIV-infected (low CD4 count) participants GMCs against serotypes were for Ia 2.7 (1.7–4.1), serotype Ib 2.6 (1.6–4.2) and serotype III 1.5 (1.0–2.4).
[26]	Madhi 2016 South Africa	Madhi 2017	CPS Ia/Ib/III (trivalent) Dose: 2.5 or 5 μg	Healthy non-pregnant and pregnant women and newborns	697	Ia/Ib/III -CRM_{197} vs placebo	**(1)** Four weeks after vaccination of pregnant women (merged data for dose 2.5 and 5 μg) GMC against serotypes were for Ia ~ 20 (10–40), Ib ~ 5.5 (2–9) and III ~ 3.5 (2–6). **(2)** GMCs were lowest in those whose baseline concentration was lower than lower limit of detection, particularly for serotype Ib and III. **(3)** Placental transfer ratio 0.5–0.8. **(4)** Vaginal colonization unchanged at delivery.
[27]	Leroux-Roels 2016 Belgium	–	CPS Ia/Ib/III (trivalent) Dose: 5 or 20 μg	Healthy non-pregnant women	678	Ia/Ib/III -CRM_{197} With/without adjuvant and vs placebo	**(1)** Two months after vaccination with trivalent 20 μg vaccine without adjuvants GMCs against serotypes were: Ia 16 (6.9–38), Ib 3.9 (1.6–9.6) and III 2.8 (1.2–6.7). **(2)** GMCs were lowest in those whose baseline concentration was lower than lower limit of detection. **(3)** Two months after vaccination against the three serotypes the GMFRs were 14–89 in the vaccine groups, and remained at 4–5-fold above baseline two years after vaccination.
[28]	Hillier 2019 USA	–	CPS III (monovalent) Dose: 12.55 μg	Healthy non-pregnant adults	667	III-TT vs tetanus/ diphtheria toxin	**(1)** One month after vaccination with the III-TT vaccine GMCs against serotype III was ~ 12 (10–16). **(2)** The GMFR was 40 one month after vaccination (III-TT) compared to baseline values. **(3)** III-TT resulted in significant delay in rectovaginal GBS colonization.
[29]	Leroux-Roels 2020 Belgium	–	CPS Ia/Ib/III (trivalent) Dose: 5 μg	Healthy non-pregnant adults	80	Ia/Ib/III -CRM_{197}, no adjuvant. Second dose 4–6 years after first dose vs a first dose	**(1)** One month after second dose vaccination (both doses without. adjuvant) GMCs against serotypes were: Ia 142.4 (54–379), Ib 56.3 (22–145) and III 111.3 (42–294). **(2)** Two months after second dose, 90–98 % of women with undetectable baseline concentrations before first dose reached the 8 μg/mL threshold across all three serotypes. **(3)** Two months after first dose, 36–56 % of women reached the 8 μg/mL threshold across all three serotypes.
[30]	Beran 2020 Czech Republic, Belgium, USA	–	CPS Ia/Ib/III (trivalent)	Healthy non-pregnant adults	1050	Ia/Ib/III -CRM_{197} Fully liquid vs lyophilized	**(1)** One month after vaccination with a liquid trivalent vaccine (5 μg) the GMCs against serotypes were: Ia 6.8 (5.5–8.4), Ib 2.9 (2.4–3.6) and III 2.4 (2.0–3.0). **(2)** One month after vaccination the GMFR was 8–16 higher than at baseline.

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Table 1 (*continued*)

Ref. nr.	Main study First author, year, country	Sub-study	Vaccine antigens and dose	Population	N	Intervention	**1.** Geometric mean concentrations (GMC) of GBS-IgG in μg/mL (95 % CI) **2.** Geometric mean fold rise (GMFR) of GBS-IgG Placental transfer ratio
							(3) GMCs were lowest in those whose baseline concentration was lower than lower limit of detection.
[31]	Swamy 2020 USA	–	CPS Ia/Ib/III (trivalent)	Healthy pregnant women, 24–34 w GA, and newborns	75	Ia/Ib/III -CRM_{197} vs placebo	**(1)** One month after vaccination GMCs against serotypes were: Ia 9.0 (4.7–17.0), Ib 7.3 (3.5–15) and III 3.6 (1.5–8.6). **(2)** The GMFR was 13–23 fold higher in vaccine vs placebo recipients on day 31 and persisted until postpartum day 90. **(3)** At birth, antibody GMCs in cord blood of infants born to GBS vaccinated. women were 8–39-fold higher than in infants born to placebo recipients. **(4)** Placental transfer ratio 0.6–0.8.
[32]	Absalon 2021 USA	–	CPS Ia/Ib/II/ III/ IV/V (hexavalent) Dose: 5 or 10 or 20 μg	Healthy non-pregnant adults	365	Ia/Ib/II/III/ IV/V -CRM_{197} in different doses vs Placebo. With/without adjuvant.	**(1)** One month after vaccination with GBS6 10 μg (no AlPO4) GMCs against serotypes were: Ia 41.8 (17.7–98.6), serotype Ib 3.6 (1.4–9.3), serotype II 57.0 (31.9–101.8), serotype III 12.8 (6.2–26.4), serotype IV 4.9 (2.9–8.3) and serotype V 5.1 (2.4–11.0). **(2)** One month after vaccination. GBS serotype-specific IgG GMFR. ranged from 25 to more than 200 for each serotype. **(3)** The GMFR remained 10–56 for all doses and formulations of GBS6 at 6 months after vaccination compared with placebo.
[33]	Fischer 2021 UK	Pawlowski 2022	Protein subunit NN/NN2 Dose: 10 or 50 or 100 μg	Healthy non-pregnant adults, (non-vaccinated pregnant women and newborns, n = 304)	240	NN/NN2 in different doses vs placebo. With/without adjuvant.	**(1)** Four weeks after vaccination, two doses of 50 μg, the GBS-NN IgG GMC was 6.0 (3.9–9.3). Maximal response was 16.9 (11.3—25.4) 85 days after vaccination. **(2)** For the 2-dose (50 μg) regimen 100 % and 89 % of the subjects achieved antibody levels above the arbitrary thresholds of 1 and 4 μg/ml, respectively. **(3)** Added effect of a second dose most pronounced for subjects with pre-existing IgG levels below the median of the entire cohort. **(4)** The natural occurring placental transfer ratio 1.1–1.2.
[46]	Madhi 2023 South Africa		CPS Ia/Ib/II/ III/ IV/V (hexavalent) Dose: 5 or 10 or 20 μg	Healthy pregnant women, 27–36 w GA, and newborns	360	Ia/Ib/II/III/ IV/V -CRM_{197} in different doses vs placebo. With/without adjuvant.	**(1)** Maternal GMCs at delivery, after vaccination with GBS6 20 μg (no AlPO4), were against serotypes: Ia 40.3 (23.9–68.2), serotype Ib 1.3 (0.6–2.9), serotype II 27.6 (15.6–48.9), serotype III 6.4 (2.8–14.4), serotype IV 2.5 (1.5–4.2) and serotype V 0.9 (0.4–2.0). **(2)** Infant GMC at birth after maternal vaccination with GBS6 20 μg (no AlPO4), were against serotypes: Ia 29.6 (17.0–51.5), serotype Ib 0.7 (0.3–1.8), serotype II 20.8 (10.7–40.5), serotype III 3.2 (1.3–7.7), serotype IV 2.1 (1.2–3.7) and serotype V 0.6 (0.2–1.4). **(3)** Placental transfer ratio 0.4–1.3 across the different serotypes.

Abbreviations: Ref. nr., reference number; CI, confidence interval; CPS, capsular polysaccharide; OPK, Opsonophagocytic killing; GMC, Geometric mean antibody concentration; TT, Tetanus toxoid conjugated vaccine; CRM_{197}, non-toxic mutant form of the 58-kd diphtheria toxin; Td, Tetanus-diphtheria toxoid vaccine; NN/NN2, N-terminal domains of the Rib and AlphaC proteins vaccine; $AlPO_4$, aluminium phosphate; GA, gestational age.

outcomes is presented in Table 1.

A second dose or a booster dose improved IgG GMC in study participants with low initial CPS-specific IgG GMC after the first dose in both the conjugated CPS-vaccine and the surface subunit protein vaccine [29,33,39]. There was no additional benefit of a booster for participants with an adequate initial CPS-specific IgG GMC concentration [27,39]. In HIV-infected pregnant women, the serotype-specific antibody concentrations were lower compared to the HIV-uninfected pregnant women [45].

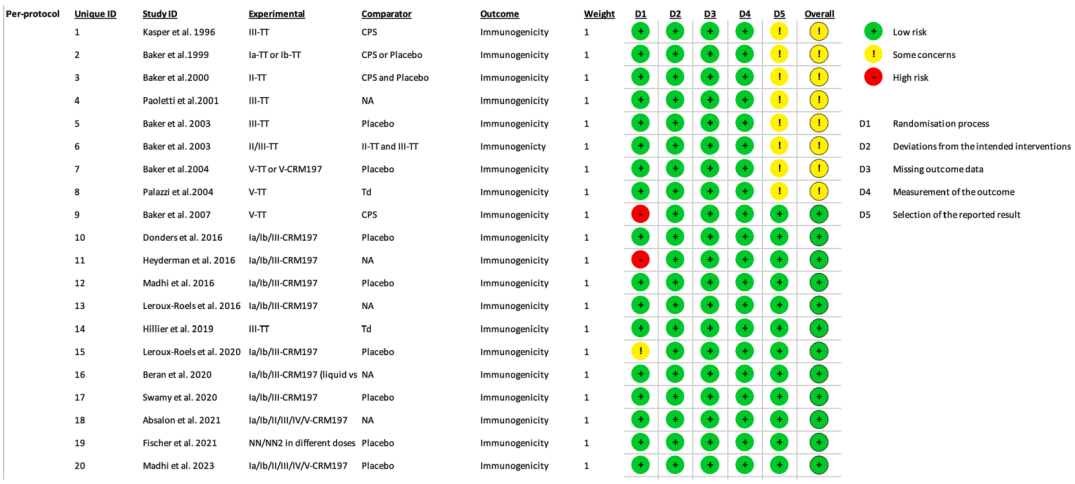


Fig. 2. Risk of bias for immunogenicity outcomes.

3.5. Placental transfer ratio

The placental transfer ratio, defined as the ratio between the level of GBS-specific antibodies in maternal serum during pregnancy and corresponding level in cord blood or infant serum shortly after birth, was investigated in five vaccine studies [25,26,40,45,46]. In three studies the IgG placental transfer ratios were 1.42 for III-TT [40], 0.66–0.79 for Ia/Ib/III-CRM$_{197}$ [25] and 0.49–0.79 for Ia/Ib/III-CRM$_{197}$ [26]. In one study the placental transfer ratio was 0.49–0.72 both in the HIV-uninfected group and the HIV-infected groups [45]. In a recent study reporting data from the hexavalent vaccine, the placental transfer ratio ranged from approximately 0.4 to 1.3. In this study the highest antigen dose provided IgG GMCs in infant sera associated with an estimated 75 % risk reduction of perinatal GBS disease in 57–97 % participants, depending on the serotype [46]. For the surface subunit protein vaccine the natural placental transfer ratio was 1.22 for αC-N-specific IgG and 1.12 for Rib-N-specific IgG, but not assessed after vaccination [51].

3.6. Reactogenicity and adverse events

All 20 original articles reported data on reactogenicity and more severe AEs/safety in non-pregnant adults [26–30,32,33,36–39,42–44], pregnant women [25,26,31,40,41,45,46] and infants [31]. Mild vaccine reactogenicity symptoms such as pain at the injection site, tenderness or local swelling were described in all studies. These were more frequently reported in studies comparing adjuvanted versus not adjuvanted vaccines [26,27,32,37,38,42,44,46]. The most frequent solicited systemic AEs were fatigue and headache [25,26,37,42]. Most solicited AEs were mild or moderate.

There were no reported deaths relating to the trial vaccines across the 20 clinical trials [25–33,36–46]. Fig. 3a-c shows an overview of serious AEs, AEs leading to withdrawal from the vaccine study and fever/systemic illness in 11 of 20 of the clinical trials included in this review [25–27,31–33,36,37,40,42,46], while Table 2 shows an overview of reactogenicity and AEs across the 20 studies. One study presented a significantly lower rate of serious AEs in the CPS vaccine conjugated with tetanus-toxoid versus tetanus-diphtheria toxoid group [28]. We did not identify any age pattern for AEs [26–30,32,33,36–39,42–44], and no higher incidence of pregnancy-related AEs reported after vaccination [25,26,31,40,41,45,46]. There were no increased systemic AEs reported after the second dose when comparing it to the first dose administration [29,33,39].

In two studies [30,33] reporting on pregnancies after receiving the GBS-vaccine, none of the adverse pregnancy outcomes were assessed as related to vaccination (Table 2). The capsular conjugate vaccine studied in HIV infected pregnant mothers showed no effect on CD4 count and viral loads [45].

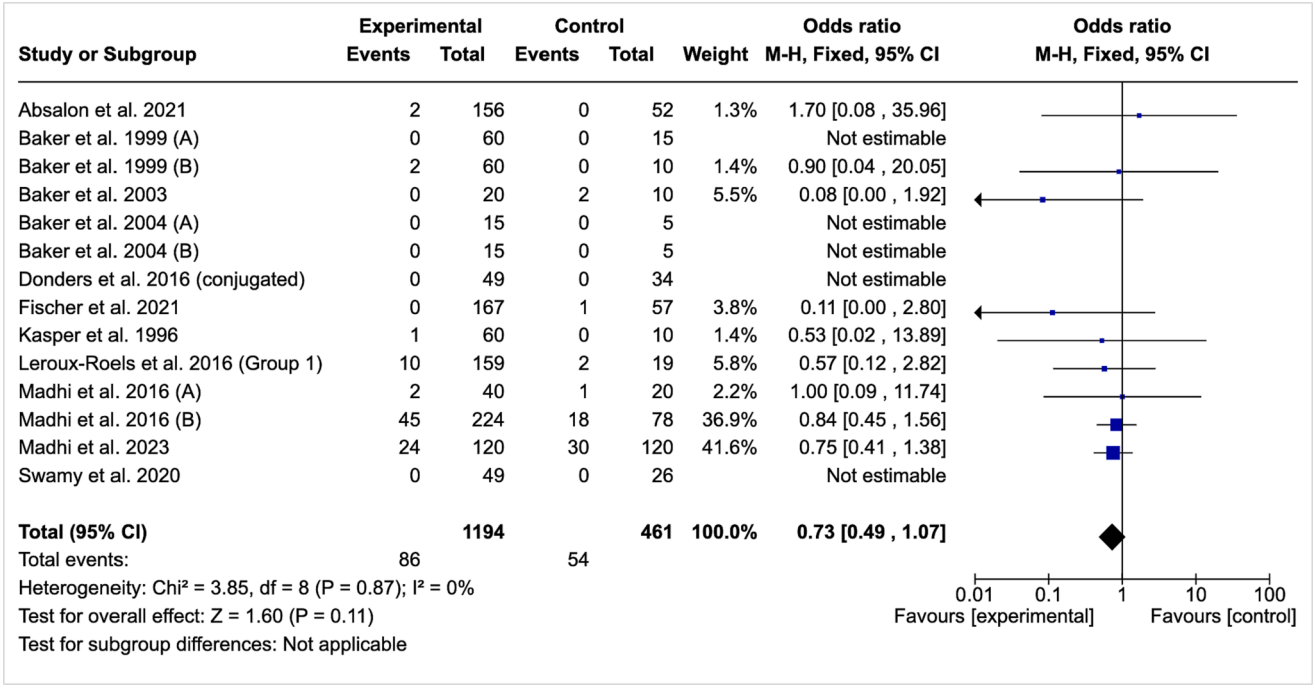
4. Discussion

The global public health impact of perinatal GBS disease is a matter of great concern and the development of GBS vaccines for maternal immunization is therefore top priority [53].

In this systematic review we identified and included a total of 20 primary studies published between 1996 and 2023. There were 5765 participants, of which only 1325 were pregnant women. Our review revealed large disparities in the methods used to measure immunogenicity and how AEs were reported. Still, there are three key findings. First, the vast majority of participants, exposed to conjugated CPS vaccines or the surface subunit protein vaccine, exhibited markedly increased IgG GMC concentrations compared to placebo. There were also an increase in the antibody GMC following a second dose in those who had low baseline antibody GMC, and antibody levels remained clearly above baseline values for at least 6–12 months [25,26,29–33,36–45]. Second, placental transfer ratios ranged from 0.4 to 1.4 indicating that antibody crosses the placenta and can protect infants from invasive GBS disease [25,26,40,45,51]. Third, we found low levels of reactogenic events and serious AEs regarding the experimental vaccines, in non-pregnant adults [26–30,32,33,36–39,42–44], pregnant women [25,31,40,41,45,46] and infants [31].

4.1. Immunogenicity

Evaluating the reported GBS-IgG levels in the studies included in this review was challenging as they varied by different serotypes covered in the vaccines, the immunogenicity assays and reagents used, and the different time schedules for assessment across studies. Thus, data were not possible to *meta*-analyze and were summarized for each study separately. Naturally acquired anti-GBS IgG concentrations associated with a reduced risk of disease among infants are reported from seroepidemiological studies [46,54–57]. However, it is important to note that suggested protective thresholds are based on a limited number of cases versus controls in seroepidemiological study, which poses a limitation to the findings. There is also no uniform agreement on how to establish "protective" GBS-IgG levels, and there is limited data in particular for the low-prevalent CPS-serotypes vaccines and the surface subunit protein vaccines [58]. Some data suggest that anti-GBS-CPS IgG concentrations at around 1 μg/mL or higher are "protective" [55,59]. In all studies evaluating CPS-IgG levels in our review the majority of elicited anti CPS-IgG concentrations were above 1 μg/mL in non-pregnant adults



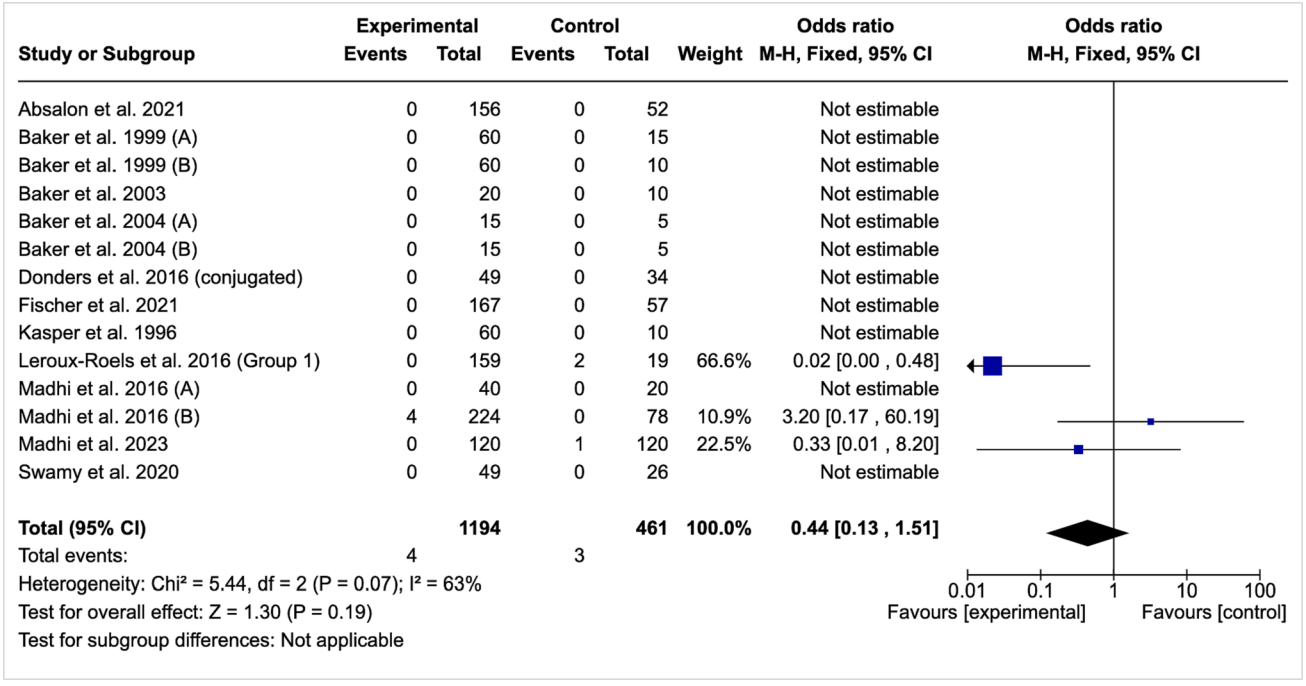


Fig. 3. Forest Plots of adverse effects in studies comparing a GBS vaccine versus placebo. **a.** Pooled results of studies comparing risk of serious adverse events between those who received a GBS vaccine versus placebo. The sizes of the squares are proportional to study weights. Diamond markers indicate pooled effect sizes. **b**. Pooled results of studies comparing risk of serious adverse events leading to withdrawal from the study between those who received a GBS vaccine versus placebo. The sizes of the squares are proportional to study weights. Diamond markers indicate pooled effect sizes. **c.** Pooled results of studies comparing risk of fever/systemic illness between those who received a GBS vaccine versus placebo. The sizes of the squares are proportional to study weights. Diamond markers indicate pooled effect sizes.

and pregnant women 4–8 weeks after vaccination. For the multivalent conjugated CPS vaccines, we observed different immunogenicity among the different serotypes. The main pattern was a markedly higher IgG GMC response to serotype Ia versus the other serotypes Ib, II, III, IV, V [25–27,30–32,37,41,46], though the potential clinical importance of this observation in unclear. Regarding the surface subunit protein vaccine, there is no specified threshold for protective anti-protein IgG concentration [60–62], and comparing the studies estimating this has been challenging due to variations in assay methods, protein sources, absence of a common reference serum, and differences in study designs [58].

Polysaccharides are weak vaccine antigens and therefore often conjugated to an immunogenic protein, eliciting a strong T-cell dependent response with establishment of B-cell memory and long-term

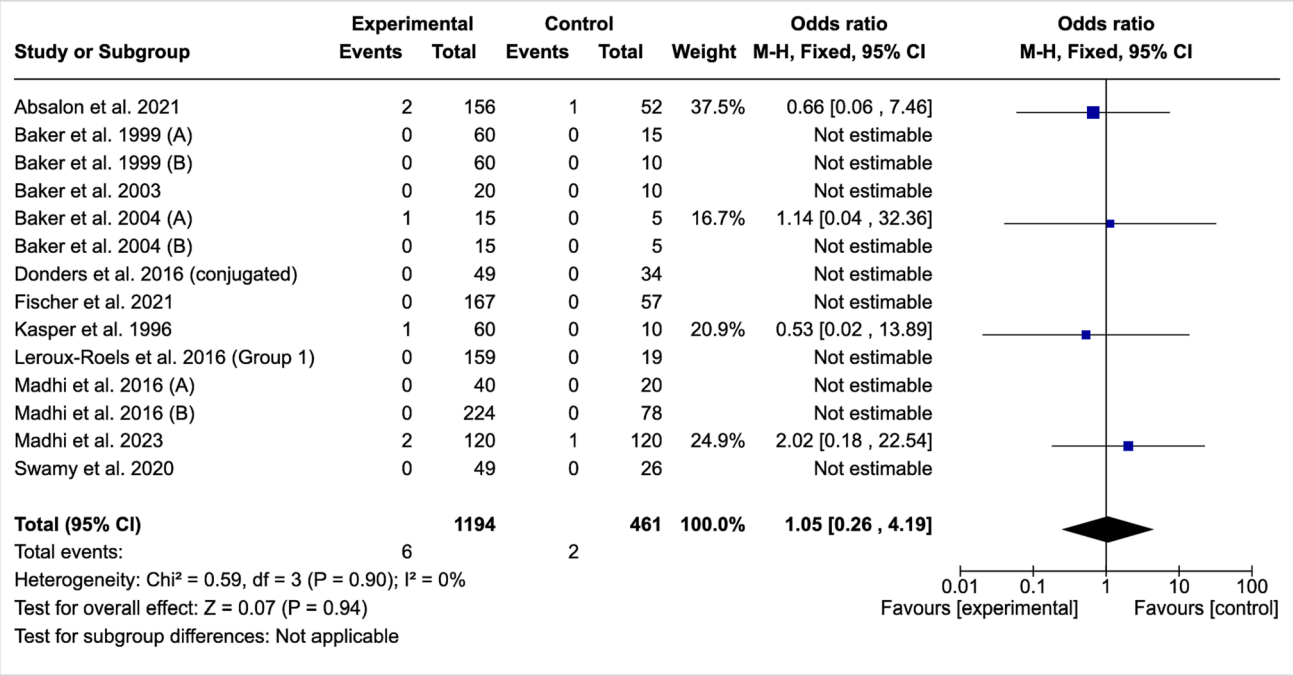


Fig. 3. (*continued*).

immunization [63]. Toxoids are often selected as the carrier proteins due to their inherent immunogenicity and the potential for a booster effect in previously immunized recipients [64]. Conjugation of the GBS-CPS with a toxoid protein carrier was essential to achieve an adequate immune response in the studies in this review comparing conjugated and non-conjugated vaccines [36–38,44]. This principle is well known from other CPS-based vaccines like the pneumococcal glycoconjugate vaccine [63]. For the surface subunit protein vaccine conjugation was not needed as proteins are more antigenic than polysaccharides. Including GBS surface subunit proteins in future vaccines offers advantages over unrelated proteins like tetanus toxoid or CRM197. It could simplify coverage for additional strains beyond the CPS serotypes included and enhance protection against some strains. However, using a range of carrier proteins in some conjugate vaccines may increase reactogenicity and potentially suppress the immune response to CPS [65].

Vaccine adjuvants are also often added to enhance the ability of a vaccine to elicit strong and durable immune responses, especially in immunologically compromised individuals like immature neonates and immunosuppressed individuals [66]. Adjuvants, e.g. aluminum salts, may also reduce the antigen dose needed and subsequently the number of immunizations [67]. For the surface subunit protein vaccine, adding an adjuvant enhanced immunogenicity [32]. When examining the conjugated CPS-based GBS vaccines in our review, we did not observe any indications that adjuvants enhanced immunogenicity [27,39]. However, it is important to acknowledge that these vaccines were predominantly evaluated in immunocompetent adults. In contrast, the commercial polyvalent pneumococcal CPS-vaccines contain aluminum salts, in order to elicit immune response in young infants from the age of 2 months and upwards [68]. We belive it is less likely that future commercial CPS-based GBS vaccines for pregnant women will be manufactured with adjuvants.

The majority of the trials had a follow-up period of 6 months [25,31–33,36,38,40,41,45,46] and some even longer [26,28,29,37,39,42–44]. These studies report a decline of antibody levels in both the mother and child, in line with the expected gradual decrease of antibodies levels over a period of 6–12 months. While the majority of studies did not assess the functionality of maternal antibodies, earlier research has demonstrated that functional GBS antibodies can endure for as long as two years after vaccination [36–38,41–44,50,51] and at least 2 months in infants [40].

4.2. Placental transfer

Our review found that conjugated CPS-based vaccines resulted in induction of anti GBS-IgG which were effectively transmitted across the placenta. The infant antibody levels, derived from transferred IgG, is also most likely more relevant for defining a level for risk reduction of acquiring invasive GBS disease compared to maternal antibody levels. Only five studies provided data from infant sera after maternal vaccination [25,26,40,45,46]. Overall, the placental transfer ratios varied between 0.4 and 1.4 across these five studies. Evaluating placental transfer ratios from different vaccines should ideally also include presentation of vaccine induced IgG subclasses. Studies indicate the IgG1 has the highest transfer ratio and IgG2 the lowest [69,70]. However, the placental transfer ratio could also be affected by the IgG subclass distribution pattern in a population [69,70]. Similarly, earlier vaccine studies have indicated that vaccination response can be influenced by racial and ethnic factors [71–77].

4.3. Safety and adverse events

Overall, the safety profile of GBS vaccines evaluated in this systematic review were reassuring. However, our data must be interpreted with caution. First and foremost, the number of participants included in our review were only 5765 participants, of which only 1325 were pregnant women. Secondly, distinguishing between pregnancy related complications and symptoms, and vaccine-related AEs is challenging in maternal vaccine studies. This difficulty arises because both pregnancy and vaccines can lead to similar symptoms, such as nausea, making it a complex task to determine whether these symptoms are solely attributable to normal pregnancy experiences or are indicative of AEs. Factors like maternal age, obstetrical history, and health conditions influence pregnancy outcomes. Understanding these factors is vital for interpreting AEs in clinical vaccine trials [78]. Additionally, a much higher number of participants will be needed to detect rare and severe side effects, like the vaccine-induced immune thrombotic thrombocytopenia

Table 2
Adverse events reported in 20 GBS vaccine studies.

Ref. nr.	First author, year, country	Population	N	Intervention	Reactogenicity	Adverse events (AEs) and serious adverse events (SAEs)	Adverse events of special interest (AESI)
[36]	Kasper 1996 USA	Healthy non-pregnant adults	100	III-TT vs III-non-conjugated vs placebo	**(1)** 7 % experienced serious redness/swelling at the injection site in the 14.5 μg III-TT group. (2) No severe systemic reactions reported.	None	1.7 % in III-TT group had a temperature of 100.38°F coupled with RTI that resolved within 24 h.
[37]	Baker 1999 USA	Healthy non-pregnant adults	190	Ia-TT vs Ia-non-conjugated vs Placebo Ib-TT vs Ib-non-conjugated vs Placebo	**(1)** Ia-TT vs Ia-non-conjugated vs Placebo: None experienced serious pain or redness/swelling at the injection site. **(2)** Ib-TT vs Ib-non-conjugated vs Placebo: 3.3 % experienced serious pain or redness/swelling at the injection site in the 63 μg Ib-TT group. **(3)** No severe systemic reactions reported.	None	No significant changes in CBC or blood chemistry values noted 2 days after vaccination in all groups.
[38]	Baker 2000 USA	Healthy non-pregnant adults	75	II-TT vs II-non conjugated vs Placebo	**(1)** 10 % experienced serious redness/swelling at the injection site in the 57 μg II-TT group and none in the II CPS group. **(2)** 6.7 % experienced chills, malaise, headache, and temperature to 37.8 °C up to 36 h after immunization in the 14.3 μg II-TT group.	None	Not retrievable
[39]	Paoletti 2001 USA	Healthy non-pregnant adults	96	III-TT vs III-TT with $AlPO_4$ 2nd dose of III-TT (without adjuvant)	**(1)** III-TT vs III-TT with $AlPO_4$: 6.7 % experienced serious pain at the injection site both with and without adjuvant. **(2)** 2nd dose of III-TT (without adjuvant): 2.8 % experienced serious redness/swelling at the injection site. **(3)** 2.8 % in the 12.5 μg, first dose, III-TT experienced severe systemic reactions.	**(1)** 1 experienced fever of 100.4°F associated with chills, malaise, and headache 18 h after receiving the first dose of GBS III-TT conjugate (accidently) combined with GBS II-TT. **(2)** No SAEs reported.	Not retrievable
[40]	Baker 2003 USA	Healthy pregnant adults, 30–32 w GA	30	III-TT vs Placebo	**(1)** No serious pain or redness/swelling reported at the injection site in either group. **(2)** No severe systemic reactions reported.	None	Not retrievable
[41]	Baker 2003 USA	Healthy non-pregnant adults	75	II-TT and III-TT vs. bivalent II/III-TT	**(1)** No serious pain or redness/swelling at the injection site reported in the groups. **(2)** 2 with reported severe systemic reactions.	**(1)** AEs: 2 experienced fever of 100.6°F and 100.4°F at 11 h and 17 h after immunization with monovalent GBS III–TT and bivalent II/III-TT, respectively. Fever combined with chills, mild headache, malaise, and myalgia. **(2)** No SAEs reported.	Not retrievable
[42]	Baker 2004 USA	Healthy non-pregnant adults	35	V-TT vs V-CRM_{197} Placebo	**(1)** No serious pain or redness/swelling reported at the injection site in the groups. **(2)** 6.7 % in the V-TT group experienced systemic reactions.	**(1)** AEs: 3.3 % in V-TT experienced headache, malaise, myalgia, and nausea a few hours after immunization. **(2)** No SAEs reported.	Not retrievable
[43]	Palazzi 2004 USA	Healthy non-pregnant adults	32	V-TT vs Td	**(1)** No serious pain or redness/swelling at the injection site reported in the groups. **(2)** No severe systemic reactions reported.	**(1)** AEs: 1 reported fatigue and myalgia within a few hours of immunization in the V-TT group, while in the Td group 1 reported moderate fatigue on day 2 after	Not retrievable

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Table 2 (*continued*)

Ref. nr.	First author, year, country	Population	N	Intervention	Reactogenicity	Adverse events (AEs) and serious adverse events (SAEs)	Adverse events of special interest (AESI)
						immunization. **(2)** No SAEs reported.	
[44]	Baker 2007 USA	Healthy non-pregnant adults	60	V-TT vs V-non-conjugated	**(1)** 6.7 % in the 38.5 μg V-TT group experienced serious pain at the injection site. **(2)** No severe systemic reactions reported.	None	1 reported fever, sore throat, malaise and myalgias 6 h after vaccination, coupled with RTI that resolved within 24 h.
[25]	Donders 2016 Belgium and Canada	Healthy pregnant adults, 24–35 w GA	172	Ia/Ib/III-CRM$_{197}$ vs placebo	**(1)** No serious pain or redness/swelling reported at the injection site in the vaccine group, while 0–6 % in the placebo group reported severe local reactions. **(2)** 0–6 % in placebo group reported systemic reactions.	**(1)** AEs: 63 % [95 % CI 48.1–75.9 %] and 74 % [95 % CI 56.7–87.5 %] reported in vaccine and placebo, respectively. **(2)** SAEs: reported in 24 % and 31 % of infants in the vaccine and placebo groups, respectively. No SAEs in maternal groups.	Obstetric outcomes were similar between the vaccine and placebo groups. 1 neonatal asphyxia occurring 28 days after maternal vaccination.
[45]	Heyderman 2016 Malawi and South-Africa	Pregnant women with/without HIV and newborns	536	Ia/Ib/III-CRM$_{197}$	**(1)** 2 %, 0 % and 4 % reported severe pain at injection site in HIV-infected low CD4 cell count, HIV-infected high CD4 cell count and HIV-uninfected, respectively. **(2)** Fever only reported in HIV-infected low CD4 cell count group (n = 3).	**(1)** AEs: 7 %, 13 % and 23 % reported AE possibly related to vaccine in HIV-infected low CD4 cell count, HIV-infected high CD4 cell count and HIV-uninfected, respectively. In infants the rates were 0 %, 2 % and 1 %, respectively. **(2)** SAEs: None at least possibly related to vaccination. **(3)** Similar rates of maternal and infant SAEs reported across all groups. **(4)** No differences in obstetric outcomes and pregnancy events were recorded across the three groups. **(5)** No association between vaccine administration and change in viral load was seen in the HIV-infected groups.	1 maternal death in the HIV-infected high CD4 cell count group. 4, 2 and 2 neonatal deaths in HIV-infected low CD4 cell count, HIV-infected high CD4 cell count and HIV-uninfected, respectively.
[26]	Madhi 2016 South Africa	Healthy non-pregnant and pregnant women and newborns	697	Ia/Ib/III-CRM$_{197}$ vs placebo	**(1)** No serious pain or redness/swelling at the injection site reported. **(2)** Systemic reactions were reported by 95 % and 90 % of the women in the vaccine and placebo groups, respectively, with the most reported reactions being myalgia, headache, and fatigue. Similar rates for pregnant and non-pregnant women.	**(1)** AEs: Unsolicited were reported by 30 (75 %) participants in the vaccine group and 16 (80 %) participants in the placebo group, with 40 % per group (23 % for pregnant) considered possibly related to study vaccination. Similar rates for pregnant and non-pregnant. **(2)** SAEs: None at least possibly related to vaccination.	Obstetric outcomes were similar between the vaccine and placebo groups. 3 stillbirths were recorded in placebo group (4 %) and 4 (2 %) in vaccine groups.
[27]	Leroux-Roels 2016 Belgium	Healthy non-pregnant women	678	Ia/Ib/III-CRM$_{197}$ With/without adjuvant (AlOH or MF59) and vs placebo	**(1)** No serious pain or redness/swelling at the injection site reported. **(2)** 50 %–85 % across vaccine groups, and 58 %–65 % in the placebo groups reported systemic reactions.	**(1)** AEs: On average 26 % (no adjuvant), 14 % (AlOH) and 0 % (placebo) in enrolment group 1. On average 11 % (MF59 half), 18 % (MF59 full) and 5 % (placebo) in enrolment group 2. Similar rates in possibly related to vaccination. **(2)** SAEs: None at least possibly related to vaccination.	None mentioned
[28]	Hillier 2019 USA	Healthy non-pregnant adults	667	III-TT vs tetanus/diphtheria toxin	**(1)** No serious pain or redness/swelling at the injection site reported. **(2)** 41 % in the III-TT and none in the Td groups reported systemic reactions (headache, malaise, muscle aches).	**1)** AEs: Around 9.8 % considered to be vaccine associated in all groups. **(2)** SAEs: None at least possibly related to vaccination.	None mentioned

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Table 2 (*continued*)

Ref. nr.	First author, year, country	Population	N	Intervention	Reactogenicity	Adverse events (AEs) and serious adverse events (SAEs)	Adverse events of special interest (AESI)
					(3) Women who received Td vaccine reported local symptoms of greater severity compared to women who received GBS III-TT vaccine		
[29]	Leroux-Roels 2020 Belgium	Healthy non-pregnant adults	80	Ia/Ib/III-CRM$_{197}$ vs non-vaccinated Second dose 4–6 years after first dose vs a first dose	**(1)** 7 % in the GBS without adjuvant group experienced serious pain at the injection site. **(2)** No severe systemic reactions reported.	**(1)** AEs: Across groups, 29 %–67 % of women reported unsolicited AEs within 31 days postvaccination. **(2)** SAEs: None at least possibly related to vaccination.	2 in the prior GBS group reported RTI and hot flush after immunization, while 2 in the no prior GBS group reported injection site erythema and nasal congestion after immunization.
[30]	Beran 2020 Czech Republic, Belgium, USA	Healthy non-pregnant adults	1050	Fully liquid vs lyophilized trivalent GBS vaccine	**(1)** 0.2 % experienced serious pain and redness/swelling at the injection site in the fully liquid vaccine group, while 0.2 % experienced serious pain in the lyophilized vaccine group. **(2)** No more than 2.1 % experienced severe systemic reactions in either group.	**(1)** AEs: 11 % and 10 % of women in Liq and Lyo, respectively. **(2)** SAEs: None at least possibly related to vaccination.	10 women became pregnant during the study; 5 singleton liveborn babies, 1 stillbirth, 2 abortions (one spontaneous and one therapeutic) and 2 pregnancies lost to follow-up.
[31]	Swamy 2020 USA	Healthy pregnant women, 24–34 w GA, and newborns	75	Ia/Ib/III-CRM$_{197}$ vs placebo	**1)** No serious pain or redness/swelling at the injection site reported in the groups. **(2)** 1 % (vaccine) and 2 % (placebo) experienced severe systemic reactions (fatigue).	**(1)** AEs: None related to maternal vaccination. **(2)** SAEs: 15 % and 12 % of infants in the vaccine and placebo groups, respectively. None related to maternal vaccination.	16 % in the vaccine group experienced ten AESI in total (amniotic cavity infection, arrested labor [five cases], gestational hyper- tension, pre-eclampsia, premature separation of placenta, prolonged labor) and 15 % in the placebo group experienced six AESI (anemia, cholelithiasis, breech presentation, pre-eclampsia, umbilical cord prolapse, nephrolithiasis). None related to vaccine.
[32]	Absalon 2021 USA	Healthy non-pregnant adults	365	Ia/Ib/II/III/ IV/V-CRM$_{197}$ in different doses vs Placebo	**(1)** No serious pain or redness/swelling reported at the injection site in the groups. **(2)** No severe systemic reactions reported.	**(1)** AEs: Rates ranging from 12 % in the 10 μg without AlPO4 group to 29 % in the 20 μg with AlPO4 group and placebo group. Most common upper respiratory tract infection and sinusitis. **(2)** SAEs: Reported on 3 GBS6 with AlPO4 recipients (diabetic ketoacidosis, suicide, metrorrhagia) and none in the GBS6 without AlPO4 and placebo groups.	None of the changes in laboratory values after vaccination were associated with clinical findings.
[33]	Fischer 2021 UK	Healthy non-pregnant adults, (non-vaccinated pregnant women and newborns, n = 304)	240	NN/NN2 in different doses vs placebo (Part A) and comparing effects of single dose versus booster (Part B). With/without adjuvant.	**(1)** No serious pain or redness/swelling reported at the injection site in either group. **(2)** No severe systemic reactions reported.	**(1)** AEs: Similar across vaccine and placebo (gastrointestinal, nervous system and infections and infestations system organ classes). **(2)** SAEs: None at least possibly related to vaccination.	12 pregnancies reported (6 in placebo and 6 in GBS-NN); 7 liveborn, 4 spontaneous abortions (2 in each group), and 1 lost to follow-up.
[46]	Madhi 2023 South Africa	Healthy pregnant women, 27–36 w GA, and newborns	360	Ia/Ib/II/III/ IV/V -CRM$_{197}$ in different doses vs placebo. With/without adjuvant.	**(1)** No serious pain or redness/swelling reported at the injection site in either group. **(2)** Severe systemic events were reported in 4 GBS6 recipients and 4 placebo recipients (fever).	**(1)** AEs: 45 to 70 % in the GBS6 groups and 61 % in placebo group reported (fetal distress syndrome most common). Only headache and vomiting related to vaccine. **(2)** SAEs: None at least possibly related to vaccination.	1 stillbirth in GBS6. 1 fatal motor vehicle accident. None related to the vaccine.

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Table 2 (*continued*)

Ref. nr.	First author, year, country	Population	N	Intervention	Reactogenicity	Adverse events (AEs) and serious adverse events (SAEs)	Adverse events of special interest (AESI)
						(3) 24 women in the GBS6 with AIPO4 and 43 in the GBS6 without AlPO4 groups reported SAEs. **(4)** Similar number on infants reported an SAE in both groups.	

Abbreviations: Ref. nr., reference number; CPS, capsular polysaccharide; OPK, Opsonophagocytic killing; GMC, Geometric mean antibody concentration; TT, Tetanus toxoid conjugated vaccine; CRM_{197}, non-toxic mutant form of the 58-kd diphtheria toxin; Td, Tetanus-diphtheria toxoid vaccine; NN/NN2, N-terminal domains of the Rib and AlphaC proteins vaccine; $AlPO_4$, aluminium phosphate; GA, gestational age.

observed after the adenoviral vector covid19-vaccine [79]. The current GBS vaccine candidates are based on bacterial surface subunit protein products and by definition inactivated or killed vaccines, and considered more safe than live vaccines. This safety extends to pregnancy, where purified macromolecule vaccine types such as subunit vaccines, conjugate vaccines, and inactivated toxoids are considered suitable. Nevertheless, continuous safety monitoring remains crucial to assess their appropriateness for this vulnerable population [80]. A recent maternal vaccination trial against respiratory syncytial virus indicated that the vaccine might increase the rate of premature births [81]. Our data did not show any signal towards increased rates of premature births, but with only 1325 pregnant participants in GBS vaccine trials this potential side effect could not be ruled out in our dataset. Hence, it is crucial to establish a robust Vaccine Adverse Event Reporting System (VAERS) and maintain vigilant safety monitoring post-licensure of a maternal GBS vaccine.

4.4. Strengths and limitations

The strengths of our systematic review include our rigorous and sensitive search strategy following an *a priori* registered protocol. Additionally, we targeted an area of global concern and importance. GBS vaccines have been focus for clinical trials since the 1990s, still only around 5800 participants were identified in the 20 studies in this systematic review. A greater volume of data is necessary, even in cases where a vaccine's licensure relies on sero-correlation information rather than clinical efficacy. Another key constraint was the inability to conduct a *meta*-analysis for the primary outcome of immunogenicity (IgG GMCs) due to the heterogeneous use of seroassays across studies. The international consortium known as GASTON (Group B Streptococcus: Standardization of Laboratory Assays) has reached a consensus on a unified protocol for GBS antibody assays. This standardized procedure marks a significant milestone in their collaborative efforts to ensure consistency and reliability in GBS-related research [82,83]. Our evaluation of adverse events data revealed no significant issues concerning the various GBS vaccine candidates. Comparable levels of reactogenicity and adverse effects were noted in both the intervention and control groups. However, limited sample sizes prevent us from drawing a definitive conclusion regarding adverse effects.

4.5. Implication and conclusion

All candidate maternal GBS vaccines presented good immunogenicity and safety data. A multivalent CPS-based vaccine or a broad-spectrum surface subunit protein vaccine are the most promising vaccine candidates. This systematic review also highlights that there are still significant uncertainties in the determinants of the antibody response, particularly in people who have low baseline GBS antibodies. Our findings also support the recent initiative to standardize measurement methods in order to facilitate direct comparison and extrapolation of results.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors AUB, SR and RM declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. CK is involved in a seroepidemiologocal study, partly funded by Pfizer, but does no receive personal honoraria in this study. KLD's University has received funds from Pfizer, Minervax and GSK for unrelated vaccine work. KLD has received no personal honoraria.

Data availability

Data will be made available on request.

Acknowledgements

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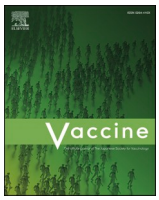

Corrigendum to "The immunogenicity and safety of Group B Streptococcal maternal vaccines: A systematic review" [Vaccine 42 (2024) 84–98]

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