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Commentary

Clinical and regulatory development strategies for GBS vaccines intended for maternal immunisation in low- and middle-income countries

Kirsty Le Doare [a,b,c,*], Virginia Benassi [a], Marco Cavaleri [d], Godwin Enwere [e], Birgitte Giersing [a], David Goldblatt [f], Paul Heath [b], Joachim Hombach [a], Richard Isbrucker [g], Kostas Karampatsas [b], Shabir A. Madhi [h], Annelies Wilder Smith [a]

[a] Immunizations, Vaccine and Biologicals, World Health Organisation, Geneva, Switzerland
[b] Centre for Neonatal and Paediatric Infection & Vaccine Institute, City St George's, University of London, London, UK
[c] Centre of Excellence in Maternal Immunisation, Makerere University Johns Hopkins University, Kampala, Uganda
[d] European Medicines Agency, EMA, Amsterdam, NL, the Netherlands
[e] Regulation and Prequalification Department, World Health Organisation, Geneva, Switzerland
[f] Great Ormond Street Institute of Child Health, University College London, UK
[g] Biologic and Radiopharmaceutical Drugs Directorate, Health Canada, Ottowa, Canada
[h] South Africa Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Infectious Diseases and Oncology Research Institute, Faculty of Health Science, University of the Witwatersrand Johannesburg, South Africa

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ABSTRACT

Group B *Streptococcus* (GBS) is a leading cause of infant mortality, particularly in low- and middle-income countries (LMICs). Several maternal GBS vaccine candidates, aimed at protecting infants, are progressing through clinical trials. The World Health Organisation (WHO) aims to ensure equitable access to safe, effective, and affordable vaccines of assured quality in LMICs, by facilitating regulatory pathways. An alternate approval pathway, based on safety and an immunological endpoint thought to predict clinical benefit (commonly referred to as serological threshold of risk reduction [SToRR]), is being considered for GBS maternal vaccines. Since this approach is new to many LMICs regulators and policymakers, WHO organized consultative meetings at national, regional, and global levels to discuss the feasibility and potential challenges of approving a GBS vaccine based on safety and immunogenicity data alone. These consultations focused on evidence supporting SToRR, their use as endpoints to infer protection, and post-licensure requirements. The aim of the consultations was to reduce the delay between vaccine development, licensure, policy recommendations and use in high-burden LMICs.

1. Introduction

Streptococcus agalactiae, commonly known as group B *Streptococcus* (GBS), is the most common cause of neonatal sepsis and bacterial meningitis globally [1,2]. It is classified by age at onset with early-onset GBS (EOGBS) defined as illness occurring in the first six days of life, and late-onset disease (LOGBS), occurring between 7 and 89 days. In infancy, invasive GBS (iGBS) disease typically presents as sepsis, meningitis, or pneumonia [3]. EOGBS is vertically acquired from a mother colonized with GBS, whereas LOGBS can also be acquired nosocomially or in the community. Of the ten GBS serotypes in circulation (Ia, Ib, II-IX), six account for majority (93–99 %) of iGBS disease, globally. [4]

In 2020, there were an estimated 20 million pregnant women colonized with GBS, 231,000 (95 % uncertainty range 114,000 to 455,000) cases of EOGBS, and 162,000 (70,000 to 394,000) LOGBS cases [2]. Together, these were estimated to have caused 58,000 to 91,000 infant deaths depending on the assumptions made about causes of mortality in cases without access to healthcare, with a disproportionate burden in sub-Saharan Africa and Asia [2]. Furthermore, recently published follow-up cohort studies beyond early childhood from low- and middle-income countries (LMICs) and high-income countries (HIC) suggest a high risk of neurodevelopmental impairment (NDI) among children who survive iGBS sepsis or meningitis [5–8]. It was estimated that 37,100 children (14,600–96,200) who recovered from iGBS disease developed moderate or severe NDI, a considerably higher number than previous estimates [2]. Maternal colonization with

* Corresponding author.
E-mail address: mehringlek@who.int (K. Le Doare).

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GBS may also contribute to adverse pregnancy outcomes, with an estimated 46,000 (20,000 to 111,000) stillbirths and 518,000 (36,000 to 1,142,000) excess preterm births attributed to GBS [2]. In addition, GBS also causes maternal disease with an estimated 41,000 (22,000 to 66,000) cases globally [2] [9].

Intrapartum antibiotic prophylaxis (IAP) to delivering women can prevent EOGBS but has limited implementation in LMICs [10]. Maternal GBS vaccines have the potential to address a broader spectrum of GBS disease, including EOGBS, LOGBS, stillbirths, preterm birth, and other maternal GBS outcomes and are likely to be a more feasible prevention strategy in LMICs. [10] In 2015, the World Health Organisation (WHO) Product Development for Vaccines Advisory Committee (PDVAC) considered maternal GBS vaccines to be among the top 10 priority vaccines warranting development [9]. The licensure of at least one affordable GBS vaccine by 2030 is also a crucial milestone in the WHO global roadmap for Defeating Meningitis by 2030 [1]. As of May 2025, two candidate maternal GBS vaccines are in late-stage clinical development, with several others in the preclinical stage [10].

A phase III double-blind, randomized controlled vaccine trial with a primary endpoint of iGBS disease in infants would provide the most compelling evidence of vaccine efficacy. However, the complexities of vaccination during pregnancy and challenges in conducting surveillance for iGBS disease in early life would make a maternal GBS vaccine trial with clinical endpoints practically infeasible. It is estimated that a GBS phase III clinical trial to demonstrate efficacy against infant iGBS disease, would require at least 60,000 woman/infant pairs (120,000 participants) in countries with an iGBS incidence >1:1000 live births. Such a trial could take a decade or more to accomplish and would be extremely challenging to conduct under investigational new drug standards that are highly stringent [12] and is unlikely to be economically viable.

The approach that is currently under discussion for licensure of maternal GBS vaccines is evaluation of safety and insights into efficacy based on evaluation of serological thresholds of risk reduction (SToRR). [11–13] [14–16].

For a GBS vaccine, it is proposed that measuring levels of anti-GBS antibodies by binding, function or a combination of these measures in infants at birth (cord blood) could be used as SToRR. As the use of SToRR as the basis for initial regulatory approval is uncommon in many LMICs, WHO convened diverse stakeholders, including vaccine manufacturers and developers, regulators, and policymakers, across country, regional, and global levels to explore the potential regulatory and implementation pathways for GBS vaccines following licensure based on SToRR. The aim was to gather opinions about barriers and opportunities to using SToRR endpoints to infer vaccine protection in regulatory approval and policy making. This report summarises the outcomes of those discussions and proposes potential scenarios for policy considerations. This report intends to inform the regulatory and policy considerations of high-burden LMICs.

1.1. Status of vaccine development for group B Streptococcus vaccines and proposed serological thresholds of risk reduction

The two leading vaccine candidates are being developed by Pfizer (hexavalent capsular polysaccharide (CPS) CRM197-conjugate vaccine against serotypes Ia, Ib, II, III, IV, and V (GBS6)) and Minervax (alum-adjuvanted multivalent alpha-like protein (Alp) vaccine against members of the Alp family of GBS surface proteins (AlpCN, RibN, Alp1N, and Alp2/3 N (GBS-NN/NN2)). The developers of these candidates each propose different approaches to SToRR.

The Pfizer GBS6 vaccine is expected to cover close to 100 % of the circulating serotypes causing iGBS disease globally [17]. Pfizer reported good tolerability and immunogenicity in a phase 1/2 dose-escalation/formulation study that recruited 365 healthy non-pregnant adults aged 18–49 in the United States (US) [18]. These results led to the initiation of a clinical trial of the vaccine in healthy pregnant and non-pregnant women in South Africa (SA), the United Kingdom (UK), and the US (NCT01755598). Based on a Bayesian analysis of a sero-epidemiologic study in SA, which was run in parallel to the clinical trial of GBS6 in pregnant women, the pooled anti-CPS IgG threshold measured by a multiplex immunoassay associated with a 75 % reduction in the disease risk for all vaccine serotypes was 0.184 μg/mL. The percentage of infants with anti-CPS IgG concentrations above this threshold varied according to serotype and formulation, with 57 to 97 % of the infants born to mothers who received the most immunogenic formulation (20 μg without alum) achieving a sero-response above the protective threshold [17].

The MinervaX GBS-NN/NN2 vaccine is expected to cover close to 100 % of clinical GBS isolates [19]. The vaccine consists of two fusion proteins comprised of either AlpCN and RibN (GBS-NN) or Alp1N and Alp2/3 N (GBS-NN2), formulated with aluminium hydroxide (AlOH) adjuvant. Minervax reported that GBS-NN displayed good safety profiles and elicited IgG responses against AlpC and Rib, as well as against the other Alp family members that were capable of both blocking the invasion of epithelial cells with GBS and killing GBS via opsonophagocytosis in a randomized, placebo-controlled, double-blind phase 1 trial in 240 non-pregnant women [20,21]. A subsequent phase 1 trial in 60 healthy adult women demonstrated equal safety of the GBS-NN & GBS-NN2 combination (AlpN), according to Minervax reports [19]. AlpN was well tolerated and elicited high levels of antibodies against all four Alp-N-terminal domains, resulting in enhanced opsonophagocytic killing of all Alp protein targets covered by the vaccine. In this study, all vaccinated participants reached IgG thresholds of ≥0.428 μg/mL and ≥ 0.112 μg/mL against RibN and Alp1N, respectively, thresholds associated with a 90 % iGBS risk reduction in a SA case-control study of naturally occurring antibodies [22]. Minervax is currently developing its regulatory strategy for SToRR against alpha-like proteins.

1.2. Near-term efforts to support clinical, regulatory, and policy-related strategic planning

It is anticipated that the mechanism of immunity derived from natural exposure and vaccine-induced immunity will be similar, although not identical. As such, natural immunity studies may enable the establishment of SToRR for each vaccine platform that could allow product licensing. If licensure is based on SToRR, there will be a need to confirm clinical benefit in post-licensure vaccine evaluation studies.

Adaptive immunity is unlikely to play a role in protection in the first months of life as infants rely on antibodies passed from the mother via the placenta for protection. It is important to measure antibodies in the infant's blood at birth since maternal antibody levels are higher than those among the infant and transfer ratios to the newborn can be affected by a range of factors [23]. Since the risk period for iGBS disease in infants is short, it should be easier to study the link between antibody levels and protection in natural immunity studies than for other diseases where the time-at-risk is longer.

To facilitate comparisons between data generated in different laboratories, studies, vaccine candidates and settings, the Group B Streptococcus Assay Standardisation (GASTON) consortium, consisting of public health, academic, regulatory, and industrial partners, has developed standardized assays and reagents that can be used across sero-epidemiological and vaccine studies. The consortium has adopted a multiplex immunoassay based on Luminex technology (dLIA) that measures surface binding of antibodies against GBS serotypes (Ia-V), developed by Pfizer and transferred to 4 additional laboratories. The GASTON consortium still needs to establish a standardized assay for alpha-like proteins. GASTON has also developed an opsonophagocytosis killing assay (OPkA) that measures antibody-mediated opsonization and killing of GBS, also referred to as functional antibody response, that could be used by either vaccine platform. In the case of natural immunity to GBS, the OPkA will provide a killing titre of all antibodies raised against GBS, including both anti-surface and anti-capsular

polysaccharide antibodies.

A global effort is underway towards establishing SToRR based on natural immunity in France, Italy, Malawi, the Netherlands, SA, Uganda, the UK, the US. These separate case-control studies aim to investigate maternal antibodies in the infant that are protective against natural iGBS that will be useful for both the capsular serotypes (Ia-V) and the alpha-like proteins.

In SA, a prospective, observational cohort of 35,000 mother-newborn pairs were enrolled between 2015 and 2017 [24]. This initial study did not use the GASTON dLIA now developed and reported higher thresholds than in a subsequent cohort of 15,000 mother-newborn pairs enrolled in 2019 which used the GASTON assays and reagents [17]. Infants were followed up by hospital-based surveillance for iGBS disease. In parallel, infants with iGBS disease not enrolled in the birth cohort were identified across multiple hospitals. Cases were matched to controls for maternal colonization status with a homotypic serotype during labour, maternal age, birth weight, newborn sex, and maternal HIV status.

The US Centers for Disease Control and Prevention (CDC) has also completed enrolment and IgG analysis in a case-control study in the US. The association between GBS serotype-specific capsular IgG antibody concentrations at birth and probability of iGBS disease have been estimated for all serotypes included within the Pfizer vaccine. Cases were identified in 2010–2022 from CDC's Active Bacterial Core surveillance program. Controls were selected from GBS-colonized mothers in the surveillance areas identified based on routine antenatal GBS screening from 2018 to 2022. Remnant newborn screening dried blood spot (DBS) samples were used for antibody measurements using the GASTON assay adapted for DBS. The study recruited 643 cases and over 3:1 matched controls. Further analysis of functional antibody responses using the GASTON OPkA is in discussion.

Other studies are underway in the UK, the Netherlands, Italy, France, Malawi, and Uganda, focusing on the association between GBS serotype III specific antibodies and the odds of serotype III-associated iGBS. However, these studies are also collecting isolates and sera for other common serotypes. These studies are recruiting a mix of prospective (birth sample) and retrospective (time of disease) samples aiming for 150 serotype III cases and 450 serotype III controls. All prospective pairs are followed up for 90 days after birth. Another infant sample is taken in case of disease, and antibody concentrations are compared to those at birth. Controls will be selected from GBS serotype III -colonized women matched on gestation and sex, aiming for up to three controls for every case. All retrospective cases have blood samples taken as soon after presentation as possible, aiming to be within 72 h.

1.3. Potential regulatory approval pathways for group B streptococcal vaccines based on SToRR

A series of regulatory science strategy workshops have been convened to gather opinions on GBS vaccine use in LMICs. The aim of these meetings is to enable early alignment among LMICs regulators, policymakers, and national, regional, and global stakeholders on the clinical trial and observational data needed for policy and program decisions for GBS vaccines. Early scientific advice meetings have also been held with regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the African Vaccine Regulatory Forum (AVAREF) and country national regulatory authorities to discuss clinical trial considerations and policy implications of a phase III SToRR trial and post-licensure (Phase IV) studies.

The traditional vaccine regulatory approval pathway includes a clinical disease endpoint study to measure efficacy, although standard approvals based on SToRR have occurred over time at least in some jurisdiction [25]. Other pathways may also be available for certain vaccines depending on the country or region and their regulatory structure. These may include an accelerated approval or conditional authorization process, where SToRR endpoints reasonably likely to predict clinical benefit are proposed. An accelerated approval or conditional authorization may be an appropriate pathway for a GBS vaccine, as it is regarded as an unmet medical need for a serious and life-threatening condition. Box 1 outlines an example of the formal requirements that need to be met for a vaccine to qualify for the EMA conditional marketing authorisation. Post-licensure studies are required if such an approach is proposed and are to be expected for GBS vaccines. Irrespective of the pathway forward, pre-licensure would require a significant safety dataset of 3000 vaccinees or more. [26]

Pathways that can expedite vaccines development and review based on SToRR poses several challenges for regulatory authorities. Many LMICs regulatory authorities, including those that serve populations with a high burden of GBS disease, do not have established expedited approval pathways. Even where such processes exist, they remain difficult to navigate. A major concern is the need for post-licensure studies to assess the vaccine's effectiveness. This issue was highlighted during the COVID-19 pandemic when these studies could only be done if the vaccine was widely used. Other challenges include establishment of a mechanism to withdraw approval if the vaccine proves ineffective or fails to deliver results on time. In the US, the Food and Drug Omnibus Reform Act (FDORA) [28] established new requirements regarding the accelerated approval, and one of these allows for the FDA to withdraw an accelerated approval within 180 days if reporting milestones are not met. [29] Generally, post-licensure studies should be planned by the time of the application for licensure to meet this target. Globally, there is a push to create a regulatory framework that allows pre-licensure pivotal clinical trials with SToRR endpoints to start in LMICs, with approval or authorization decisions based on the results. Additionally, acceptability studies and engagement with civil society may be needed to gauge demand and risk perception for GBS vaccines.

1.4. Specific considerations for the determination of SToRR for a GBS vaccine

In the past, SToRR endpoints have been used for the assessment of new or higher valency *Haemophilus influenzae* type b (Hib), meningococcal serogroup C, and pneumococcal polysaccharide-protein conjugate vaccines (PCV) [30–32]. This is also how the four-component, protein-based meningococcal serogroup B (4CMenB) vaccine was licensed, followed by implementation in the UK in the infant immunisation schedule with the generation of vaccine effectiveness data to fulfil regulatory commitments [33]. These SToRR were initially derived from evidence from clinical trials conducted with first-in-class vaccines or similar pathogens. In contrast, for GBS vaccines, there will be no initial assessment of vaccine efficacy for any GBS vaccine formulation.

Regulatory approval of GBS vaccines could rely on an IgG-based SToRR if a strong link between IgG levels and clinical outcomes is established. If IgG levels following vaccination correlate well with OPkA, this could help support the vaccine's effectiveness for rarer serotypes with less available evidence, allowing confidence in an aggregate SToRR approach. However, if the IgG-disease relationship is uncertain for major serotypes, it may be necessary to directly correlate OPkA with protection or at least assess how well IgG correlates with OPkA to justify antibody protection for each serotype. Differences in the vaccine's antigenic makeup might lead to differences in the strength of the evidence that would impact the regulatory pathways. Regardless, post-licensure data on vaccine effectiveness will likely be needed to confirm clinical benefit.

1.4.1. Value of mechanistic SToRR

Developing a single, widely accepted antibody-based marker for licensure of each GBS vaccine candidate would be ideal. IgG-binding antibodies in cord or infant blood could serve as this marker if they consistently correlate with functional antibodies and if vaccine-induced antibodies behave similarly to those produced during natural infection.

Box 1
– Example of an accelerated approval pathway: the EMA conditional market authorisation (CMA) [27].

In cases where less comprehensive clinical data referring to the safety and efficacy of the medicinal product have been supplied, conditional market authorisation may be granted if all the following criteria are met:
(a) the risk-benefit balance of the medicinal product is positive;
(b) it is likely that the applicant will be able to provide comprehensive post-authorization data;
(c) the medicinal product will allow fulfilling unmet medical needs; and
(d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.
CMA are valid for one year and can be renewed annually. Once a CMA has been granted, the marketing authorisation holder must fulfil specific obligations within defined timelines. These could include completing ongoing or new studies or collecting additional data to confirm that the medicinal product's benefit-risk balance remains positive. The CMA can be converted into a standard marketing authorisation (no longer subject to specific obligations) once the CMA holder fulfils the obligations imposed and the complete data confirm that the medicinal product's benefits continue to outweigh its risks.
EMA can take regulatory action, such as suspending or revoking the marketing authorisation, if new data show that the medicinal product's benefits no longer outweigh its risks.

Numerous case-control studies over the past three decades have established antibody thresholds linked to relative and absolute risk reduction of iGBS while accounting for confounding variables such as gestational age [17,22,34–37]. One concern with this approach is whether it is valid to use a threshold for antibody-mediated immunity from natural GBS exposure as a guide for what is needed after vaccination. This concern comes from the fact that natural exposure might activate other immune responses, like antibodies against sub-capsular antigens, which can pass to the foetus but are not triggered by vaccination. Therefore, finding a predictive immunological threshold (SToRR) that accurately reflects the immune response after vaccination could be helpful.

1.4.2. Direct or indirect measure of functional activity

To establish the SToRR, the ideal antibody assay should directly assess the functional activity that provides protection. Several such assays exist, such as antitoxin assays for tetanus and diphtheria, bactericidal assays for Hib and meningococcus, opsonophagocytic assays for pneumococcus, and direct virus neutralization assays for measles and other viruses. However, due to technical challenges and variability in complex functional bioassays, a simpler binding or binding inhibition assay that correlates well with functional activity is often preferred. Consistency, reproducibility, and the ability to handle large numbers of samples make it difficult to use a complex functional assay as the main outcome in a GBS vaccine trial. However, several studies have demonstrated good correlations between antibody binding and function in natural immunity for iGBS [36,38]. Even when considering SToRR with a functional readout, some caution is still required as functional assays can only provide information on a specific part of the protective immune response (bactericidal killing in the presence of cells and complement), in vitro.

1.4.3. Antibiotic use and the effect on SToRR

In a maternal vaccine trial, it is expected that a high number of women (at least 40 % globally) have been exposed to antibiotics at the time of sample collection because of the need for IAP or chemoprophylaxis for caesarean section. Many infants will also have received antibiotics at the time of disease and before the sample collection. Unless selectively removed from the blood sample prior to analysis, antibiotics can confound the measurement of functional antibodies in OPkA assays, making a functional SToRR challenging to interpret.

1.4.4. Aggregate or individual SToRR and lessons learnt form pneumococcal vaccines

Different SToRR might be needed for EOGBS compared with LOGBS, due to potential biological differences in how these diseases develop and the levels of exposure to GBS. In addition, when assessing SToRR for GBS, it is important to consider that there are multiple serotypes, with some being rare causes of disease. In the past, aggregate thresholds were used for initial approval of PCV7 vaccines, when data were insufficient for minor serotypes. For pneumococcal vaccines, antibody threshold concentrations for invasive pneumococcal disease based on serum anti-pneumococcal CPS IgG were developed after protection had been demonstrated by the 7-valent [39] and 9-valent conjugate vaccines [32] in clinical efficacy studies. The aggregate IgG putative threshold was agreed by consensus to be 0·35 μg/mL based on results from three phase III vaccine trials, and was subsequently used to license 13-valent pneumococcal conjugate vaccine (PCV13) and other newer PCV formulations. This initial SToRR was not serotype-specific, and a few serotypes were found to be inferior to the aggregate at the time of initial licensure of PCV13, although vaccine efficacy had been demonstrated overall for the original 7 serotypes. Following this approach, confirmatory post-licensure vaccine effectiveness assessments were conducted including for those serotypes that were below the aggregate used for initial licensure.

Key to arriving at the aggregate IgG putative threshold was the ELISA that WHO adopted as the standardized assay for pneumococcal vaccine development to combine data from the different trials and laboratories. This internationally accepted standardized assay was transferred to multiple laboratories to facilitate the measurement of IgG antibodies for serotype-specific pneumococcal CPS and identify a putative threshold of protection for pneumococcal disease. Similarly, for GBS vaccines options for aggregation of serotypes could be considered, acknowledging the additional complexity that would derive from any splitting of SToRR values for EOGBS vs LOGBS across serotypes.

1.5. Beyond regulatory approval: evidence to support national and global policy recommendation

Regardless of the trial design, it is important to involve host countries and communities in planning and conducting pre-licensure clinical trials and in making plans for vaccine implementation and evaluation after approval. Pre-licensure clinical trials should take place in countries or regions where the vaccine will likely be introduced quickly due to high disease rates and the unmet medical need. Local or regional clinical data in the target population may help national policy-makers in these areas, especially since approval will be based on SToRR data. There are ongoing efforts to design multi-country, multi-site post-licensure studies for GBS vaccines intended for use during pregnancy to protect infants in LMICs.

Once a vaccine has been approved and is available, the National Immunisation Technical Advisory Group (NITAG) in each country that intends to use the vaccine will undertake a systematic decision-making process based on a review of the available burden, safety, and effectiveness data in the context of their specific broader health and economic priorities. It is also likely that the delivery system will be critical to the implementation of this vaccine and will need to be reviewed as part of this process. For vaccines intended for LMICs, a recommendation from the WHO Strategic Advisory Group of Experts on Immunisation (SAGE) and WHO prequalification will help support the decision to introduce the vaccine at the country level. WHO SAGE may initially recommend the vaccine conditionally for areas with high disease burdens, with a commitment to collect more safety and effectiveness data from early-adopting countries, such as was recommended for typhoid vaccine. [40] However, local neonatal iGBS disease burden data are

challenging to obtain and this approach could greatly limit where the vaccine can be implemented early. WHO SAGE recommendations and WHO prequalification are important for Gavi funding and UNICEF procurement, and are essential for decision-making in countries not supported by Gavi. Thus, early consideration of the criteria and evidence requirements for vaccine recommendation and introduction is needed to avoid any delay in vaccine implementation.

1.6. Post-licensure studies

Post-licensure studies (or Phase IV studies) are most commonly designed as observational studies to monitor the safety, effectiveness, and overall impact of a drug or vaccine after its approval and public release. They assess long-term safety, real-world vaccine impact and effectiveness, and potential rare or delayed side effects. These studies also assess the vaccine's performance in different populations, compare it with existing treatments, and gather data that may support expanded uses. Ultimately, post-licensure studies provide critical information to ensure ongoing safety and efficacy, guiding healthcare providers, regulatory authorities, and policymakers. Table 1 outlines the types of studies that can be considered.

Since SToRR for GBS vaccines used during pregnancy in LMICs will be based on iGBS disease (EOGBS, LOGBS, or both), the primary endpoint for vaccine effectiveness and impact in post-licensure studies must also be iGBS disease in neonates and young infants. However, there are significant challenges in conducting surveillance for iGBS in neonates and infants, including difficulties in case ascertainment due to the rapid and fulminant onset of the disease, as well as difficulties in confirming invasive disease. Additionally, post-licensure studies would require follow-up of women through late pregnancy and consistent detection of iGBS cases in newborns in the early days and months of life. The infrastructure needed for such studies is often limited in LMICs, where the burden of GBS disease is highest, and could deter many countries from carrying out such studies or could result in studies being carried out inappropriately, leading to underestimations of vaccine impact and effectiveness.

Given these challenges, conducting country-specific vaccine evaluation studies might be impractical unless justified by differences in standard of care and/or epidemiological considerations. One alternative could be establishing pregnancy registries, but logistical challenges in clinical settings, especially if the vaccine is not widely administered to pregnant women quickly, make this difficult. However, some international efforts are in place in potential early-adopter countries to gather observational data after the vaccine is introduced at selected sites using patient registries.

Table 1
– Types of Post-licensure (Phase IV) studies.

Type	Description
Safety surveillance studies	Monitor the safety of a vaccine after it has been approved and is available to the public. It normally targets specific AESI (adverse events of special interest), while accounting for the background rate of AESI before vaccine introduction.
Absolute or Comparative Effectiveness studies	Compare the effectiveness of the new vaccine with no-vaccination matching comparison group or with other existing vaccines for the same condition. These studies are observational.
Long-term follow-up and impact studies	Assess the long-term safety and impact of a vaccine, including potential side effects and benefits.
Implementation studies	Evaluate how well a vaccine is adopted and used in clinical practice, including adherence and accessibility.
Health Outcomes and Economics studies	Assess the impact of a vaccine on quality of life, cost-effectiveness, and overall economic impact. It can be embedded in studies with a primary focus on efficacy.
Label expansion studies	Investigate additional uses for an approved vaccine beyond the original indications.

2. Conclusion

GBS remains a leading preventable cause of invasive bacterial disease and death in early infancy, yet no vaccine has advanced beyond Phase II trials despite the existence of several candidates. The SToRR approach, where immunogenicity data thought to predict clinical benefit, are used in Phase III trials, could potentially accelerate the regulatory approval process for GBS vaccines. However, while a SToRR pathway can expedite approval and build a safety database, it does not provide direct evidence of clinical benefit. It also has limitations in providing evidence of vaccine protection against rarer serotypes or surface proteins. For both these reasons, collection of post-licensure vaccine impact and effectiveness data is likely to be needed.

To address these gaps, it is crucial to engage with regulators and policymakers early on to establish a consensus on using real-world evidence in the post-licensure phase. Building demand through burden data and raising the profile of GBS within Member States is essential to ensure timely introduction of the vaccine. Engagement with civil society organizations will also be key to understanding the acceptability of an SToRR approach and achieving high vaccine uptake when available.

To achieve the goals of defeating GBS-related meningitis and reducing neonatal and infant mortality and disability, a robust regulatory and policy framework that is appropriate for use in high burden LMICs must be developed in parallel with Phase III trials. This approach will help expedite the global availability of a safe and effective GBS vaccine, particularly in regions where the disease burden is highest and the need for protection is most urgent.

CRediT authorship contribution statement

Kirsty Le Doare: Writing – review & editing, Writing – original draft, Visualization, Funding acquisition, Conceptualization. **Virginia Benassi:** Writing – original draft. **Marco Cavaleri:** Writing – review & editing, Writing – original draft, Conceptualization. **Godwin Enwere:** Writing – review & editing, Writing – original draft. **Birgitte Giersing:** Writing – review & editing, Writing – original draft, Conceptualization. **David Goldblatt:** Writing – review & editing, Methodology, Conceptualization. **Paul Heath:** Writing – review & editing. **Joachim Hombach:** Writing – review & editing, Writing – original draft. **Richard Isbrucker:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Kostas Karampatsas:** Writing – review & editing. **Shabir A. Madhi:** Writing – review & editing, Writing – original draft. **Annelies Wilder Smith:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

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Data availability

No data was used for the research described in the article.

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