GROUP B STREPTOCOCCUS VACCINE

POLICY AND IMPLEMENTATION ISSUES
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## Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AEFI</td>
<td>Adverse event following immunization</td>
</tr>
<tr>
<td>AFR</td>
<td>WHO African Region</td>
</tr>
<tr>
<td>AIARA</td>
<td>American Immunization Registries Association</td>
</tr>
<tr>
<td>AMI</td>
<td>Advancing Maternal immunization</td>
</tr>
<tr>
<td>AMR</td>
<td>WHO American Region</td>
</tr>
<tr>
<td>ANC</td>
<td>Antenatal care</td>
</tr>
<tr>
<td>ANISA</td>
<td>Aetiology of Neonatal Infection in South Asia study</td>
</tr>
<tr>
<td>CLAP</td>
<td>Centre for Perinatology, Women and Reproductive Health</td>
</tr>
<tr>
<td>CRVS</td>
<td>Civil registration and vital statistics</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Survey</td>
</tr>
<tr>
<td>EIR</td>
<td>Electronic immunization registry</td>
</tr>
<tr>
<td>EMR</td>
<td>WHO Eastern Mediterranean Region</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
</tr>
<tr>
<td>EU/EEA</td>
<td>European Union and European Economic Area</td>
</tr>
<tr>
<td>EUR</td>
<td>WHO European Region</td>
</tr>
<tr>
<td>EUROCAT</td>
<td>European network of population-based registries for the epidemiological surveillance of congenital anomalies</td>
</tr>
<tr>
<td>FPHVP</td>
<td>Full public health value proposition</td>
</tr>
<tr>
<td>GAIA</td>
<td>Global Alignment of Immunization Safety Assessment in Pregnancy</td>
</tr>
<tr>
<td>GBS</td>
<td>Group B streptococcus</td>
</tr>
<tr>
<td>GN-MNHR</td>
<td>Global Network’s Maternal Newborn Health Registry</td>
</tr>
<tr>
<td>HDSS</td>
<td>Health and Demographic Surveillance System</td>
</tr>
<tr>
<td>HIC</td>
<td>High-income country</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMIS</td>
<td>Health management information system</td>
</tr>
<tr>
<td>IAP</td>
<td>Intrapartum antibiotic prophylaxis</td>
</tr>
<tr>
<td>IGME</td>
<td>UN Interagency Group for Child Mortality Estimation</td>
</tr>
<tr>
<td>INDEPTH</td>
<td>International Network for the Demographic Evaluation of Populations and their Health</td>
</tr>
<tr>
<td>IPAC</td>
<td>Immunization Practices Advisory Committee</td>
</tr>
<tr>
<td>IPIE</td>
<td>Influenza Post-Introduction Evaluation</td>
</tr>
<tr>
<td>JRF</td>
<td>Joint reporting form</td>
</tr>
<tr>
<td>LAC</td>
<td>Latin America and the Caribbean</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>LIC</td>
<td>Low-income country</td>
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<tr>
<td>LMIC</td>
<td>Lower middle-income country</td>
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<tr>
<td>MCH</td>
<td>Maternal and child health</td>
</tr>
<tr>
<td>MIACSA</td>
<td>Maternal Immunization and Antenatal Care Situation Analysis</td>
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<tr>
<td>MMGH</td>
<td>MM Global Health Consulting</td>
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<tr>
<td>MNCH</td>
<td>Maternal neonatal and child health</td>
</tr>
<tr>
<td>MNH</td>
<td>Maternal and neonatal health</td>
</tr>
<tr>
<td>MPDSR</td>
<td>Maternal and Perinatal Death Surveillance and Response</td>
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<tr>
<td>NBBD</td>
<td>Newborn and birth defects</td>
</tr>
<tr>
<td>NIP</td>
<td>National Immunization Programme</td>
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<tr>
<td>NITAG</td>
<td>National Immunization Technical Advisory Groups</td>
</tr>
<tr>
<td>PAB</td>
<td>Protection at birth</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PDVAC</td>
<td>Product Development for Vaccines Advisory Committee</td>
</tr>
<tr>
<td>RITAG</td>
<td>Regional Immunization Technical Advisory Groups</td>
</tr>
<tr>
<td>RMNCAH</td>
<td>Reproductive Maternal Newborn Child and Adolescent Health</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Committee of Experts on Immunization</td>
</tr>
<tr>
<td>SARA</td>
<td>Service Availability Readiness Assessment</td>
</tr>
<tr>
<td>SEAR</td>
<td>WHO South-East Asian Region</td>
</tr>
<tr>
<td>SEARO</td>
<td>WHO Regional Office for South-East Asia</td>
</tr>
<tr>
<td>SPA</td>
<td>Service Provision Assessment</td>
</tr>
<tr>
<td>TIP</td>
<td>Tailoring immunization programmes</td>
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<tr>
<td>TIPFlu</td>
<td>Tailoring immunization programmes for seasonal influenza</td>
</tr>
<tr>
<td>TTCV</td>
<td>Tetanus toxoid containing vaccine</td>
</tr>
<tr>
<td>TWG</td>
<td>Technical working group</td>
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<tr>
<td>UMIC</td>
<td>Upper middle-income country</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
</tr>
<tr>
<td>UR</td>
<td>Uncertainty range</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WPR</td>
<td>WHO Western Pacific Region</td>
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</table>
Executive summary

Maternal immunization can play an important role in improving maternal, fetal and neonatal health and has the potential to be an important tool in the public health armamentarium, particularly in low- and middle-income countries (LMICs). This report summarizes the key considerations for the operationalization of maternal Group B Streptococcal (GBS) vaccination. The report will contribute to describing the full public health value assessment of GBS vaccines. The report identifies several actions that merit consideration in preparing LMICs to strengthen their maternal immunization platforms for the introduction and scale-up of GBS vaccination.

The report addresses the following four domains:

1. Policy formulation
2. Service delivery
3. Acceptability and demand for vaccination
4. Monitoring and evaluation

The key findings of the report are briefly summarized below.

Policy formulation at the national level

Establishing national policies, goals and targets for GBS vaccination is an important first step for its implementation in LMICs. A stakeholder survey showed a reasonably high level of awareness among pediatricians and obstetricians of GBS disease and its prevention, but low levels of awareness among public health specialists, especially in LMICs. Survey respondents from Asia perceived that the burden of GBS disease in their region was lower than in North America and Europe and that it did not constitute a public health priority. While estimates of the burden of maternal and neonatal sepsis and stillbirths exist, there are several limitations to the data. It is likely that national immunization technical advisory groups will require better local data to justify prioritizing GBS vaccination in their respective countries. LMICs are likely to require guidance and technical support for designing and implementing studies to generate good-quality data to inform decision-making.

Options for service delivery

Most LMICs have national policies for maternal vaccination, mainly for tetanus toxoid containing vaccines (TTCV) and increasingly for influenza. GBS vaccination in the second or third trimester of pregnancy would ideally be delivered during antenatal care (ANC) visits but will require strong collaboration between the national immunization and Maternal and Neonatal Health programmes. Strengthening this collaboration and including GBS vaccination are likely to enhance the uptake of ANC services. However, human and financial resource constraints will need to be addressed for the implementation of planned activities and for achieving the desired coverage levels.
Factors affecting uptake of vaccination and measures to address them

A reasonable amount of data exists on the factors affecting the acceptance and uptake of ANC and maternal vaccination. Many of the elements that influence acceptance and uptake are contextual and are driven by local sociocultural practices, religious beliefs, and the extent of access to and quality of health care. Most available data on factors affecting uptake of maternal vaccination are from high- and middle-income countries and are chiefly related to maternal influenza vaccination. This highlights the need for more data from LMICs which are likely to require guidance and technical assistance to conduct studies in order to assess demand-side barriers to maternal immunization and design appropriate interventions to improve uptake.

Baseline information on pregnancy outcomes is important for risk communication for maternal vaccination. While empirical data are lacking in many LMICs, data from systematic reviews and estimates from modelling approaches may be used as an alternative for this purpose.

Monitoring the coverage, impact and safety of vaccination

Monitoring and evaluation are key components of vaccination services and provide the ability to monitor GBS vaccination coverage, impact and safety.

While systems for monitoring vaccination coverage through collection of administrative data and through household surveys exist in almost all countries, these systems mainly monitor coverage of infant immunization. The availability and quality of data outside the infant age group is limited in LMICs. Many LMICs collect data on ANC services in their national health management information system, though information on the availability, completeness and quality of data are limited. The existing mechanisms can be leveraged and strengthened to collect high-quality monitoring data relevant to GBS vaccination, though close collaboration between national immunization and Maternal and Child Health programmes will need to be established.

The outcome measures for monitoring the impact of GBS vaccination include stillbirths, invasive GBS disease in neonates and infants, and maternal sepsis. Few LMICs have well-developed systems to collect these data, though opportunities exist that can be leveraged to strengthen these systems in preparation for the introduction of maternal GBS vaccination. Ideally, efforts to establish or strengthen these systems should start a few years in advance of vaccine introduction to ensure that robust data on background rates are available to measure impact.

Safety monitoring of maternal vaccination is complex and few LMICs have well-functioning systems for monitoring maternal immunization safety. The Global Alignment of Immunization Safety Assessment in Pregnancy – the GAIA project – has established case definitions and guidelines for monitoring adverse events, a roadmap for establishing or strengthening maternal immunization safety monitoring has been published, and technical assistance is available to LMICs to establish or strengthen their safety monitoring systems in preparation for GBS vaccination.
1. INTRODUCTION

Maternal immunization can play an important role in improving maternal, fetal and neonatal health and has the potential to be an important tool in the public health armamentarium, particularly in low- and middle-income countries (LMICs) where maternal and neonatal mortality and stillbirth rates remain unacceptably high. Globally, Group B streptococcal (GBS) disease is estimated to cause at least 409,000 (UR, 144,000 – 573,000) cases of serious infections in mothers, their fetuses or infants, and 147,000 (UR, 47,000 – 273,000) stillbirths and infant deaths annually (1). Maternal immunization is now considered an essential component of life-course vaccination; an increasing number of vaccines aimed at protecting pregnant women, their fetuses and infants are likely to become available in the coming decade (2).

In most LMICs, the only vaccination provided during pregnancy is tetanus toxoid containing vaccine (TTCV) (3). The proportion of neonates protected at birth against tetanus is high with the estimated coverage ≥ 80% in 91 of 104 countries from which data are available. While many countries report coverage with two or more doses of TTCV (TT2+) during pregnancy, these coverage rates are influenced by prior vaccination history and may not reflect coverage with vaccination during any particular pregnancy. As an increasing number of LMICs strengthen their life-course vaccination platforms and can provide five or more doses of TTCV prior to pregnancy, the number of doses of TTCV given in pregnancy is likely to decline. However, it may take several years before all LMICs have introduced the required TTCV boosters.

Other vaccines currently given during pregnancy include those against influenza and pertussis. Implementation of these vaccines in the national immunization programme (NIP) varies. Many high-income countries (HICs) report modest coverage and variation in coverage within countries has been reported (4). Several middle-income countries have been able to achieve very high rates of coverage with maternal influenza vaccination. For instance, 8 of 22 countries in Latin America and the Caribbean from which data were available reported coverage of 80% or more in 2018 (5). However, even in these countries, coverage between different vaccines provided in pregnancy may vary; in Argentina, maternal influenza vaccination coverage of 96% was achieved in 2014 although coverage with Tdap (tetanus, diphtheria, pertussis) in pregnancy was lower (57% in 2014) (6).

Because of the high burden of disease and the technical feasibility of developing an effective vaccine, GBS was identified as a high priority for the development of a vaccine for maternal vaccination by the WHO Product Development for Vaccines Advisory Committee (PDVAC) (2, 7). In the absence of GBS vaccination, the main preventive strategy to reduce the burden of GBS, notably of early-onset disease, is intrapartum testing for GBS carriage based on microbiological or clinical risk factors and subsequent targeted intrapartum antibiotic prophylaxis (IAP). However, such strategies are currently implemented almost exclusively in higher middle-income and high-income countries (8).

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1 A pregnant woman is considered protected against tetanus if she is still in the period of protection that follows the last dose of TTCV she received during her previous pregnancies or outside of pregnancies – i.e. any TTCV administered in infancy, in the second year of life, by school health services, during periodic SIAs/campaigns in high-risk areas, post-injury, etc.

This report should be read in conjunction with the Maternal Immunization and Antenatal Care Situation Analysis (MIACSA) Project report 2016–2019 which contains information collected through a desk review of published and grey literature on factors related to the operationalization of maternal vaccination, as well as an online survey and visits to selected LMICs with in-depth interviews and observations assessing the current situation with maternal immunization, primarily with TTCV (3). While the present report cites relevant information from the MIACSA report, readers are directed to the MIACSA report itself for more detailed information. The present report attempts to complement the findings of the MIACSA project and focuses more on the issues relevant to GBS disease and vaccination, although there is an inevitable overlap.

The present report, along with the reports from other WHO workstreams, will contribute to describing the full public health value assessment (FPHVP) of GBS vaccines, which includes the full health, economic and societal value of a vaccine to a broad range of global stakeholders, including from an LMIC perspective, and aims to articulate the full direct (individual) and indirect (population) effects of a vaccine. WHO has drafted a template for an FPHVP for vaccines that is intended to describe the global public health rationale for vaccine development and inform investment decisions.
2. OBJECTIVES

This report aims to consolidate, summarize and interpret the available data on the operationalization of maternal immunization and use it to identify and address operational and programmatic aspects that are relevant to maternal GBS vaccination.
3. METHODS

In this report, it is assumed that the impact of GBS vaccination will depend on timely vaccine administration during pregnancy and high coverage with an effective GBS vaccine. It is also assumed that the vaccine will be provided as a single dose during the second or third trimester of pregnancy, with no preconception priming dose and that vaccination will be universal – i.e. provided to all pregnant women irrespective of GBS colonization status or prior history of vaccination or infection.

The report covers the following four domains:

1. Policy formulation
2. Service delivery
3. Acceptability and demand for vaccination
4. Monitoring and evaluation

In consultation with a Technical Working Group (TWG, see Annex 1), key questions to be addressed within each domain were developed and were used to inform the content of each domain. These questions are described in the relevant chapters.

Information to address each of the key questions was collected through reviews of the published literature, relevant documents published by international and national health agencies, relevant websites and an online survey that collected information on the level of different stakeholders’ awareness of GBS disease and on the important disease outcomes that would influence policy decisions and uptake of vaccination. The primary sources of information were recent systematic reviews, the information from which was supplemented by additional reports from the published and grey literature. The published literature included relevant articles identified in the Advancing Maternal Immunization (AMI) gap analysis report, those shared by TWG members, and additional publications identified through PubMed searches as relevant to the four domains in the report. Grey literature, defined as publications not listed in PubMed, was identified through a review of relevant websites. The TWG remained closely involved in the development of each chapter as well as in the review and finalization of the report.

Limitations

A structured systematic review of the published literature was not conducted to compile this report. Instead, existing systematic reviews and databases such as the publication list in the AMI Gap Analysis report and the reference lists of the systematic reviews served as the primary sources of information.
4. ESTABLISHING NATIONAL POLICY FOR GBS VACCINATION

Establishing national policy recommendations for GBS vaccination is an essential first step for including the vaccine in the NIP and making it available to pregnant women. The establishment of policies, goals and targets for vaccination is associated with greater potential for protecting pregnant women and children against vaccine-preventable diseases (3).

This chapter addresses the following questions related to establishing an immunization policy:

1. What is the existing level of awareness of GBS disease and how is GBS vaccination likely to be prioritized?

2. What policy-relevant evidence is required to enable the vaccine to be optimally prioritized for introduction and what are the evidence gaps for:
   - the burden of GBS disease;
   - economic issues relevant to policy-making;
   - policies on intrapartum antibiotic prophylaxis (IAP)?

The contents of this chapter are informed by information collected through an online survey of relevant stakeholders and a review of both published and grey literature.

4.1 Existing level of awareness of GBS disease and its prioritization

The existing level of awareness and management of GBS disease and its prioritization in different countries was investigated through a global online survey of major stakeholders. The survey covered the following areas: 1) awareness of GBS disease; 2) awareness and use of GBS screening and IAP; 3) knowledge of clinical manifestations and GBS disease outcomes; 4) perception of GBS disease as a public health problem; and 5) perceptions of the need for, and priority of, prevention strategies. The survey also explored existing country policies and approaches for screening and IAP, including counselling in ANC services, their coverage, and barriers to their implementation. Finally, respondents were asked to provide their thoughts about potential future GBS vaccines, their prioritization and anticipated level of acceptance, and potential barriers to vaccine implementation (see Annex 2 for the survey questionnaire).

The stakeholder survey was conducted in late 2019 and targeted representatives of national pediatric associations, gynecology and obstetrics associations, national immunization technical advisory groups (NITAGs), national regulatory agencies, academia and United Nations organizations. The included pediatricians, obstetricians, immunization specialists and public health policy-makers residing and working in high-income coun-
tries (HICs), upper middle-income countries (UMICs), lower middle-income countries and low-income countries (LICs). Respondents were approached via email (obtained from the membership lists of the International Pediatric Association and the International Federation of Gynecology and Obstetrics). The survey was distributed to 420 email addresses via the online survey tool Qualtrics™; 25 of the addresses were not reachable. A total of 101 of 395 individuals (26%) from 66 countries who received the email responded to the survey. While the response rate is consistent with rates of similar online surveys, it is acknowledged that some selection bias could have been introduced and findings may not be fully representative of all global stakeholder views. Table 1 provides an overview of the number of individuals to whom the survey was sent, the number who provided full or partial responses, and the response rate.

Table 1. Survey response rates by categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Surveys sent</th>
<th>Full/partial response</th>
<th>Response rate</th>
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</thead>
<tbody>
<tr>
<td><strong>Stakeholder group</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrics/obstetrics-gynecology</td>
<td>259</td>
<td>54</td>
<td>20%</td>
</tr>
<tr>
<td>Public health policy</td>
<td>52</td>
<td>19</td>
<td>37%</td>
</tr>
<tr>
<td>Academic/research</td>
<td>26</td>
<td>7</td>
<td>27%</td>
</tr>
<tr>
<td>Government institutions</td>
<td>20</td>
<td>8</td>
<td>40%</td>
</tr>
<tr>
<td>Implementing partners (e.g. NGOs/UN)</td>
<td>33</td>
<td>9</td>
<td>27%</td>
</tr>
<tr>
<td>Industry/manufacturers</td>
<td>5</td>
<td>4</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Income Group</strong></td>
<td></td>
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<tr>
<td>Low-income</td>
<td>38</td>
<td>10</td>
<td>26%</td>
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<tr>
<td>Lower middle-income</td>
<td>88</td>
<td>18</td>
<td>20%</td>
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<tr>
<td>Upper middle-income</td>
<td>99</td>
<td>22</td>
<td>22%</td>
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<tr>
<td>High-income</td>
<td>169</td>
<td>51</td>
<td>30%</td>
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<td><strong>WHO Regions</strong></td>
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<tr>
<td>Africa</td>
<td>67</td>
<td>20</td>
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<td>Americas (PAHO)</td>
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<td>Eastern Mediterranean</td>
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<tr>
<td>Western Pacific</td>
<td>42</td>
<td>8</td>
<td>19%</td>
</tr>
</tbody>
</table>

Note: Public health policy includes members of WHO’s Strategic Advisory Group of Experts on Immunization (SAGE), members of a country’s National Immunization Technical Advisory Group (NITAG), and Regional Immunization Technical Advisory Group (RITAG), as well as the Technical Working Group (TWG) for Workstream 3 of this project. Government institutions include NIP managers. Those in the Pediatrics/obstetrics-gynecology group were all members of their respective national associations and it is likely that most were physicians.

The subsequent results take into account only the 101 individuals who provided full or partial responses (respondents). All respondents provided their primary area of expertise. The distribution of respondents by their stated area of expertise is shown in Fig. 1.
Among the respondents, 36% were pediatricians, 25% obstetricians/gynaecologists, 21% immunization specialists, and 18% public health specialists. Approximately half of the respondents were from HICs, 40% from middle-income countries and 10% from LICs. Thirty-nine per cent of respondents worked in countries in the WHO European Region (EUR), 20% in the African Region (AFR), 19% in the Region of the Americas (AMR), and slightly less than 10% each in the Eastern Mediterranean (EMR), South-East Asia (SEAR) and Western Pacific (WPR) regions, respectively.

More than half (58%) of respondents considered themselves to be very familiar with GBS disease as a public health problem. This familiarity, however, varied by country income level, being highest in HICs and lowest in LICs (HIC 70%; UMIC 52%; LMIC 47%; LIC: 30%). Knowledge of GBS disease also varied by WHO Region, being greatest in the Americas (68%), Europe (66%), and Africa (55%) and lowest in Asia (Western Pacific 38%; South-East Asia 13%).

The stakeholders were asked their opinions about whether pediatricians, obstetricians and policy-makers considered GBS to be a public health priority in their respective countries. The survey responses (Fig. 2) indicated that the perception of GBS disease as a public health problem was highest among pediatricians (71%) across all country groupings (HIC 78%; UMIC 52%; LMIC 68%; LIC 80%) and WHO regions (38–75%). The perception among obstetricians that GBS was a public health problem was estimated to be 66%; this perception was high across all country groupings (HIC 78%; UMIC 33%; LMIC 74%; LIC 60%). In contrast, the perception among policy-makers that GBS was a public health problem was only 30% (HIC: 37%; UMIC: 19%; LMIC: 26%; LIC: 20%). In HIC, where one would have expected higher awareness about GBS disease, only 37% of respondents felt that policy-makers in their countries considered GBS as a public health problem; this could possibly be influenced by the fact that in the majority of countries IAP is being implemented, resulting in a reduction of the GBS disease burden. Thirty-four per cent of respondents indicated that their countries had a national policy or guideline to prevent GBS disease in pregnant women. However, this percentage differed substantially by income group (HIC: 61%; UMIC: 10%, LMIC: 5%; LIC: 0%).
Respondents considered pediatricians – and specifically neonatologists – to be generally aware and knowledgeable of the disease. However, they also stated that GBS detection was not routinely done in many countries and that culture results even in suspected cases were often negative, partly due to the indiscriminate use of antibiotics prior to admission or because of absent or inadequate laboratory infrastructure. Neonatal sepsis may thus often be diagnosed syndromically, without microbiological confirmation (10). Respondents from several regions were also concerned about the absence of systematic population-based studies to document the burden of GBS disease. This lack of data appeared to limit severely the ability of several respondents \( n=34 \) to convince public health decision-makers of the extent of the problem, including of economic impact. Several respondents from Asia, however, also considered the prevalence of GBS neonatal sepsis to be lower in Asia than in Western countries (e.g. in Europe and North America). Consequently, in the absence of adequate local data, they did not believe that routine screening of pregnant women would be beneficial in their countries.

The respondents estimated that less than one quarter (25%) of pregnant women have some degree of awareness of GBS disease and this did not vary substantially between clinicians (pediatricians and obstetricians) and other respondents (Fig. 3). A stark difference is apparent here between country groupings. While in HICs, half of pregnant women were considered somewhat familiar with the disease, only 18% were deemed aware of GBS disease in UMICs and none in the lower income countries. Respondents from the SEAR, WPR and AFR regions felt that pregnant women in their respective countries were likely to be completely unaware of GBS disease. A similar picture emerged when respondents were asked about the proportion of pregnant women who would be counselled about GBS disease during ANC visits. Based on the survey results, only 23% of pregnant women globally were estimated to receive such counselling, including almost half of pregnant women in HICs (41%), but only 10% in UMICs and none in the lower middle-income and low-income countries. Responses indicated that in Europe and the Americas and the Western Pacific Region around 30–40% of women received counselling but that such counselling was not performed in the other three regions. While the responses are as expected from low-income and lower middle-income countries where preventive interventions during pregnancy are not generally offered, the relatively low rates of counselling in higher-income settings is notable.
Approximately half of survey respondents (49%) considered the introduction of a GBS vaccine as a priority, with more than 60% of obstetricians/gynaecologists, 45% of pediatricians and over 50% of immunization specialists indicating that they perceived it to be a priority. About half of respondents believed that pregnant women across country groups and regions would eventually accept a GBS vaccine (Fig. 4). This finding may contrast with studies where pregnant women have been asked directly about their theoretical acceptance of the vaccine (11).

The public health arguments that respondents felt would support a policy decision for the introduction of a GBS vaccine included (in order of priority):

1. the reduction of neonatal mortality by preventing sepsis;
2. reduction of stillbirths;
3. reduction of maternal sepsis;
4. the perceived cost-effectiveness of vaccination versus treatment of invasive disease;
5. the reduction of long-term impairment;
6. the perceived high acceptability of vaccination among pregnant women and the ease of inclusion of a GBS vaccine in existing NIPs.

The main barriers to inclusion of a GBS vaccine in NIPs were deemed to be the potential vaccine costs and affordability, including cost-effectiveness, lack of acceptance and awareness of the disease or vaccine, lack of reliable data or low prevalence of GBS disease, the inability to implement vaccination (e.g. low capacity, no platform for routine immunization of pregnant women, low antenatal coverage), vaccine characteristics (e.g. poor efficacy, effectiveness and safety) and other (e.g. competing priorities, the use of alternative prevention methods) (Fig. 5). Since lack of data or perceptions of low burden of disease contribute to low awareness of the disease, these two factors together would constitute an important barrier to vaccine uptake.
Fig. 4. Respondents’ view of GBS vaccine prioritization and of perceived acceptance of GBS vaccination among pregnant women (as reported by health professionals and policy-makers)

**Priority to introduce GBS vaccines by income group**

<table>
<thead>
<tr>
<th>Income Group</th>
<th>Yes</th>
<th>No</th>
<th>Neutral / No response</th>
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<tr>
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<tr>
<td>LMIC (N=19)</td>
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<td>5</td>
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<tr>
<td>LIC (N=10)</td>
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<td>8</td>
</tr>
<tr>
<td>Total (N=101)</td>
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<td>49</td>
<td>10</td>
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</table>

**Priority to introduce GBS vaccines by WHO Region**

<table>
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<th>Neutral / No response</th>
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<tr>
<td>EUR (N=39)</td>
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<tr>
<td>WPR (N=8)</td>
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<td>2</td>
</tr>
<tr>
<td>Total (N=101)</td>
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<td>49</td>
<td>10</td>
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**Perceived acceptance of GBS vaccination among pregnant women**

<table>
<thead>
<tr>
<th>Income Group</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIC (N=51)</td>
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<tr>
<td>Total (N=101)</td>
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<td>33</td>
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</table>

**Perceived acceptance of GBS vaccination among pregnant women**

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR (N=20)</td>
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<td>28</td>
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<tr>
<td>AMR (N=19)</td>
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<td>1</td>
</tr>
<tr>
<td>EMR (N=7)</td>
<td>1</td>
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<td>3</td>
</tr>
<tr>
<td>EUR (N=39)</td>
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<td>1</td>
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<tr>
<td>SEAR (N=8)</td>
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<td>39</td>
</tr>
<tr>
<td>WPR (N=8)</td>
<td>1</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Total (N=101)</td>
<td>16</td>
<td>28</td>
<td>33</td>
</tr>
</tbody>
</table>
For logistical reasons, this online survey was limited to health professionals and policy-makers. The perceptions and views of the community were not captured but could provide useful additional information that would be relevant for formulating vaccination policy and delivery strategies. Additional in-depth interviews with health professionals may also be helpful, especially in Asia where GBS disease is perceived to be a low public health priority, to better understand the drivers of this perception and what steps would be required to address the perception and facilitate policy-making.

4.2 Policy-relevant evidence to enable the vaccine to be optimally prioritized for introduction

A more detailed and updated analysis of the available evidence and evidence gaps on GBS disease is presented as part of workstreams 1 and 2 which examine respectively the evidence on the burden and epidemiology of GBS disease and on its economic impact.

This section examines, on the basis of the available published literature, some of the challenges regarding GBS that are likely to be faced in formulating policy. These issues will be further elaborated in developing the value assessment for a GBS vaccine administered to pregnant women.

The decision-making capacity for new vaccine introduction has increased significantly in the past decade, with 114 countries now served by a NITAG. With an increasing number of NITAGs fulfilling the WHO functionality criteria, they are more likely to require and scrutinize local data to make evidence-based decisions within the context of local public health priorities. With an increasing number of vaccines being added to national immunization schedules in LMICs, national immunization budgets have increased substantially. Middle-income countries that are not eligible for Gavi support are already lagging behind with the introduction of new vaccines (12). While the reasons for the lag are not only financial constraints, the impact of adding new vaccines to immunization and health budgets is an important consideration (13). Countries that have never been eligible for Gavi support are currently estimated to invest US$ 90 per live birth for immunization (12). Further increases in immunization budgets may be difficult to sustain in several of these countries. An increasing
number of Gavi-eligible countries will have transitioned out of Gavi support in the coming decade and will no longer be eligible to receive support to introduce new vaccines; it is projected that, by the end of 2020, 19 of the 73 Gavi-eligible countries will cross the eligibility threshold \( (14) \). LMICs that will continue to benefit from Gavi support will need to increase their co-financing of vaccines and ultimately fully finance the vaccines they have introduced through Gavi support. Under these circumstances, national governments will require stronger justification for adding further vaccines to their national schedules to ensure that they are making appropriate investment choices in the face of competing public health priorities.

4.2.1 Prevailing knowledge gaps for policy

Estimates of the burden of GBS disease for pregnant women, stillbirths and children exist for most countries \( (1) \). Systematic reviews that summarize the other available evidence on GBS disease and prevention are also published in the same special supplement of the journal *Clinical Infectious Diseases* (2017, Volume 65, Supplement 2). While the burden estimates are useful, there are limitations in the input data used in the models from which these estimates are derived and there are wide uncertainty ranges around the burden estimates. In a prospective cohort study conducted at five sites in three South Asian countries (Bangladesh, India and Pakistan) (the ANISA project), the incidence of culture-confirmed bacterial infection was 1.6 per 1000 live births. Of the 102 bacterial isolates, six were GBS but five of these were from a single site; three sites did not isolate any GBS while one had a single isolate \( (15) \). The findings from this study where newborn infants were followed in up to 10 home visits during the first 59 days of age, with referral for blood culture when serious bacterial infection was suspected, raise legitimate questions about the burden of GBS in these settings in Asia and may contribute to the perception of low burden of disease in Asia. The fact that five of the six isolates were from a single site that accounted for 27% of the serious bacterial infections also suggests that there may be heterogeneity in rates of disease within this region that may lead policy-makers to demand more local data and to rely less on data from other countries. Differences in virulence of GBS strains circulating in the region, with less frequent reports in Asia of GBS clonal complex 17, associated with serotype III could provide a possible biological explanation for the low observed rates of disease in some Asian countries \( (16, 17) \).

The findings on the low prevaccination burden of disease in Asia are reminiscent of the situation with invasive *H. influenzae* type b (Hib) disease a few decades ago, when the burden of disease in countries in the Asian continent was more difficult to establish than in other regions and was an impediment to vaccine introduction \( (18) \). The low observed rates of GBS disease in Asian studies may similarly become an impediment to decision-making unless steps are taken to explain the reasons for the differences. The results of the survey described above indicate that a high proportion of stakeholders in Asia were either unaware of the public health importance of GBS or did not perceive it as a public health priority; this in turn suggests that local stakeholders are likely to seek better local data before they would be ready to change their existing perceptions about the burden of GBS.

While scepticism about modelled estimates may lead to increasing demand for local empirical data, there are challenges to generating accurate burden data. A number of factors influence the accuracy of burden data and contribute to heterogeneity in the observed burden of disease, including:

1. access to health care;
2. lack of capacity to confirm GBS disease, including factors that impede laboratory confirmation (e.g. prior antibiotic therapy, sample collection and transport, and the type and quality of laboratory procedures);
3. lack of comprehensive reporting systems, resulting in under-reporting of confirmed cases.
Local decision-making bodies need to be aware of these challenges and must carefully assess the extent to which they may influence the burden estimates in local studies, taking this into account when making policy decisions. As standardized definitions and methods are developed, they should be employed in future studies to improve the quality and use of data for informed decision-making. Study reports should present data on factors affecting data quality in order to facilitate assessment of the results. A series of reviews discuss the limitations of data and the influence of methodological factors on the observed burden of disease (16, 17, 19–22). Further guidance and technical support from WHO and other international agencies will be required – including establishing surveillance standards and methods (such as laboratory methods for collecting epidemiological data), providing technical support to strengthen surveillance and laboratory capacity for identifying and confirming GBS-related outcomes, and strengthening NITAG capacity for assessing and using surveillance and epidemiological data for decision-making.

4.2.2 Economic issues relevant to policy-making

The economic burden of GBS and the potential economic benefits of vaccination will be described in the report: Group B streptococcus value assessment report: financial analysis from this project. These data are likely to play an important role in decision-making and in building the economic case for investing in GBS vaccination. The available economic data should extend beyond the conventional cost-effectiveness analysis to also take account of the impact of vaccine introduction on immunization and health budgets, permit comparison with other public health priorities, and estimate the broader economic returns on the investment if the policies established by the NITAGs lead to introduction and sustained use of the vaccine (23, 24).

4.2.3 Available evidence on the use and impact of intrapartum antibiotic prophylaxis

IAP consists of the administration of high-dose intravenous benzylpenicillin or ampicillin during labour to pregnant women colonized with GBS, with GBS bacteriuria, previous infant GBS disease, premature rupture of membranes or fever during labour. A generic WHO recommendation on IAP exists (25) but IAP policies, strategies and implementation are quite heterogeneous (8). Countries that already have policies on IAP are likely to be among the early adopters of GBS vaccination since this represents an acknowledgement that prevention of GBS disease is a health priority. Consequently, accurate and up-to-date information on the existence of such policies will be useful for informing long-term strategic demand forecasts for vaccines (see Workstream 4). However, the relevant evidence to allow the development of optimal approaches to tailor strategies and maximize the impact of vaccination plus IAP in these settings is still missing in many places. The impact of IAP on the maternal and infant gut microbiome and the emergence of antimicrobial resistance in infants has been described (26) but further data will be required. An increase in infections due to Escherichia coli, especially in preterm infants, was reported in the USA (27, 28). However, larger epidemiological studies have not confirmed this effect (29). There are also theoretical concerns about the effect of IAP on the neonatal microbiome and subsequent immunological priming (30), as well as on possible future risk of allergy, asthma and obesity (31). Further evidence on these effects will be needed and should be included in discussions on IAP policy.

In countries with weaker health systems – i.e. in most parts of the WHO African and South-East Asian regions, IAP policies either do not exist or are not being fully implemented (8) (also see survey results reported on pages 7–11). In these countries there is also likely to be low awareness of GBS disease and its public health priority. These countries may require greater emphasis on understanding data needs and more support to generate high-quality data that will inform decision-making. Furthermore, the capacity to screen and administer IAP may be limited in many LMICs, making maternal GBS vaccination an attractive alternative to IAP provided that a vaccination-only policy is effective in addressing the public health needs of these countries.
There is reasonably high awareness of GBS disease and its prevention among pediatricians and obstetricians in all regions and in countries with different income levels. However, there are low levels of awareness among public health specialists and policy-makers, especially in LMICs and LICs.

Stakeholders in South-East Asia perceive the burden of GBS disease in the region to be lower than in Europe and North America and do not consider it a public health priority.

With rising immunization budgets and competing priorities, and with perceptions about the heterogeneity in GBS burden, NITAGs in some regions are likely to require local data for decision-making.

While estimates exist of the GBS disease burden, there are limitations to the data and there is uncertainty about some of the estimates.

Generating local data on GBS disease will be challenging in many resource-constrained LMICs.
5. SERVICE DELIVERY

This chapter addresses issues related to the delivery of a GBS vaccine to pregnant women, examines the respective roles of NIPs and Maternal and Newborn Health (MNH) programmes, and explores opportunities for integration as well as some of the likely challenges and barriers to service delivery.

The chapter addresses the following questions:

1. What is the mode of delivery of vaccination to pregnant women?
2. What are the opportunities and challenges related to integrating GBS vaccination and ANC services?
3. What would be the expected coverage of maternal GBS vaccination in LMICs?

5.1 Mode of delivery of vaccination to pregnant women

Delivery of vaccination in LMICs is generally through the NIPs. The scale-up of immunization delivery in LMICs took place following the establishment of the Expanded Programme on Immunization (EPI) in 1974 and the Universal Childhood Immunization initiative in 1984. In many LMICs the term EPI is used synonymously with NIP and is seen as an effective system that achieves high coverage with infant vaccination. The EIP/NIP has reasonably well-functioning systems for the procurement and distribution of vaccines, stock management, microplanning for service delivery, and monitoring and evaluation. However, many countries face challenges in delivering vaccination with high and equitable coverage (32). Many NIPs in LMICs use outreach services, mobile clinics and supplemental immunization activities to fill gaps in coverage (32).

In most LMICs, TTCV is the only vaccine provided during pregnancy, although an increasing number of countries – mainly middle-income countries – also provide seasonal influenza vaccination during pregnancy. Different LMICs have different strategies for maternal immunization – which may be delivered either during ANC visits or in immunization clinics, with some nongovernmental agencies also providing vaccination services (32). In many LMICs the roles and responsibilities for maternal immunization are distributed between the NIP and the MNH programme. The online survey conducted in 95 LMICs as part of the MIACSA project indicated that vaccine procurement and distribution was mainly the responsibility of the NIP, whereas planning, management, training and supervision was often a shared responsibility, although the NIP appeared to take the major share of that responsibility (Table 2).
Table 2. Maternal immunization service delivery responsibilities at the national level (data from an online survey in 95 LMICs)

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Vaccine procurement</th>
<th>Planning &amp; management</th>
<th>Vaccine distribution</th>
<th>Training &amp; supervision</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIP only</td>
<td>88</td>
<td>49</td>
<td>86</td>
<td>69</td>
</tr>
<tr>
<td>ANC only</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>NIP &amp; ANC jointly</td>
<td>2</td>
<td>39</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Other*</td>
<td>5</td>
<td>–</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Unsure</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Other government entities of international nongovernmental agencies.

Source: Maternal immunization and antenatal care situation analysis: report of the MIACSA project 2016–2019 (3).

The provision of maternal immunization often occurs along with ANC services in the majority of countries, with 54% of countries assessed in the MIACSA project providing TTCV to > 50% of pregnant women along with ANC (3). Countries with limited ANC capacity were more likely to provide vaccination at immunization clinics. A variety of approaches were used for delivering immunization services, with delivery at static ANC services being the commonest approach, followed by static immunization programme services, outreach services and campaigns (Fig. 6) at the facility level, staff providing immunization and ANC services are often shared.

Fig. 6. Strategies to deliver maternal tetanus vaccination (data from 90 LMICs)

Source: Maternal immunization and antenatal care situation analysis: report of the MIACSA project 2016–2019 (3).

Given the need to vaccinate pregnant women within a specific time window during pregnancy, ANC visits are optimally suited for provision of GBS vaccination if contact occurs in the 2nd or 3rd trimester. ANC coverage is steadily improving globally. While 86% of pregnant women worldwide access ANC with skilled health personnel at least once, only two in three (65%) receive at least four antenatal visits. The coverage varies by region with only about 50% of women in South Asia and sub-Saharan Africa accessing ANC services four times (Fig. 7) (33). Timeliness of ANC visits remains an issue; one study found that fewer than half of women in LMICs had a timely first ANC visit and that those who had a timely visit were about five times more likely to receive the currently recommended eight visits (34).
WHO has revised its ANC recommendations to increase the number of contacts from four to eight times (35). Currently, 58 countries report having a policy recommending at least eight antenatal visits (36). Four of these proposed contacts (at 26, 30, 34 and 36 weeks) provide an opportunity for GBS vaccination.

In many LMICs, pregnancy is often a women’s first encounter with formal health services and the ANC system can serve as an effective platform for delivering a broad range of health interventions. WHO has identified the integration of ANC with other services as a key strategy for reducing missed opportunities and for addressing the health and social needs of pregnant women and their children (37, 38). However, the quality of care remains a significant gap that hinders the likelihood of achieving the desired coverage with maternal vaccines using ANC services (39). In many LMICs where the quality of ANC has been evaluated, only 10–50% of women received all six ANC components that were measured (39, 40). EPI compensates for low TT2+ coverage during ANC by using outreach services of supplemental immunization activities for women of child-bearing age to increase the proportion of women and infants protected at birth. Similarly, pre-season vaccination campaigns have been used for maternal influenza vaccination (41). However, such approaches would not be suitable for GBS vaccination for pregnant women since the disease is not seasonal and vaccination has to be delivered within a relatively narrow time window during pregnancy.
5.2 Opportunities and challenges for the integration of ANC and immunization services

There has been a longstanding debate about the benefits and challenges of integration, which has often been driven by narrow binary considerations of integrated (horizontal) and non-integrated (vertical) systems, with polarized views on the value of each approach (42). To these terms have been added new ones such as diagonal or oblique approaches that describe different combinations of these approaches. The relative merits of integration in different contexts have not been studied extensively and such evaluations are hampered by the lack of a commonly accepted definition of integration. Systematic reviews of the integration of ANC services with other health programmes included only studies in which HIV care or testing and treatment of syphilis were integrated into routine ANC (37). Similarly, a review of integration of other MCH services with immunization looked mainly at studies in which MCH services were delivered during immunization contact and not vice versa (43). Experiences from integrating previously siloed programmes – such as malaria control (intermittent preventive treatment in pregnancy) and prevention of mother-to-child transmission of HIV – into ANC suggests the possibility of greater efficiency and sustainability.

The MIACSA project showed that coverage with maternal vaccination was highest when a "one-stop-shop" approach for ANC and vaccination was in place (44). Providing TTCV at the same time and location as a routine ANC visit not only resulted in higher coverage and higher protection at birth overall, but also in a more efficient and positive experience for the ANC provider and fewer demands on the pregnant woman (3, 44).

The maternal tetanus vaccination platform could be further leveraged for GBS vaccination. In the MIACSA project, a correlation was seen between high-performance vaccination with TTCV (protection at birth [PAB] > 90%) and receipt of TTCV at the same time as the woman’s ANC visit (44, 45). PATH studies on maternal influenza vaccination in Africa (Malawi) (46), and Central America (El Salvador) (41) also documented high acceptance of vaccination in pregnancy; this improved over time and was largely attributed to health workers’ positive views about the introduction of additional maternal vaccines.

If maternal vaccination is provided at the same location as ANC, close coordination with the immunization programme will be required to optimize service delivery, with a clear definition of roles and responsibilities and appropriate allocation of resources. Such a model is likely to improve the coverage of vaccination in pregnancy and the coverage of ANC in general. It is also responsive to women’s preferences (47).

The results of the MIACSA project indicate that there is a reasonable division of roles and responsibilities between NIPs and MNH programmes, mainly at the higher levels of the health system. Managers of both programmes reported frequent interaction, although the quality of these interactions was not assessed. As indicated earlier, the responsibility for vaccine procurement and distribution usually remained with the NIP.

The MIACSA project also showed that in most LMICs TTCV is already being delivered along with ANC. However, in some countries the capacity of the ANC services to deliver vaccination is limited. Furthermore, even in countries where TTCV is currently delivered during ANC, health workers’ and programme managers’ concerns about the increased workload, inadequate resources, logistical challenges, increased waiting time and inadequate training will need to be addressed (48). These concerns must be taken into account if GBS vaccination is to be successfully implemented in many LMICs.
5.2.1 Human resources for delivering vaccination during ANC

The results from the telephone interviews and country visits of the MIACSA study showed that human resource constraints depended on the level of the facility. At the primary level, 33% of the countries participating in the telephone survey (N=24) mentioned not having enough skilled staff, with this being reported in 17% of countries at the secondary level and 13% at the tertiary level.

Addition of GBS vaccination to the package of services to be delivered during ANC is likely to stress the system further. For instance, studies have shown that the median time for delivering routine infant immunization across three countries ranged from 1:40 to 5:06 minutes, while the median time to provide ANC ranged from 2:35 to 9:11 minutes (49). This included the time spent for prevaccination counselling about the disease and vaccination risks and benefits, which will be important to ensure uptake of GBS vaccination (see section 6). Such issues will need to be considered carefully when planning ANC sessions and when allocating human resources for the delivery of GBS vaccination.

5.2.2 Financial resources for maternal immunization

The online survey of 95 LMICs in the MIACSA study showed that 68% of countries were partly or fully dependent on external funding for maternal tetanus vaccination (3). This was especially true for those countries with low potential for maternal immunization. Similarly, over 50% of countries reported receiving external funding for ANC, although mainly for interventions for HIV testing and counselling and/or malaria testing and treatment. Even in countries where domestic funding was the primary source, the full allocation of funds was not always received; as a result, not all planned activities could be implemented. As an increasing number of countries transition out of Gavi support, the need to increase domestic funding to accommodate GBS vaccine and implement all the planned activities is likely to pose a challenge.

The following issues merit consideration in order to achieve effective integration of maternal immunization against GBS disease into routine ANC services:

- Policies for GBS vaccination will need to be jointly developed and reflected in both the ANC and immunization policies and guidelines.
- Operational plans for both MNH and NIP at all administrative levels should include maternal immunization and describe and delineate respective roles and responsibilities, such as the responsibility for vaccine procurement and logistics, vaccine administration, recording and reporting of immunization data, and safety monitoring.
- As with TTCV, the procurement, storage and logistics functions for GBS vaccination are likely to be managed by the NIP in most countries. Collaboration and coordination between immunization and MNH programmes will be required for streamlining the GBS vaccine supply chain and ensuring adequate and sustained supply at the point of delivery of ANC.
- Both programmes will need to collaborate to ensure that health workers have the required skills for the safe and timely delivery of GBS vaccination.
- Information systems will need to be strengthened and streamlined between the two programmes in order to facilitate data reporting and sharing on GBS disease, GBS vaccination and safety of the GBS vaccine.

Experience in a several countries indicates that, with the right level of planning, collaboration and coordination, integrated delivery of GBS vaccination services is likely to create programme efficiencies and be more acceptable to health workers and the community. Factors for successful integration of services include: 1) close and effective coordination between programmes; 2) joint planning at all levels in the health sys-
tem; 3) timely and accurate programming and distribution of supplies; 4) training of health workers and provision of technical guidelines; 5) proper adaptation of data recording instruments; and 6) joint monitoring and supervision (50).

With an increasing focus on vaccination through the life course and with the uptake of HPV vaccination in pre-adolescent girls, these contacts could be used for preconception counselling to increase the uptake of maternal vaccination, or even to provide a priming dose of GBS vaccine should this be seen to enhance the impact of maternal vaccination and be a cost-effective approach.

On the basis of experience with TTCV, there is no evidence that vaccination would adversely affect ANC coverage. GBS vaccination may rather be seen as an opportunity to stimulate ANC attendance. In immunization programmes, new vaccines have strengthened vaccine delivery and health systems in many countries via additional support for programme management, logistics, human resources capacity-building, and monitoring and evaluation (51).

5.3 Expected coverage with GBS vaccination delivered through ANC

Coverage with at least four ANC visits during pregnancy ranged from 29% to 90% in the MIACSA study (44). UNICEF’s ANC4+ coverage estimates range from 50% in South Asia to 90% in Latin America. An unpublished analysis based on data on the frequency and timing of ANC visits collected from household surveys (Demographic and Health Surveys and the Multiple Indicators Cluster Surveys) showed that 55–85% of women receive ANC services between the 24th and 38th week of gestation in a number of African and Asian LMICs – i.e. the time window for GBS vaccination.3

Projections of coverage for maternal vaccination with maternal respiratory syncytial virus (RSV) vaccine have been developed and used for strategic demand forecasts for maternal immunization. Since maternal RSV vaccination is provided during pregnancy in a timeframe similar to that for GBS vaccination, these projections could also be used for GBS vaccination. These projections have been made for 110 LMICs based on the World Bank’s 2018 classification of countries by income group. The model used for making these projections uses data on coverage and timing of ANC visits and the ANC service quality data available from household surveys. The median coverage projected for these 110 countries on the basis of ANC coverage, timing and quality is 73% (range 19–96%).4 These projected coverage rates are higher than reported coverage with maternal influenza vaccination in Latin America and the Caribbean (LAC) and European countries. The mean reported coverage with maternal influenza vaccination from 22 LAC countries for 2018 was 61% (range 0–91%) (5), whereas the reported coverage from 11 European countries for 2014/2015 varied considerably from <1% in four countries to 87% in one country with a median of 9% (52). Although the reported coverage in some countries has been very low, the data suggest that – with the provision of timely and high-quality ANC services together with measures to enhance uptake of vaccination during ANC (see section 6) – moderately high vaccination coverage is possible, even in LMICs.

3 Lamberti L, personal communication, 2019.
4 Pecenka C, PATH, personal communicaton, 2019
GBS vaccine targeting pregnant women may be delivered either the NIP or the MNH programme, and potentially through a combination of both.

Based on MIACSA data the timely delivery of vaccination in the 2nd or 3rd trimester is likely to be easier if delivered along with ANC, and a substantial proportion of LMICs already use ANC to administer vaccine to pregnant women.

ANC and NIPs report having coordination mechanisms and defined roles and responsibilities for maternal immunization. However, the nature and quality of these collaborations will need to be examined and possibly strengthened for the timely delivery of GBS vaccination.

The MIACSA project found that many LMICs have weak potential for protecting mothers and infants from vaccine-preventable diseases because their human and financial resources are inadequate. These inadequacies will need to be addressed and capacities strengthened to ensure the delivery of high-quality ANC services and the achievement of timely coverage with GBS vaccination.
6. ACCEPTABILITY AND DEMAND FOR MATERNAL IMMUNIZATION

A variety of factors may influence the acceptance of and demand for GBS vaccination during pregnancy. Most of these factors are contextual and may vary between and within countries as well as between the various diseases targeted for maternal vaccination. It is important to understand these factors and the measures that may be taken to improve acceptance and demand and optimize the impact of vaccination.

This chapter addresses three questions related to the acceptability of and demand for maternal immunization, namely:

1. What factors influence acceptability and demand for vaccination during pregnancy?
2. How have vaccine hesitancy and demand been managed for other vaccines administered during pregnancy?
3. What baseline data on adverse pregnancy outcomes are available to communicate about the safety of vaccines during pregnancy and to respond effectively to reports of serious adverse events?

6.1 Factors that influence the uptake of vaccination during pregnancy

A considerable amount of literature exists on the factors influencing acceptance of ANC in general and the acceptance of vaccination during pregnancy in particular. A recently published Cochrane review is an important source of data on acceptance of ANC. Three systematic reviews on the determinants of vaccine acceptance during pregnancy were identified. Of these, one review considered only the determinants of pandemic influenza vaccination while another reviewed only the determinants of maternal seasonal influenza vaccination. The third review, which includes information from the two previous reviews, serves as the primary source of information. These reviews were supplemented by additional articles identified through a PubMed search. Only two studies report on the factors that would influence the uptake of a hypothetical GBS vaccine.
6.1.1 Factors that influence the uptake of antenatal care in general

When preparing this report, factors influencing the acceptance of ANC were reviewed on the assumption that ANC visits would be an important mode of delivery of GBS vaccination, especially during the third trimester. Hence, factors influencing the uptake of ANC would also indirectly influence the uptake of GBS vaccination; indeed, the provision of GBS vaccination during routine ANC could in turn influence the seeking of care during the third trimester of gestation.

The recent Cochrane review on routine ANC uptake included 85 qualitative studies, of which 46 explored the views and experiences of healthy pregnant or postnatal women, 17 explored the views and experiences of health workers and 22 explored the views and experiences of both groups (53). These studies were conducted in 41 countries, including 8 high-income, 18 middle-income and 15 low-income countries in rural, semi-urban and urban locations. The findings were organized into three thematic domains: sociocultural context; service design and provision; and a third domain that was further subdivided into two conceptual areas (personalized and supportive care and information and safety):

Factors from this systematic review that influence the uptake of services are summarized in Table 3. The number of studies contributing to each finding and the level of confidence in the findings varied for the different influencing factors. Readers are referred to the full review for further details, including the rationale for application of confidence levels.

Table 3. Factors that influence the uptake of antenatal care (ANC): summary of findings

<table>
<thead>
<tr>
<th>Sociocultural context</th>
<th>Level of confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influence of traditional beliefs</td>
<td>Spiritual and supernatural beliefs Moderate</td>
</tr>
<tr>
<td>Influence of others</td>
<td>Moderate</td>
</tr>
<tr>
<td>Influence of local beliefs and maternity practices</td>
<td>Cooperation with influential community members Moderate</td>
</tr>
<tr>
<td></td>
<td>Traditional, societal and community norms, practices and beliefs Moderate</td>
</tr>
<tr>
<td>Pregnancy as a health state</td>
<td>Women seeing pregnancy as a normal event that does not require medical intervention High</td>
</tr>
<tr>
<td>Selective use of ANC</td>
<td>ANC seen only as a means to confirm pregnancy Low</td>
</tr>
<tr>
<td></td>
<td>Visit used only to obtain a card to guarantee access to health facility for delivery if required Low</td>
</tr>
<tr>
<td><strong>Gender issues</strong></td>
<td><strong>Level of confidence</strong></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Financial dependence on husband</td>
<td>Low</td>
</tr>
<tr>
<td>Shame and embarrassment attached to pregnancy</td>
<td>Low</td>
</tr>
<tr>
<td>Gender of the health-care provider</td>
<td>Low</td>
</tr>
<tr>
<td>Women’s freedom of movement</td>
<td>Very low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Service philosophy, design and provision</strong></th>
<th><strong>Level of confidence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local infrastructure</strong></td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>Poor infrastructure</td>
<td>Moderate</td>
</tr>
<tr>
<td>Proximity of clinic to residence</td>
<td>Moderate</td>
</tr>
<tr>
<td>Availability of transport</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cost of services</strong></th>
<th><strong>High</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect cost of services</td>
<td>High</td>
</tr>
<tr>
<td>Staff corruption</td>
<td>Very low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Clinic environment</strong></th>
<th><strong>Low</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for privacy</td>
<td>Low</td>
</tr>
<tr>
<td>Waiting time</td>
<td>Moderate</td>
</tr>
<tr>
<td>Time spent with health provider</td>
<td>High</td>
</tr>
<tr>
<td>Condition of the clinic</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Organization of services</strong></th>
<th><strong>Low</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusing, inconsistent messages on timing of clinic and future visits</td>
<td>Low</td>
</tr>
<tr>
<td>Flexibility of appointments</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Resource issues and working conditions</strong></th>
<th><strong>Moderate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of clinical resources</td>
<td>Low</td>
</tr>
<tr>
<td>Shortage of staff</td>
<td>High</td>
</tr>
<tr>
<td>Staff training and working conditions</td>
<td>Moderate</td>
</tr>
<tr>
<td>Management support and supervision</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Emphasis on risk</strong></th>
<th><strong>Moderate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphasis or risk-focused screening at the expense of meeting patient needs</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>What matters to women and providers</strong></th>
<th><strong>Low</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Involvement of women in the organization and running of ANC services</td>
<td>Low</td>
</tr>
<tr>
<td>Peer support from other pregnant women</td>
<td>High</td>
</tr>
<tr>
<td>Continuity of care from the same health provider</td>
<td>Moderate</td>
</tr>
<tr>
<td>Provision of individualized woman-centred care</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Attitude of staff</strong></th>
<th><strong>High</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rude and hostile behavior of health staff</td>
<td>High</td>
</tr>
<tr>
<td>Attribution of apathy or laziness</td>
<td>Very low</td>
</tr>
<tr>
<td>Impersonal nature of ANC, with reliance on tests rather than on conversation</td>
<td>Moderate</td>
</tr>
<tr>
<td>Friendly, attentive and respectful approach of staff</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ANC as a source of information</strong></th>
<th><strong>High</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Provision of information in a useful, appropriate and culturally sensitive manner</td>
<td>High</td>
</tr>
<tr>
<td>Lack of awareness of pregnancy as a reason for delayed ANC</td>
<td>Very low</td>
</tr>
<tr>
<td>Lack of information from health provider leads to seeking information from other sources</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ANC in the context of clinical safety</strong></th>
<th><strong>Low</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-related complications act as an incentive to seek ANC services</td>
<td>Low</td>
</tr>
<tr>
<td>ANC as a source of medical safety: availability of medicines, medical tests and screening is an incentive</td>
<td>High</td>
</tr>
</tbody>
</table>

*Source: Downe S et al. (2019)(53).*


Sociocultural context

This domain was influenced by several subdomains, including:

1. the influence of traditional beliefs;
2. the influence of local beliefs and traditional maternity practices;
3. the notion of pregnancy as a healthy state;
4. selective use of ANC;
5. gender issues.

A variety of medical, spiritual and supernatural beliefs may influence the uptake of antenatal services. If biomedical services do not take these beliefs into account, they may influence the uptake of these services, especially if women feel that their beliefs were ignored or not respected. For instance, the belief that pregnancy disclosure may result in someone casting an “evil eye” and affecting the health of the fetus may restrict or delay seeking ANC. Where health providers took such beliefs into consideration and took measures to allay fears and concerns, the uptake of care was better.

Various people may influence a woman’s decision to engage with antenatal services, including family members, community representatives and health providers. The influence may be positive or negative, based on financial considerations, community beliefs and familial hierarchies. When communities and families are consulted and are included in the design of service delivery, many of these barriers to ANC can be overcome or even used to promote care-seeking.

Across a variety of settings and contexts, pregnancy is viewed as a healthy state and women may not see a reason to seek preventive care. In some instances, women may use antenatal services selectively – e.g. only to confirm the pregnancy or to secure an antenatal card if this is a precondition for institutional births. In this context, the provision of an intervention such as vaccination that is perceived by women to be of benefit to them, or more importantly to their babies, may be a motivator for them to seek antenatal services.

Gender issues may affect the freedom of movement of women and as a result may restrict their ability to seek ANC. Similarly, financial dependence on the husband may restrict care-seeking in some communities. Another gender-related issue is a sense of shame in being pregnant in some communities – for instance, when it is associated with sex or criticism about the size of their families.

Quantitative data on sociocultural determinants of ANC were examined in the report on State of inequality: reproductive, maternal, newborn and child health (59). Data from 86 LMICs were analysed, including from 42 countries that had more than one data point. The ANC1 coverage was 10% higher among the richest quintile compared to the poorest in about half of the countries. ANC4 coverage differed by 25% or more between the most and least educated and between the richest and the poorest quintiles, respectively. Large differences in coverage were also seen between rural and urban populations, especially in LICs but also in some large middle-income countries (e.g. Bangladesh, India, Nigeria, Pakistan). In some middle-income countries (e.g. Armenia, Belarus, Maldives) as well as LICs (e.g. Burundi, Gambia, Rwanda), there was little difference between the two groups, indicating that such barriers can be overcome. Updated information on inequalities by wealth, educational status and residence are available online at the WHO Health Equity Monitor.5

Analysis of data from household surveys in India and Pakistan identified social status (caste) as an important determinant of access to ANC. An initial review of data collected during the MIACSA project across a range of 136 LMICs showed that both the female literacy rate (positively) and low gross national income per capita (negatively) were significantly associated with protection at birth against tetanus.

**Service philosophy design and provision**

Several organizational factors may influence the use of antenatal services. Proximity and convenient access to the point of service delivery facilitate the uptake of services, especially because of the cost and time savings to the families of pregnant women. Convenient access also overcomes the transportation barriers that many pregnant women face. On the other hand, if services are provided closer to home for pregnant women, the health services would need to ensure that all the required services are available at the service delivery point, especially when it is located outside a health facility. Many countries provide both ANC and immunization services through outreach programmes at the community level. The provision of integrated services will require joint planning and logistical support to ensure that all the supplies required to deliver the full complement of services are available at each outreach session (see section 5).

The clinic environment (including privacy), the waiting time and the time that each woman has with the health provider can all be strong influencers of the use of ANC. Ensuring that the organization of services take these factors into account would be an important facilitator of service utilization.

The lack of sufficient supplies, inadequate numbers of health workers and lack of proper training, supervision and support are identified by health workers as important barriers to the provision of high-quality services which would improve the uptake of ANC.

In a systematic review on access and delivery of Intermittent Preventive Treatment (for malaria) in pregnancy (IPTp) in sub-Saharan Africa, the key supply-side barriers to the provision of IPTp and insecticide-treated bed nets were: 1) unclear policy and guidance on IPTp; 2) general health-care system issues, such as stockouts and user fees; 3) health facility issues stemming from poor organization and leading to poor quality of care; and 4) poor health-care provider performance, including confusion over the timing of each dose of IPTp.

In several countries, including high-, middle- and low-income countries, the excessive focus on screening for risk status to the detriment of provision of services that women consider important to them may deter women from seeking ANC. For example, the fact that much of the time during an ANC visit is spent on assessing risks that are not clearly explained to the pregnant woman, leaving little or no time to address issues that women feel are important to them may be a source of dissatisfaction, affecting future uptake.

**What matters to women and health workers**

This domain encompasses two subdomains that are important to both women and health workers.

1. **Personalized, supportive care**

   Engaging with communities and including them in the design and provision of ANC can be a strong enabler for the uptake of services. Beyond the provision of health services, providing for social interaction between the pregnant women and health staff, as well as between the women themselves, was welcomed by both women and health workers as a means of sharing information and receiving emotional and psychological support.

   Women are more likely to seek care if they perceive the interactions to be genuine, caring and responsive to the needs of both the fetus and the woman herself. Continuity of care and the attitudes of health workers...
are important facilitators of care-seeking. However, disrespectful, rude and even abusive behavior of health workers can be strong deterrents to care-seeking.

2 Information and safety
In most countries and contexts women visit antenatal clinics to acquire knowledge and information about their pregnancy. Well-informed and supportive health providers who take the time to provide information in a way that is understandable will facilitate follow-up visits and avoid the risk of women turning to more informal sources of information that may be misleading or confusing. Interventions, including vaccination, that are perceived by a woman to enhance her safety and that of the fetus are likely to be strong motivators for seeking care and improving antenatal attendance.

6.1.2 Factors that influence uptake of vaccination during pregnancy
The MIACSA project desk review of 137 LMICs examined selected development indicators that influenced protection at birth against maternal and neonatal tetanus and the potential to protect pregnant women and their children through immunization. The human development index, gender development index and female literacy rates were all associated with the potential to protect women and their children against vaccine-preventable diseases.

This section focuses mainly on demand-side factors that influence the uptake of vaccination during pregnancy and draws from a recent systematic review that included 155 relevant articles on factors influencing vaccination uptake during pregnancy. Most of the studies focused on influenza vaccine and most of these were conducted in North America. Studies focusing on TTCV were mainly in Asia and Africa. There was a spike in the number of articles after 2008, coinciding with the H1N1 influenza pandemic, and the number has since declined. There were seven articles focusing on Tdap that were published in 2014 and 2015, and 16 articles on TTCV which were all published prior to 2005. The findings from this review were supplemented by additional publications identified through a PubMed search, including two articles that specifically collected information on factors influencing uptake of a hypothetical GBS vaccine that were not included in the systematic review.

Perceptions of benefit and risks
Perceptions about risks and benefits were the main factors that influenced the uptake of vaccines during pregnancy. The safety of vaccination during pregnancy was the primary concern with the influenza, pertussis and GBS vaccines; most of these studies were from higher-income countries. In the USA, vaccine acceptance of influenza vaccination during the H1N1 pandemic was lower during the first trimester compared to the second and third trimesters. Addressing concerns about first-trimester vaccination is particularly important, including for obstetricians and other providers of ANC, if vaccination during this period is anticipated. Although safety was cited as a reason for low acceptance in many studies, few provided details on the specific safety concerns that led to refusal or low acceptance. One study noted that, although pregnant women expressed concerns about the safety of the vaccine, the majority of them nevertheless received vaccination. On the other hand, another study found that a substantial proportion of women who perceived influenza vaccine as safe still did not intend to be vaccinated.

A web-based survey in a convenience sample of 461 pregnant women in the USA on the factors affecting the uptake of a hypothetical GBS vaccine found that 75% agreed that vaccination is a good way to protect their baby’s health. While there were concerns about the safety of the vaccine, 23% indicated that they would definitely have the vaccination while 56% indicated that they probably would have it.
The lack of knowledge and information on the vaccines, the diseases they prevent and their severity, and concerns about the efficacy of the vaccine were also reasons for not accepting vaccination during pregnancy. Perceptions of the severity of disease were an important determinant of vaccination (65). In a study in the United Kingdom, among persons who knew about the diseases, pertussis and GBS were rated as very or fairly serious diseases (58). Less was known about GBS compared to pertussis or influenza; nevertheless, when information on GBS was provided, a larger proportion of women indicated their willingness to accept vaccination (58). However, the authors of the study noted that, while over 70% of survey respondents reported that they would be likely to have antenatal vaccination, the coverage of pertussis and influenza vaccination in pregnancy in England during that period was only 62% and has dropped further since then. Similarly, another study showed that, while over 80% of women agreed that influenza and pertussis would be serious or very serious for themselves or their infants, only 36% and 44% reported that they were likely to receive influenza or pertussis vaccine, respectively, during their current pregnancy (65). While perceptions of the safety of influenza vaccines contributed to lower uptake, a substantial proportion of women who perceived vaccines to be safe during pregnancy still did not intend to be vaccinated (52% and 47% for influenza and pertussis, respectively) (65). Together these data indicate gaps between knowledge, intent and actual uptake of vaccination.

Dual benefit to the mother and the baby was identified as a predictor of acceptance of vaccination (55). Several studies noted that women were more concerned about the risk from disease to their infants than to themselves. As a result, they were more likely to accept vaccination against pertussis – which they perceived as being a more severe disease and vaccination as a means of providing protection for the baby – rather than influenza (66, 67). Messages on the impact of vaccination on the well-being of their infants were found to be a strong motivation for acceptance of vaccination in several countries (68, 69).

Channels of communication and the importance of strong health worker recommendations

A recommendation from the health worker to receive vaccination during pregnancy was reported in most studies to increase vaccination uptake (41, 46, 54, 55, 70). In the USA, 71% of women who received both a recommendation and an offer for influenza vaccination accepted the vaccination, compared to only 10% who did not (71). A recent review showed a moderately positive linear correlation (r = 0.66) between the health worker recommendation rate and maternal influenza vaccination coverage (72).

Several studies showed that women trusted information or recommendations from their health worker more than information they received through other channels (73). WHO’s influenza post-introduction evaluation (IPIE) in three middle-income countries (Belarus, Morocco and Thailand) highlighted the importance of health workers’ knowledge, attitudes and practice in stimulating vaccine acceptance in pregnant women (74). This was also highlighted in the study on maternal influenza vaccination in El Salvador (41). In Thailand, lack of knowledge of the national policy or ambiguity of the policy were major reasons for physicians not to recommend influenza vaccination even though they had a favourable attitude to vaccination (75). Even in situations where knowledge of policy recommendations is very high, health providers may not always recommend vaccination to their patients or offer it in their clinics (73). The review by Morales et al. showed that health workers who were themselves vaccinated against influenza were more likely to recommend vaccination to pregnant women (72). Other common determinants for health worker recommendations were greater awareness of vaccination policies, awareness of the vaccines, and vaccine knowledge and confidence. Common barriers included concerns about safety and efficacy, financial barriers such as concerns about insurance reimbursements, and perceptions about the seriousness of influenza (72).

Most available studies on vaccine acceptance take into account the client’s perspective, but few consider it from the health worker’s perspective, which could also be important – especially regarding workload, train-
ing and adequate reimbursement, all of which are particularly relevant to LMICs (54, 73). Those studies that were available did not use a theoretical framework (73). Thus, while recommendations from health workers and their offer of vaccination are strong influencers for vaccination uptake, the reasons for the failure of the health workers to recommend and offer vaccination, despite knowledge of policy recommendations, need to be understood in order to find solutions to improve vaccination uptake (74).

Contextual issues

Ethnicity was a factor that influenced vaccine uptake in several studies, with lower uptake of vaccines among ethnic minorities (54). Language barriers, acculturation and lack of literacy may be associated with lower uptake in some ethnic and minority communities (64). However, contextual factors vary between countries and local data may be required to understand the local context and develop measures to address the factors that influence vaccination uptake.

6.2 Strategies and approaches to improve demand and acceptance

6.2.1 Evidence on the impact of strategies to increase vaccination acceptance

Available data are mainly from studies in a limited number of settings – predominantly HICs – and measure the intent to accept vaccination rather than actual receipt of vaccination and consequent increase in coverage. A recent systematic review compiled and assessed the findings from these studies (76). The review used the psychological framework proposed by Brewer et al., and organized findings under three headings: 1) thoughts and feelings; 2) social processes; and 3) changing behavior directly (77). Many of the studies evaluated multicomponent intervention packages, hence the impacts of individual interventions within the package are difficult to determine.

Thoughts and feelings

Motivation to be vaccinated depends on the thoughts and feelings of the person concerned – in this case the pregnant woman. Several studies have assessed interventions to improve the risk appraisal of pregnant women, to increase their confidence in vaccination and to improve their motivation.

Different approaches to enhance risk appraisal, which focuses on the perceived severity and susceptibility of disease and the risks and benefits of vaccination, have been studied. Enhancing a woman’s risk appraisal improves vaccination uptake, though the means of communicating risks and benefits influences the outcomes. Message framing and the modes of transmission are important for improving acceptance (78). Messages transmitted by interpersonal networks and social media strongly influence motivation to accept immunization during pregnancy (79). In a randomized controlled trial of intention to vaccinate in the USA, both gain-framed and loss-framed messages were positively associated with increased maternal intent to immunize infants against influenza. Message resonance was enhanced among those who saw the film Contagion (80). Another randomized controlled trial that assessed weekly text messages to pregnant women reinforcing the recommendations and safety of influenza vaccination did not increase vaccination acceptance (81).

There is evidence that interventions aimed at increasing confidence in vaccination among pregnant women can increase uptake, especially when the messages emphasize the benefits of vaccination for their infants (76, 82).
Social processes

Individual decisions are often influenced by social factors, including social dyads, social networks and social norms. Interventions that leverage social processes have the potential to influence individual decisions and affect the uptake of vaccination.

The most influential social dyad for maternal immunization is the pregnant woman and her ANC provider. There is evidence that provider recommendation is strongly associated with vaccine receipt, making it extremely important that the health worker is adequately informed and empowered to make the right recommendations and address the client’s questions (55, 73).

There is evidence that vaccine acceptors tend to cluster with other vaccine acceptors in social networks, but there are no studies on interventions at the social network levels (76).

Targeting peers to apply social pressure to change behavior may also influence uptake of vaccination. Two studies have shown that vaccination champions increase uptake, though in both studies the use of champions was part of a multicomponent intervention package (83, 84).

Changing behavior directly

This category includes behavior change without attempting to change attitudes. This includes reminder and recall systems. The most commonly-used mechanism was the use of text messages, although this was found not to be very effective (85, 87). Several studies have shown that health provider prompts improve vaccination uptake (76).

Standing orders empower health workers to present vaccination as a social norm. Several studies in which standing orders were part of a package of interventions demonstrated an improved uptake of vaccination (83, 84).

6.3 Existing tools for improving uptake of vaccination

Several tools and guides exist for developing strategies and approaches to improve demand and acceptance. Some of these, such as the Communications handbook for polio and routine EPI (88) and Global routine immunization strategies and practices (89) provide step-by-step guidance on developing national communication plans for improving demand and acceptance of vaccination in general, although mainly focused on childhood immunization. The emerging evidence on vaccine-related communications is being used to develop evidence-based guidance for tailored approaches to increase vaccine acceptance (90). The stages of behavior change to create awareness and translate this increased awareness into positive action have been described, but implementation of behavior change activities requires a thorough understanding of the environmental, social and personal factors that influence vaccination uptake (91).

6.3.1 The Tailoring Immunization Programmes (TIP) approach to improve uptake of maternal influenza vaccination (91)

The Tailoring Immunization Programmes for maternal influenza vaccination (TIPFlu) tool provides a framework for diagnosing demand-side and supply-side barriers and facilitators of vaccination during pregnancy by building on an understanding of the behavioral, social and environmental factors that influence vaccination behaviors and demand in a given context. The information obtained is used to design evidence-based interventions that are tailored to the local context and to deliver, monitor and evaluate the interventions aimed
at increasing uptake. The TIPFlu tool uses the socioecological model to explore the determinants of vaccination uptake in pregnant women, with the assumption that individual behaviors are determined by multiple layers of influence that interact with each other (Fig. 8).

**Fig. 8.** Socioecological model for improving vaccination uptake during pregnancy (adapted from UNICEF’s model for communication for development and TIPFlu)

The TIPFlu tool uses the social marketing framework to systematically plan, implement and evaluate health-promoting interventions – in this case uptake of vaccination during pregnancy. It encourages programmes to view their target population as a heterogeneous group of individuals, who must first be understood, then engaged to respond to their needs and then attracted to accept vaccination. It employs the traditional four Ps of commercial marketing (product, price, place and promotion) and adds three additional Ps (partnerships, policy and purse strings) to reflect the needs of public health programming (Fig. 9).

**Fig. 9.** The seven Ps of social marketing
The tool provides a step-by-step guide for design, implementation and monitoring of maternal vaccination. Although it was designed primarily for maternal influenza vaccination, it may be adapted for maternal vaccination with other vaccines.

The TIP approach follows 11 steps, as depicted in Table 4.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Steps</th>
<th>Time needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe the situation, target population and partners to involve</td>
<td>1. Decide the scope</td>
<td>A few hours to 1 week</td>
</tr>
<tr>
<td></td>
<td>2. Review the situation</td>
<td>Up to 2 weeks</td>
</tr>
<tr>
<td></td>
<td>3. Analyze the situation</td>
<td>A few days to 2 weeks</td>
</tr>
<tr>
<td></td>
<td>4. Write a preliminary problem statement</td>
<td>A few hours to 1 day</td>
</tr>
<tr>
<td>Diagnose the demand- and supply-side facilitators and barriers</td>
<td>5. Collect new information</td>
<td>2–6 months</td>
</tr>
<tr>
<td></td>
<td>6. Describe the target populations and the determinants of their behaviors</td>
<td>A few hours to 1 week</td>
</tr>
<tr>
<td></td>
<td>7. Complete a problem statement with a behavioral analysis</td>
<td>1–7 days</td>
</tr>
<tr>
<td>Design evidence-informed interventions</td>
<td>8. Set up the TIP objectives</td>
<td>A few hours to 1 day</td>
</tr>
<tr>
<td></td>
<td>9. Use the social marketing framework to design the interventions</td>
<td>One to several months</td>
</tr>
<tr>
<td></td>
<td>10. Develop a communication strategy, messages and communications materials</td>
<td>1–6 months</td>
</tr>
<tr>
<td>Deliver, monitor and evaluate interventions</td>
<td>11. Deliver, monitor and evaluate the interventions</td>
<td>Ongoing before, throughout and after implementation</td>
</tr>
</tbody>
</table>

Source: TIPFlu for seasonal influenza: a guide for promoting uptake of maternal influenza vaccination (91).

Given the paucity of information on the determinants of vaccination uptake in most LMICs countries, and since these determinants may differ from those in countries where data are available, the TIPFlu tool or an adaptation of the tool may be used to generate the evidence to design, implement and evaluate maternal GBS vaccination. The estimated time required to collect the information and to design and implement the TIP approach depends on the scope of the project. The estimated timelines for each step are provided in Table 4. The TIP-flu pilot project in Lithuania took 18 months to complete. While this represents a significant improvement, the coverage is still not optimal and follow-up is required to determine if further improvements occurred or additional interventions are required to achieve optimal coverage.

6.4 Availability of data on adverse pregnancy outcomes

Awareness of the background rates of pregnancy outcomes that may represent or be interpreted as vaccine-related adverse events will be crucial to the assessment of possible vaccine safety concerns and will also help to separate legitimate safety concerns from events that are temporally associated with, but not caused by, vaccination. The use of baseline rates of such events could be part of the risk communication strategy and can serve to allay unfounded fears about the safety of the vaccine (92).
This section assesses the availability of baseline data on key events that will allow for assessment of the safety of vaccines administered during pregnancy, namely: miscarriage (spontaneous abortions) by trimester; stillbirths; neonatal deaths; and congenital malformations. Prospective collection of data on impact and safety following implementation is covered in section 7.

### 6.4.1 Miscarriage

The need for information on background rates of selected medical events, including spontaneous abortions, was raised in mass vaccination programmes during the H1N1 influenza pandemic. Additionally, the importance of geographical variations in such incidence has been recognized in the assessment of vaccine safety (92). In one systematic review of studies in the USA, the cumulative risk of miscarriages for weeks 5 to 20 of gestation ranged from 11–22 per 100 women (11–22%), with rates being highest in the first trimester and progressively declining in the second trimester (93). Other studies have reported this to be in the range of 10–15% (94). Published data on the frequency of miscarriages reported varies according to the definition used, the age of the pregnant woman, her race and the trimester of pregnancy. Since GBS vaccines are likely to be given in the 2nd or 3rd trimesters of pregnancy when miscarriages are less common, this issue may be less of a concern with this vaccine.

### 6.4.2 Stillbirths

Data on stillbirths are collected through civil registration and vital statistics (CRVS) systems, health management information systems (HMIS) or household surveys. However, where available, the quality of data collected through CRVS is suboptimal in many LMICs and investments to improve the quality of data from household surveys have not been made (95). Data available from CRVS, published literature and Demographic and Reproductive Health Surveys were used to estimate rates of stillbirth at global, regional and national levels. In all, 157 countries contributed data for the analysis. High-quality CRVS data were available from 45 countries, while 65 countries had lower-quality CRVS data. In addition, 127 household survey data were available from 57 countries (95). The estimates may be used as a source of baseline data when national data from CRVS or other credible sources are not available.

### 6.4.3 Neonatal deaths

In many LMICs, the CRVS are suboptimal for collecting accurate data on neonatal deaths. However, the UN Interagency Group for Child Mortality Estimation (IGME) uses these data to derive estimates for neonatal and child mortality every year. These data are available through an interactive website and serve as a source of baseline data for countries lacking high-quality local data. These data may be used until such time as the availability of data from maternal and perinatal death reviews improves.

### 6.4.4 Congenital disorders

Fear of congenital disorders is an important cause of hesitancy or refusal to accept vaccination during pregnancy. Conversely, the occurrence of a congenital disorder may be attributed to vaccination received during pregnancy even though there may not be a causal relationship. Information on the background rates of congenital disorders is important for risk communication in relation to maternal immunization. In most LMICs, accurate data on the rates of congenital disorders are not available or are grossly underestimated (96). With an increasing focus on birth defects, a number of online databases have been established to monitor rates of congenital disorders. These are described in more detail in section 7 and represent a source of information on background rates.
6.5 Conclusion on data availability for risk communication

Having information on baseline rates of outcomes that could be ascribed to maternal vaccination is vital for risk communication. Empirical data are lacking from many LMICs. Nevertheless, data from systematic reviews and estimates from modelling are available and may be used for risk communication until more robust local empirical data become available. However, the availability of estimates should not preclude the establishment or improvement of surveillance systems to generate high-quality local data.

Highlights

- Factors influencing the uptake of ANC and maternal vaccination are likely to be contextual and vary between and within countries, although some factors may be common to most countries.
- Most available data on factors influencing the uptake of maternal vaccination are from HICs. Formative research will be required to generate more information from LMICs to inform local strategies to increase the uptake of GBS vaccination.
- Conceptual frameworks used in HICs may be adapted for use in LMICs to generate local data on factors that influence the uptake of maternal vaccination.
- The TIPFlu tool and other similar tools may be adapted to collect information on demand-side barriers to GBS vaccination and may be used to design appropriate interventions to improve uptake.
- Estimates of background rates are available for important pregnancy outcomes such as stillbirths, neonatal deaths and congenital malformations and may be used for risk communication in the absence of high-quality local data.
7. MONITORING AND EVALUATION

Monitoring and evaluation are key components of vaccine delivery as they generate information on performance and impact that informs strategic and operational decisions for optimizing programmes and monitoring vaccine safety. This chapter evaluates the potential for monitoring GBS vaccination in pregnant women, specifically assessing the monitoring systems that currently exist and that can be leveraged or adapted to monitor GBS vaccination.

This chapter addresses three questions:

1. What are the existing mechanisms for monitoring immunization coverage and how could they be leveraged or adapted for monitoring coverage of GBS vaccination?
2. What are the existing mechanisms that could be leveraged or adapted for monitoring the impact of GBS vaccination on pregnancy outcomes and GBS disease in pregnant women and their infants?
3. What are the existing mechanisms that could be leveraged or adapted for monitoring all adverse events following GBS vaccination in pregnancy?

7.1 Monitoring vaccination coverage

It is essential to monitor vaccination coverage in order to assess programme performance and inform strategies and operational planning to optimize the impact of vaccination. Vaccination coverage is usually monitored by NIPs, though MNH programmes may participate in monitoring maternal vaccination. Immunization data, together with other data, are collected in the HMIS, but the quality and completeness of the data vary between countries. This section examines existing systems for monitoring vaccination coverage and discusses how they may be leveraged to collect data on GBS vaccination.

All countries routinely report data on immunization coverage annually to WHO and UNICEF through the WHO-UNICEF Joint Reporting Form (JRF) (97). These data are analysed and published annually. WHO and UNICEF also triangulate the reported coverage data with data from other sources, including coverage surveys, to develop the WHO-UNICEF Estimates of National Immunization Coverage (98). Currently, the only coverage estimate for vaccination during pregnancy published by WHO is TT2+ coverage as reported by countries. However, whether and how many doses of TTCV a woman receives in each pregnancy depends on the prior vaccination history; the reported data are considered unreliable. Nevertheless, immunization programmes in most
countries have well-established systems for collecting and reporting immunization coverage data that could be leveraged or adapted to report coverage data on GBS vaccination. Immunization information systems are not uniform across countries; they range from electronic immunization registries to aggregated paper-based recording and reporting systems. In addition, many countries conduct household immunization or multi-indicator cluster surveys that collect information to estimate immunization coverage.

7.1.1 Immunization registries

Electronic immunization registries (EIRs) are computerized, confidential, population-based systems that contain individual-level information on vaccine doses received. Such registries permit coverage monitoring by provider, vaccine, age or other target group, and geographical area, as well as facilitating individualized follow-up (99, 100). Registries can be an important tool for monitoring vaccination coverage, including during pregnancy. When linked with data from other sources, they may be used to estimate vaccination coverage and monitor the impact and safety of vaccination (101, 102). An increasing number of high- and middle-income countries have EIRs or are in the process of establishing them. In a recent survey of European Union and European Economic Area (EU/EEA) countries, 27 of 30 countries reported either having a registry at the national or subnational level or piloting a system/having plans for setting up a system (100). An increasing number of countries in Latin America have established EIRs or are in the process of implementing or developing them (99). A few countries such as Argentina, Canada, China and the USA have state or provincial-level registries. In the USA, the American Immunization Registries Association (AIRA) provides a forum through which members combine efforts, share knowledge and promote activities to advance immunization information systems and immunization programmes (103). In China, 27 of the 32 provinces report having EIRs; 20 of them have the ability to exchange information with other provincial EIRs (104). Several LMICs have received support to establish or pilot EIRs (105–108). Where these registries are available or under development, they should be leveraged or adapted not only to monitor coverage but also to link to other health databases to monitor impact and possible adverse events following vaccination.

7.1.2 Aggregate administrative data collection systems

Most LMICs use aggregate data systems that are paper-based or electronic, or a combination of the two. In most countries, data are collected at the point of delivery using paper-based systems, including tally sheets and registers with the latter collecting individual data. The aggregate data are fed into electronic systems at some point in the reporting chain, as illustrated in Fig. 10 (32).

In these systems, only aggregate data by vaccine and dose are reported to the higher levels, as opposed to the individual data available in immunization registries (Fig. 10). Hence individual data on vaccination status cannot be linked to data on disease or adverse events (32). It is likely that the electronic databases reported by many countries in the MIACSA study contain such aggregated data.

The District Health Information Software 2 (DHIS2), which is an open source web-based HMIS platform, is the world’s largest HMIS platform. Many LMICs currently use this platform or are planning to use it to collect and manage immunization data (109). Since the platform is used broadly in national HMIS, it is possible to link the immunization data to other health data (e.g. to other data from the maternal and child health programme). WHO has published guidelines and tools for national and mid-level programme managers on monitoring of NIPs (110). Guidelines and tools are also available for data quality assessment and data analysis (111, 112). Furthermore, DHIS2 has developed an e-tracker and is building an EIR module that was rolled out in Rwanda in 2019 (113).
While many countries collect ANC data in their national HMIS, these data are not systematically reported to WHO through an official, routine process although through different initiatives and at different levels (regional, country) these data might be shared. Hence, there is little standardized information on the availability and quality of ANC data in the national HMIS in LMICs (T Diaz, personal communication). WHO and UNICEF have recently published a toolkit for Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCAH) that includes a core list of ANC indicators to be collected. 

An assessment of factors affecting implementation of vaccination during pregnancy in 92 LMICs surveyed as part of the MIACSA project revealed that maternal immunization records exist in the form of personal ANC records (80%), vaccination cards (66%), clinic-held records (90%) or electronic databases (43%). The quality and content of the information available in these records and databases is not known. Reporting by the private sector is variable and in one third of countries assessed in the MIACSA project, the HMIS contained data only from the government sector.

The existing systems for collecting administrative data on immunization coverage should be feasible – whether through the immunization or ANC monitoring systems or both. In recent years, the monitoring of several new vaccines added to the infant immunization schedules has been successfully integrated into the administrative monitoring systems in most LMICs. However, collaboration between the NIP and MNH programmes needs to be strengthened in order to define roles and responsibilities and ensure the timely collection and reporting of data.
7.1.3 Household surveys

Household surveys are another method of collecting demographic and health data, including on immunization. The UNICEF Multiple Indicators Cluster Surveys (MICS) and the Demographic and Health Surveys (DHS) are important sources of data on ANC coverage in LMICs (115, 116). These surveys are the primary sources of data for the WHO and UNICEF estimates of ANC coverage. For immunization, in addition to MICS and DHS, countries may also conduct Immunization Cluster Surveys (117). Information on maternal tetanus vaccination is generally collected in these surveys and it would be feasible to collect information on GBS vaccination as well. However, household surveys are time- and resource-intensive and are conducted only periodically – generally once in five years. Hence, data are not available on an ongoing or timely basis and the sample sizes may not permit subnational estimates of reasonable precision. Furthermore, the surveys are subject to selection and information biases (118). Non-availability of records (e.g. home-based records) and dependency on recall may lead to inaccuracies in estimating coverage (119, 120). However, surveys are useful tools for validating the coverage estimates from administrative systems and for collecting additional information on the determinants of vaccination. Promoting the use and retention of home-based records will improve the quality of coverage estimates from household surveys by reducing dependency on recall while also improving collaboration between ANC and immunization programmes.

7.1.4 Service Provision Assessments (SPA) and Service Availability Readiness Assessment (SARA).

The Service Provision Assessments (SPA) and Service Availability Readiness Assessment (SARA) are the most widely employed health facility assessment tools that generate information on the quality of service delivery, including ANC, in LMICs. These assessments are conducted only periodically and are limited to health facilities; private facilities may be included in part or not at all, depending on the country’s master facility list. Both assessments focus mainly on the availability of services and cover some domains of service quality but do not assess coverage (121). However, the use of these assessments is growing and they could be leveraged to assess the information systems and the quality of the available data.

7.2 Monitoring the impact of GBS vaccination

Demonstration of the impact of GBS vaccination in the LMICs that introduce it early would be important for communicating the value of vaccination to the countries that begin to use it later and who may wish to see more evidence before making a decision to prioritize GBS vaccine for introduction. Continued monitoring of impact may also be necessary to sustain maternal GBS vaccination in national health programmes or to take strategic decisions to optimize its impact.

The important outcomes to monitor for possible adverse events following immunization include the following (see also WS1 and section 4 and section 6 of this report):

1. **Stillbirths**: Stillbirths are common, although often underreported, in LMICs. Rates are as high as 25.5 and 28.7 per 1000 live births in South Asia and sub-Saharan Africa, respectively (95). GBS is likely to be a significant cause of stillbirths, especially in Africa, although data on GBS-associated stillbirths are not available from Asia (22).
2. **Invasive GBS disease (sepsis, meningitis) in neonates and infants**: GBS is a leading cause of neonatal and early infant sepsis with the highest incidence reported in Africa (1.12 per 1000 live births) and the lowest in Asia (0.30 per 1000 live births) (17).

3. **Maternal sepsis**: An incidence of 0.38 per 1000 pregnancies is reported in HICs, though no data were found from LMICs (20).

Although there is some evidence of an association between GBS colonization and preterm births, the effect is variable and is subject to bias and confounding; the effect is more pronounced with proven GBS bacteriuria (19). The effect of maternal vaccination given during the second or third trimester on preterm births may be addressed in specific studies before routine monitoring is established.

### 7.2.1 Stillbirths

Data on stillbirths are not systematically collected through CRVS, HMIS or demographic surveillance in LMICs. However, opportunities exist to strengthen surveillance for stillbirths in at least a representative set of countries in order to monitor the impact of GBS vaccination on stillbirths. With the inclusion of a full pregnancy history module in the revised DHS questionnaires, more reliable data on stillbirths may be available in future from household surveys.

Despite the well-documented benefits of CRVS, many countries do not have adequate systems in place. However, there is an opportunity to overcome deficiencies in CRVS by focusing global attention on improving the health of women and children. The CRVS scale-up investment plan 2015–2024 has the goal of universal civil registration of births, deaths and other vital events by 2030 (122). As of May 2014, 25 of the 75 priority countries in the Global Strategy for Women’s and Children’s Health had national CRVS plans based on comprehensive assessments of their CRVS. This number has undoubtedly increased since then. The target for 2030 is to have 80% of all deaths registered by 2030. WHO guidelines and tools are available to conduct comprehensive assessments of CRVS and to strengthen them (123). The efforts to strengthen CRVS provide opportunities to capture stillbirth rates in at least a representative set of countries. Information on whether the stillbirth is fresh or macerated will facilitate causality assessment since GBS-related stillbirths occur prior to delivery and are more likely to be macerated (124).

LMICs are progressively undertaking maternal and neonatal death audits as part of Maternal and Perinatal Death Surveillance and Response (MPDSR) activities (125). In view of the varying availability of data in Asia, WHO’s South-East Asia Regional Office is strengthening country capacity for MPDSR. The Regional Office aims to develop a 5-year plan, a 3-year plan and a plan to implement and expand MPDSR in each country (126). These audits will be a useful source of data for monitoring stillbirths in countries.

Health and Demographic Surveillance Systems (HDSS) exist in many LMICs. The International Network for the Demographic Evaluation of Populations and their Health (INDEPTH) network has 49 HDSS field sites in 19 LMICs in Africa, Asia and Oceania (127). Additional sites may exist outside this network. The network of sites provides another means to monitor the impact of GBS vaccination on stillbirths provided that the capacity to monitor stillbirths at these sites is optimized.
7.2.2 Invasive GBS disease in infants

Data from the MIACSA project show that passive surveillance was the most common form of disease surveillance performed in LMICs, with surveillance of neonatal tetanus and of maternal death being the ones most commonly reported (3, 44). Thirty of the 95 countries (32%) which responded to the MIACSA online survey in 2018 reported conducting surveillance for neonatal sepsis, although it was unclear whether this included case-based surveillance with laboratory confirmation in all cases.

WHO has commissioned a study to assess the feasibility of establishing a multicountry GBS surveillance network in order to establish baseline rates of stillbirths and young infant disease in LMICs prior to the introduction of a GBS vaccine. Surveillance standards are currently being developed (Cohen A, personal communication). If such a network is established, surveillance could be sustained in at least a subset of high-performing sites to monitor the impact of GBS disease. The study examined all existing surveillance networks, using a set of metrics to assess their suitability for infant GBS surveillance. The preliminary findings from the assessment have indicated that no existing network can easily incorporate surveillance of young infant (neonatal and early infancy) GBS disease. However, with suitable investment at least a subset of sites in these networks could be strengthened to conduct GBS surveillance for young infant disease in order to establish baseline rates of stillbirths and invasive disease and then document the impact of vaccination. WHO’s Global Invasive Bacterial Vaccine-Preventable Diseases Laboratory Network collects data on invasive bacterial diseases in infants of 1–59 months and could potentially be expanded to carry out surveillance in hospitalized newborn infants with suspected meningitis and sepsis (128, 129).

7.2.3 Maternal sepsis

No similar assessment has been done for maternal sepsis yet such surveillance systems would need to be established if maternal disease is considered to be an important outcome to monitor. Here again, the scope and age range of the existing WHO invasive bacterial disease surveillance network could be enhanced at selected sites to conduct such surveillance for maternal sepsis, including laboratory confirmation of etiology (129).

7.3 Safety monitoring

The safety of any interventions given during pregnancy is a primary concern of expectant mothers and is the subject of intense professional and public scrutiny. This can often impede the use of such interventions even when they have the potential to safeguard the health of pregnant women, improve pregnancy outcomes and protect the health of newborn infants. Women with perinatal loss are more likely to experience depression, guilt and prolonged grieving, and any intervention that improves physical and psychological well-being should be considered (130).

Multiple initiatives are ongoing to improve maternal and child health, and the use of harmonised approaches, standards and tools across programmes is paramount to synergise efforts in monitoring the various health interventions (131). Systems that monitor the safety of maternal immunization should have specific features for monitoring not only safety in the pregnant woman who is the recipient of vaccination, but also for monitoring adverse pregnancy outcomes and assessing causal links to vaccination. Adverse pregnancy outcomes such as miscarriage, fetal death, stillbirth, neonatal death and congenital anomalies are not typically monitored in most pharmacovigilance systems. When one vaccination is delivered to pregnant women as part of
ANC and another through the NIP, new mechanisms for reporting of adverse events need to be established with clear definition of roles, responsibilities and accountability (132).

Mechanisms and technical capacity to monitor the safety of vaccination during pregnancy is currently limited in LMICs. While the majority of 95 of the 137 LMICs which participated in the online survey in the MIACSA project reported having a system for monitoring adverse events following immunization (AEFI), only 11% distinguished between pregnant and non-pregnant women (3, 45). While sample safety reporting forms for collecting and reporting data on AEFI during pregnancy have been published by WHO (133), few countries implement them fully (134). In addition, the quality of data collected is variable as observed in the WHO Global Vaccine Safety in pregnancy multi-country project (135).

In HICs and in some middle-income countries, pregnancy outcomes are monitored through vital registration and data from medical records. In many countries, however, vital registration and medical record data are incomplete or of poor quality. Nevertheless, a number of mechanisms exist, several of which have been mentioned earlier in this report, that can be leveraged to monitor the safety of maternal immunization (131). A roadmap is available for establishing or strengthening maternal immunization safety monitoring in LMICs, including recommendations on the actions required and guidance for setting up an implementation plan (132). WHO is well positioned to convene the various stakeholders and propose a mechanism to coordinate these initiatives and propose standards for safety monitoring (29).

A scoping review was conducted to identify existing electronic and mixed paper-electronic systems that collect continuous maternal, neonatal and child health (MNCH) data in LMICs with the potential to inform active safety electronic surveillance for novel vaccines using standardized definitions (136). Preliminary findings from this review showed that three existing MNCH registries can be used to inform future active surveillance systems in maternal immunization. These are DHIS2, Global Network’s Maternal Newborn Health Registry (GN-MNHR) and INDEPTH. Each system recorded exposure to vaccines and drugs during pregnancy and had the flexibility to modify and add variables. These systems are able to record maternal death, postpartum haemorrhage, spontaneous abortion, neonatal death, congenital anomalies, neonatal infections, preterm birth, stillbirth abortion, low birth weight and small for gestational age6.

The GAIA project aims to improve the quality of outcome data from clinical vaccine trials in pregnant women with a specific focus on the needs and requirements for safety monitoring in LMICs. GAIA has established a network of professionals concerned with monitoring the safety of immunization in pregnancy (137). Case definitions and guidelines have been developed and published by the Brighton Collaboration for a number of maternal, fetal and neonatal outcomes for monitoring the safety of vaccination during pregnancy (138–147). The outputs of the GAIA network could be used effectively for capacity-strengthening in LMICs for monitoring the safety of immunization during pregnancy (137).

The Uppsala Monitoring Centre, established in Sweden as the WHO Collaborating Centre for International Drug Monitoring, provides technical support to WHO Member States in strengthening pharmacovigilance capacity and is another resource for capacity strengthening (148).

Several resources to monitor the impact of GBS vaccination, as noted earlier (e.g. monitoring of stillbirths), may also be leveraged to monitor adverse events. In addition, a number of surveillance networks and online resources that are available for monitoring birth defects could also be leveraged to monitor birth defects associated with vaccination (149–153).

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In WHO’s Region of the Americas, 12 countries have surveillance systems for birth defects. To help countries with no existing surveillance systems, the Centre for Perinatology, Women and Reproductive Health (CLAP) of the Pan American Health Organization (PAHO) provides technical cooperation services to professionals such as neonatologists, geneticists, epidemiologists and obstetricians – as well as to decision-makers in ministries of health – to improve the monitoring of birth defects (154).

EUROCAT is a European network of population-based registries for the epidemiological surveillance of congenital anomalies. The network has 39 active registries with 33 full and 6 associate members in 21 countries. EUROCAT started in 1979 and is surveying more than 1.7 million births per year (149).

WHO Regional Office for South-East Asia has a Newborn and Birth Defects (NBBD) database that is designed to support data management for newborn health, birth defects and stillbirths. Some 220 hospitals in 9 countries are currently registered as a part of the NBBD surveillance network and 170 hospitals in 7 countries reported data on birth defects since 2014. Nine member countries of the South-East Asia region have developed national plans on prevention and surveillance of birth defects, though country-specific rates are not publicly available (151). In 2019, WHO initiated training of health workers in African countries to improve surveillance for birth defects (155).

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**Highlights**

- Almost all countries report vaccination coverage data collected through administrative or coverage surveys, and often from both. Many LMICs also collect ANC data in their national HMIS. One or both of these systems can be leveraged to collect GBS vaccination data, although close collaboration between the NIP and ANC programmes would be essential to ensure data completeness.

- There are limitations in the quality of data and coverage of interventions delivered by private providers since these are not captured in many countries. If the private sector is likely to play a significant role in the delivery of ANC and GBS vaccination, efforts should be made to promote private-sector reporting to the national HMIS.

- Few LMICs have systems for collecting data on GBS outcomes to monitor impact, including invasive disease and stillbirths. However, several opportunities exist that may be leveraged to establish surveillance for these outcomes. Such surveillance should ideally be established to start collecting baseline data a few years prior to the introduction of vaccination.

- Safety monitoring for vaccination during pregnancy is complex and does not exist in many LMICs. Definitions and guidelines for safety monitoring during pregnancy have been established and support is available to establish or strengthen systems in preparation for the introduction of GBS vaccination. Three existing systems may be leveraged to collect data on the safety of maternal GBS vaccination.
8. CONCLUSIONS

This report summarizes the key issues related to operationalization of GBS vaccination, including:

1. policy formulation at the national level;
2. options for service delivery;
3. factors affecting uptake of vaccination and measures to address them;
4. monitoring of the coverage, impact and safety of vaccination.

8.1 Policy formulation at the national level

Establishing national policies and targets for GBS vaccination are an important first step for its implementation in LMICs. Available evidence suggests that policies and coverage targets are essential for achieving high coverage. An online stakeholder survey in late 2019 showed a reasonably high level of awareness about GBS disease and its prevention among pediatricians and obstetricians in all WHO regions and in countries with different income levels. However, the survey revealed low levels of awareness among public health specialists, especially in lower middle-income and low-income countries. Stakeholders from Asia perceived that the burden of GBS disease in Asia was lower than in North America and Europe and that it did not constitute a public health priority in the WHO South-east Asia region. While estimates of the burdens of maternal and neonatal sepsis and stillbirths exist, there are several limitations to the data. As immunization budgets increase, NITAGs are likely to require more local data in order to prioritize GBS vaccination. This will be especially true for countries in the WHO South-east Asia region. When planning and implementing studies to assess the local burden of disease, standard definitions and methods should be used and consideration given to factors that may influence the observed burden of disease. In addition to data on the disease burden, data on economic impact, budgetary impact and expected return on investments will be needed to convince decision-makers to invest in maternal GBS vaccination rather than other public health priorities. LMICs are likely to require technical support in generating and using local data to make informed policy decisions on GBS vaccination.

8.2 Options for service delivery

Most LMICs have national policies for maternal vaccination, mainly with TTCV but increasingly for influenza. A large proportion of LMICs use ANC to deliver maternal vaccination and a reasonable degree of collaboration between the NIP and ANC programmes is reported although the nature and quality of this collaboration are yet to be assessed. However, many LMICs were assessed as having weak potential for delivering maternal vaccination and achieving the desired coverage. While the inclusion of immunization as part of ANC services is likely to enhance the uptake of both ANC and maternal immunization, collaboration between the NIP and ANC programmes will need to be further enhanced. Furthermore, human and financial resource constraints will need to be addressed before planned activities can be implemented and the desired coverage
If ANC programmes provide timely and high-quality services that are well-utilized, reasonable coverage with GBS vaccination may be achieved. Nevertheless, timely vaccination may pose a challenge in some LMICs.

### 8.3 Factors affecting uptake of vaccination and measures to address them

A reasonable amount of data exists on the factors that influence the acceptance and uptake of ANC and maternal vaccination. While there are several factors that appear to be common across countries (e.g. the influence of health worker recommendations on vaccine uptake), many of the factors that influence acceptance and uptake are contextual and vary both between and within countries. Such differences may be driven by local sociocultural practices, religious beliefs and access to – and the quality of – health care. Available data on the factors affecting the acceptance and uptake of maternal vaccination come mainly from high- and middle-income countries, with most of the data related to maternal influenza vaccination. This highlights the challenges of introducing vaccines for maternal immunization and the need for more data from LMICs. Conceptual frameworks used for collecting data in higher-income countries could be adapted for use in LMICs. Similarly, tools such as the TIPFlu tool could be adapted to collect information to diagnose demand-side barriers to maternal immunization and to design appropriate interventions to improve uptake.

Baseline information on pregnancy outcomes (background rates) are important for risk communication on maternal vaccination. While empirical data are lacking in many LMICs, data from systematic reviews and estimates from modelling approaches may be used as an alternative for the purposes of risk communication.

### 8.4 Monitoring the coverage, impact and safety of vaccination

Monitoring and evaluation are key components of vaccination services and provide the ability to monitor GBS vaccination coverage, impact and safety.

Systems for monitoring vaccination coverage through collection of administrative data and through household surveys exist in almost all countries although they vary in terms of their sophistication and the quality of the data collected. Currently, however, these systems mainly monitor coverage of infant immunization. The availability and quality of data outside the infant age group is still limited in LMICs. Many LMICs collect data on ANC services in their national HMIS, although information on the availability, completeness and quality of data are limited. Existing mechanisms can be leveraged and strengthened to collect high-quality monitoring data relevant to GBS vaccination but close collaboration between NIPs and MNH programmes will need to be established.

The outcome measures for monitoring the impact of vaccination should ideally include stillbirths, invasive GBS disease in neonates and infants and maternal sepsis. Few LMICs have well-developed systems to collect these data but opportunities exist that can be leveraged to strengthen these systems in preparation for the introduction of maternal GBS vaccination. Ideally, efforts to establish or strengthen these systems should begin several years in advance of vaccine introduction to ensure that robust baseline data are available for measuring impact.
Safety monitoring of maternal vaccination is complex and requires the monitoring of adverse events in pregnant women as well as of adverse pregnancy outcomes. Few LMICs have well-functioning systems for monitoring the safety of maternal vaccination. Here again, opportunities exist that can be leveraged to strengthen safety monitoring. The GAIA network has established case definitions and guidelines for monitoring adverse events, a roadmap for establishing or strengthening maternal immunization safety monitoring has been published, and technical assistance is available to LMICs to establish or strengthen their safety monitoring systems in preparation for GBS vaccination.

The following actions should be considered in support of the successful introduction and scale-up of GBS vaccination in LMICs:

- The available data on the burden of GBS should be seen in the context of public health priorities in LMICs (e.g. reduction of neonatal mortality or stillbirths to demonstrate how GBS vaccination could contribute to established national priorities).

- Efforts should be made to improve the availability and quality of disease burden data in LMICs, especially in Asia, to facilitate decision-making.

- WHO should establish surveillance standards for GBS and should support capacity-strengthening for surveillance studies to generate information on the disease burden.

- NITAGs and other national decision-makers should be sensitized to GBS disease and its relevance to national public health priorities; the capacity of NITAGs to assess and use data for decision-making should be strengthened where required.

- The roles of the NIPs and ANC programmes in the delivery of maternal vaccination, including GBS, should be defined and formal coordination mechanisms established to promote cohesive actions for integrating the delivery of GBS vaccination within the ANC package.

- The additional human and financial resource requirements for adding GBS vaccination should be estimated to allow for appropriate costing and budgeting for inclusion of the vaccine in national programmes.

- In preparation for GBS vaccine introduction, formative research should be conducted to understand the determinants of uptake of maternal and GBS vaccination and to inform introduction planning. The TIPFlu or similar tools may be adapted for this purpose.

- National HMIS in early introducer countries should be assessed to inform plans to integrate the monitoring of GBS vaccination.

- Sentinel surveillance should be established in a representative set of early introducer countries to start collecting baseline data to monitor the impact of vaccination on key outcome measures such as invasive GBS disease in young infants, stillbirths and maternal sepsis.

- Capacity-strengthening for safety monitoring should be initiated in early adopter countries in preparation for vaccine introduction.
References


37. de Jongh TE, Gurol-Urganci I, Allen E, Jiayue Zhu N, Atun R. Barriers and enablers to integrating maternal and child health services to antenatal care in low and middle income countries. BJOG. 2016;123(4):549–57.


Annex 1. Technical Working Group of Workstream 3

Flor M. Munoz, Baylor College of Medicine and Texas Children’s Hospital, Houston, USA

Michelle Giles, Monash University, Australia

Elizabeth Mason, Director, Global Public Health, Geneva, Switzerland

Martina Baye, Ministry of Public Health, Yaoundé, Cameroon

Sonja Merten, Swiss Tropical Public Health Institute, Switzerland Lumbwe Chola, Norwegian Institute of Public Health, Norway

Baoping Yang, Medical Doctor, Independent Consultant and Immunization Practices Advisory Committee member, China

Asma Khalil, St George’s, University of London, UK
Annex 2. Stakeholder survey on Group B streptococcal (GBS) disease and vaccine prioritization

Q1 Dear Colleague,

This survey is organized as part of an investigative work organized for the World Health Organization, Geneva and under the auspices of a Scientific Advisory Group which provides inputs to the development of a Group B streptococcal (GBS) vaccine value assessment.

The goal of this questionnaire is to investigate the existing level of awareness of GBS disease in your country and how GBS vaccination would likely be prioritized in the future. As an important stakeholder whose thoughts, ideas and expert advice will be of utmost importance to the success of this process, we would like ask you to complete this survey by responding to its questions related to GBS disease, national policies and guidelines, existing GBS prevention strategies, screening and prophylaxis approaches and the potential acceptance of GBS vaccination among pregnant women in your country.

Your answers will be automatically saved in the cloud once provided. This may take some time depending on the speed of your internet connection and we kindly ask for your patience. Please note that the survey can be interrupted at any time and will remain active for one week from the first login. At the subsequent login you will be taken back to where you left off.

You can now start the survey by moving to the next page. Thanks in advance for your contribution.
Start of Block: Demographics

Q2  What is your area of expertise/work?

- Public health and policy (1)
- Pediatrics (2)
- Obstetrics (3)
- Antenatal care (4)
- Immunization (5)
- Other (please specify) (6)  

Q3  What is your current level of awareness of GBS as a public health problem?

- Extremely familiar (1)
- Very familiar (2)
- Moderately familiar (3)
- Slightly familiar (4)
- Not familiar at all (5)

End of Block: Demographics
Q4  Do you consider GBS disease a public health problem in your country?

- Yes (1)
- No (2)

Q5  In your opinion, do pediatricians, obstetricians, public health policy-makers in your country perceive GBS disease as a public health problem?

<table>
<thead>
<tr>
<th></th>
<th>Strongly agree (11)</th>
<th>Somewhat agree (12)</th>
<th>Neither agree nor disagree (13)</th>
<th>Somewhat disagree (14)</th>
<th>Strongly disagree (15)</th>
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</thead>
<tbody>
<tr>
<td>Pediatricians (1)</td>
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<td>Obstetricians (2)</td>
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<td>Public health policy-makers (6)</td>
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</table>

Q6  Please summarize the possible reasons for your response

________________________________________________________________________
________________________________________________________________________
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________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
Q7  Are you aware of the GBS disease manifestations and/or outcome in pregnant women, neonates and/or infants?

☐ Yes (1)
☐ No (2)

Display this question:
If “Are you aware of the GBS disease manifestations and/or outcome in pregnant women, neonates and/or infants?” = Yes

Q8  If yes, please list up to five GBS disease manifestations or outcomes that you are aware of in pregnant women, neonates and/or infants (once listed, please attribute them a ranking between 1 and 5).

__________  Click to write Item 1 (1)
__________  Click to write Item 2 (2)
__________  Click to write Item 3 (3)
__________  Click to write Item 4 (4)
__________  Click to write Item 5 (5)

Q9  Are you aware of any GBS infection and disease prevention strategies in pregnant women?

☐ Yes (1)
☐ No (2)
Q10 If yes, please describe:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Q11 Are you aware of any GBS infection and disease prevention strategies in neonates?
   ○ Yes (1)
   ○ No (2)

Q12 If yes, please describe:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
Q13  Does your country have a national policy or guideline for pregnant women to prevent neonatal GBS disease?

- Yes (1)
- No (2)
- Do not know (3)

Q14  Is screening for GBS in pregnant women and subsequent antibiotic prophylaxis – if GBS screening is positive – performed in your country?

- Yes (1)
- No (2)
- Do not know (3)

Display this question:
If "Is screening for GBS in pregnant women and subsequent antibiotic prophylaxis – if GBS screening is positive – performed in your country?" = Yes

Q15  If GBS screening is performed, what would is your estimate of the coverage of GBS screening? (please drag the slider to indicate your coverage estimate)

Coverage (%)

Q16  Are there any actual or potential barriers to screening pregnant women for GBS in your country?

- Yes (1)
- No (2)
If screening for GBS in pregnant women and subsequent antibiotic prophylaxis - if GBS screening i... = Yes

Q17 If yes, please list the three most important barriers (once listed, please attribute them a ranking between 1 and 3).

___________ Click to write Item 1 (1)

___________ Click to write Item 2 (2)

___________ Click to write Item 3 (3)

Q18 In your opinion, what is the level of awareness of pregnant women about GBS disease in your country?

- Extremely familiar (1)
- Very familiar (2)
- Moderately familiar (3)
- Slightly familiar (4)
- Not familiar at all (5)

Q19 Are pregnant women routinely counselled about GBS disease during antenatal visits?

- Yes (1)
- No (2)
- Do not know (3)

End of Block: GBS
Q20  A GBS vaccine is currently in development to be given to pregnant women. Would a GBS vaccine be a priority to introduce in your country if available at an acceptable cost?

- Yes (1)
- No (2)
- Do not know (3)

Q21  In your opinion what would be the level of acceptance of GBS vaccination among pregnant women in your country?

- Extremely fast (1)
- Somewhat fast (2)
- Average (3)
- Somewhat slow (4)
- Extremely slow (5)

Q22  Please rate the following items in terms of importance for public health policy-makers in your country in order to prioritize GBS vaccination for inclusion in the national immunization schedule (rank in order of importance by dragging the various boxes in order – a first move is required to make the ranking numbers appear)

1. Contribution to reduction of neonatal sepsis
2. Contribution to reduction of neonatal mortality
3. Contribution to reduction of still-births
4. Contribution to reduction of maternal sepsis
5. Contribution to reduction of long-term impairment
6. Cost-effectiveness of vaccination versus treatment
7. Ease of inclusion in national immunization programmes
8. Vaccine acceptability among pregnant women
Q23 Please list the 3 most important barriers to inclusion of GBS vaccination in the national immunization programme in your country (once listed, please attribute them a ranking between 1 and 3).

_______ Click to write Item 1 (1)
_______ Click to write Item 2 (2)
_______ Click to write Item 3 (3)

Q24 What could be some key communication messages to convey the importance of GBS disease and its prevention in the general population?

_______ Click to write Item 1 (1)
_______ Click to write Item 2 (2)
_______ Click to write Item 3 (3)

Thank you so much for your important input!

End of Block: GBS Vaccine