WHO/IVB/17.09

WHO Preferred Product Characteristics for Group B Streptococcus Vaccines

DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS

Family, Womens's and Children's Health (FWC)

World Health Organization

This document was produced by the
Initiative for Vaccine Research (IVR)
of the Department of Immunization, Vaccines and Biologicals

Ordering code: WHO/IVB/17.09
Published: 2017

This publication is available on the Internet at:
http://www.who.int/immunization/documents/en/

Copies of this document as well as additional materials on immunization, vaccines and biologicals may be requested from:
World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• Fax: + 41 22 791 4227 • Email: vaccines@who.int •

Suggested citation. WHO Preferred Product Characteristics for Group B Streptococcus Vaccines. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO..

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

CONTENTS

Acknowledgements

This work was built on critical input from the WHO Group B Streptococcus Vaccine Advisory Group members (Carol J. Baker (Baylor College of Medicine, Houston, USA), Paul T. Heath (Vaccine Institute, St Georges, University of London, London, UK), Kirsty Mehring-Le Doare (Imperial College Faculty of Medicine, London, UK), Shabir A. Madhi (National Institute for Communicable Diseases, Johannesburg, South Africa), Samir Saha (Institute of Child Health, Dhaka, Bangladesh), Stephanie Schrag (Centre for Disease Control and Prevention, Atlanta, USA) and observers (Mark Alderson (PATH, Seattle, USA), David Kaslow (PATH, Seattle, USA), Ajoke Sobanjo-Ter Meulen (Bill & Melinda Gates Foundation, Seattle, USA)). We are grateful to all individuals and represented institutions who attended a WHO consultation meeting on group B Streptococcus vaccine development on 27–28 April 2016 in Geneva *(20)* and contributed to the discussions, and to the members of the WHO Product Development for Vaccines Advisory Committee (http://www.who.int/immunization/research/committees/pdvac). The document was available for public consultation in December 2016/January 2017 and we are grateful to the individuals and institutions who provided feedback.

WHO Secretariat

Martin Friede, Birgitte Giersing, Vasee Moorthy, Johan Vekemans.

Funding

This work was supported by the Bill & Melinda Gates Foundation, Seattle, WA [Global Health Grant OPP1134011].

Credits

Cover: CDC/United Parcel Service (UPS)
Page 5: WHO Pallava Bagla
Page 7: CDC/Cynthia Goldsmith
Page 8: David Spitz
Page 10: CDC/Minnesota Department of Health, R.N. Barr Library; Librarians Melissa Rethlefsen and Marie Jones
Page 11: WHO Sergei Volkov

A. INTRODUCTION

I. Background and purpose

Vaccine preferred product characteristics (PPCs) published by the World Health Organisation (WHO) describe preferred parameters pertaining to vaccine indications, target population, data collected for safety and efficacy evaluation, research and development (R&D) and immunization strategies. Selected disease areas are identified as WHO priorities based on the unmet public health need for vaccines, technical feasibility assessment and suitability for use in low- and middle-income countries.

The PPCs are intended to encourage innovation and the development of vaccines for use in settings most relevant to the global unmet public health need. They do not include minimally acceptable characteristics and it is important to note that if a vaccine does not meet the PPC criteria, it could still be assessed by WHO for policy recommendation. Any GBS vaccine that becomes licensed and potentially available will undergo evidence-based assessment for policy recommendations by the Strategic Advisory Group of Experts (SAGE) on Immunization.

The primary target audience for WHO PPCs is any entity intending to eventually seek WHO policy recommendation and prequalification for their products. WHO preferences can be useful to all those involved in vaccine development activities, including academic groups, funders and manufacturers.

WHO PPCs intend to provide early guidance on vaccine development strategies and targets, and are to be updated regularly to account for innovations or any other change in the identified need and R&D landscape. WHO PPCs do not override existing WHO guidance on vaccine development. Useful links to existing documents are provided in Appendix 1.

II. GBS vaccines, a strategic priority for WHO

Group B streptococcus (GBS) is a leading cause of sepsis and meningitis in neonates and young infants. It is also an important cause of stillbirth. GBS can be transmitted from the maternal ano-genital tract through mucosal surfaces to cause invasive disease in the foetus, newborn and young infant, potentially leading to stillbirth, early onset disease (<7 first days of life) and late onset disease (day 7 to first 3 months of life). Case fatality is high, particularly in early onset disease and resource poor settings. Maternal colonization in pregnancy has been found in a proportion of women (about 10–40%) in all geographical settings evaluated. Reported incidence of neonatal and infant invasive GBS disease varies geographically. The vast majority of the disease burden lies in low-and-middle-income

countries, with estimates as high as 3 cases per 1000 live births in some areas, excluding stillbirth. GBS is also a cause of invasive disease in women during and after pregnancy, and in the elderly, but precise disease burden estimates are lacking. Intra-partum antibiotic prophylaxis (IAP), based on pregnancy screening for GBS colonization or on the presence of other risk factors, has been only partially effective in reducing the risk of disease in high income countries, and is neither available nor practical in most resource-limited countries *(1–4)*. IAP also raises concerns about emerging antimicrobial resistance and neonatal microbiome development.

Ten GBS envelope polysaccharide-based serotypes have been described, five of which (Ia, Ib, II, III, V) are estimated to account for the vast majority of the disease burden, although regional differences have been reported and more data are needed. Currently, no vaccine exists for prevention of GBS disease, but evidence suggests maternal immunization with protein-conjugated GBS capsular polysaccharides may reduce the disease risk in neonates and young infants in a serotype-specific manner through trans-placental passage of protective immunoglobulins *(1, 5, 6)*. Protein-based vaccine candidates aiming to provide protection across the serotype spectrum are also under evaluation *(7)*.

In its 2015 and 2016 meetings, the Product Development for Vaccines Advisory Committee (PDVAC), which informs SAGE on vaccine R&D matters and contributes to prioritize topics for WHO Initiative for Vaccine Research involvement, identified the development of GBS vaccines suitable for maternal immunization in pregnancy and use in low and middle income countries as a priority.

III. WHO strategic goal for GBS vaccines

To develop and license safe, effective and affordable GBS vaccines for maternal immunization during pregnancy to prevent GBS-related stillbirth and invasive GBS disease in neonates and young infants, appropriate for use in high-, middle- and low-income countries.

IV. Clinical research and development considerations

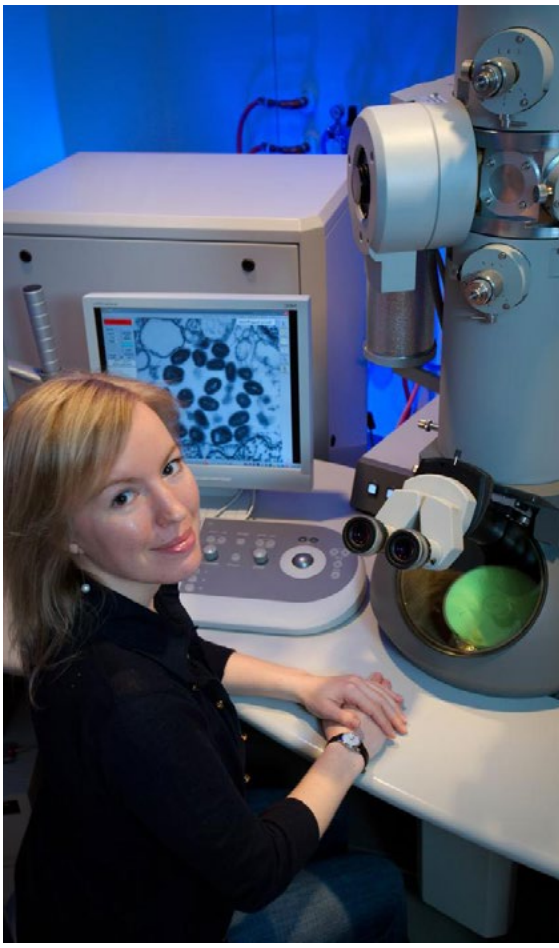
1. Early clinical development pathway

GBS vaccine candidate testing in pre-clinical animal models must demonstrate favourable safety and immunogenicity before human testing. Valuable data can also be derived from animal GBS disease models. Favourable outcomes in relevant animal reproductive toxicology studies must have been demonstrated before studies in pregnant women proceed.

Phase 1 and 2 studies would initially be conducted in non-pregnant women of childbearing age, for initial characterization of safety, immunogenicity, schedule, optimal vaccine dose and potential requirement for an adjuvant. Studies in pregnant women would be expected to start after favourable safety and immunogenicity has been documented in non-pregnant women of childbearing age, for further characterization of safety and immunogenicity in both the mother and her offspring.

2. Role of correlates of protection in the vaccine development pathway, licensure and policy decision

A clinical efficacy trial of a GBS candidate vaccine candidate will need to be of substantial size due to the incidence rates of outcomes of interest. Vaccine developers may therefore consider applying for licensure based on a surrogate of protection determined to be reasonably likely to predict clinical benefit. In addition, established correlates of protection can be very useful to compare results across studies, to allow bridging studies supporting the extrapolation of pivotal data from one population to another (such as, for instance, different risk groups or geographical areas) and in licensing further vaccines.



Correlates of protection can be derived from demonstration of a strong association between a validated immunological assay or other clinical biomarkers and protection against disease. In the case of neonatal and infant protection derived from passive transfer of maternal antibodies, supportive evidence to identify correlates could be derived from either an efficacy trial that incorporates an immunological assessment, or observational studies showing an association between antibody levels (acquired following natural GBS exposure) in mothers or infants at birth (or through the period at-risk) and protection against invasive GBS disease. One source of complexity relates to the serotype-specific nature of the putatively protective antibodies targeting envelope polysaccharide antigens. It will likely be difficult to establish an evidence basis for less common capsular serotypes.

As maternal GBS colonization is a critical precursor to GBS-related stillbirth and early onset invasive disease, a vaccine-induced reduction or prevention of colonization might be considered a relevant surrogate endpoint. It should be considered, however, that various factors (such as bacterial virulence factors) may influence the risk of invasive disease and the estimate of vaccine efficacy against colonization may not be reflective of vaccine efficacy against invasive GBS disease. Similarly, the lack of an effect on colonization may not necessarily translate into the lack of an effect against invasive disease, as immune effectors and protective thresholds against mucosal infection and invasive disease may be different.

These issues should be discussed in advance with regulatory authorities and decision makers. An FDA accelerated approval pathway exists for products targeting serious or life-threatening diseases leading to non-traditional licensure based on a surrogate endpoint, with a requirement for post-licensure studies to verify and describe clinical benefit *(8, 9)*.

Beyond licensure, additional criteria will be relevant for policy decision making on vaccine implementation in national health programs, including cost-effectiveness and clinical impact.

3. Vaccine efficacy evaluation

As mentioned above, alternative licensure pathways may be considered, with a role for correlates of protection studies. The generation of clinical efficacy data and a comprehensive evaluation of the risk-benefit balance and potential public health impact of a vaccine candidate are however generally required for product licensure and policy decision . Randomized, double-blind placebo-controlled trial designs with a relevant, well-defined, specific disease entity as primary endpoint provides the strongest evidence to support proof-of-efficacy estimates.

a. Trial site considerations

Research should be conducted in a variety of settings including areas where the medical need is highest, generating results to support local decision-making. The consequences of regional differences in predominant serotypes should be evaluated. Research centres should have the ability to conduct GCP trials with appropriate regulatory and ethical oversight. Laboratory testing should be conducted under GLP with quality-assured testing tailored to the vaccine development phase. Baseline studies are usually necessary to demonstrate local feasibility of protocol-defined study procedures as well as to confirm the baseline incidence rate of relevant study safety and efficacy endpoints, informing statistical power analyses and required sample size estimation. The capacity for accurate determination of gestational age should be ensured.

b. Standards of care

In settings in which preventive measures are part of the standard of cvare, the baseline GBS-related disease incidence may be low and the conduct of an efficacy trial may not be feasible. In high GBS burden settings where universal screening is not the local standard of care and IAP has not been routinely implemented, the conduct of a trial without introducing screening-based IAP