The Italian arm of the PREPARE study: an international project to evaluate and license a maternal vaccine against group B streptococcus

Alberto Berardi 1*, Tiziana Cassetti 2, Roberta Creti 3, Caterina Vocale 4, Simone Ambretti 5, Mario Sarti 2, Fabio Facchinetti 6, Stephen Cose 7,8, the Prepare Network, Paul Heath 9 and Kirsty Le Doare 10

Abstract

Background: Group B streptococcus (GBS) is a leading cause of sepsis, pneumonia and meningitis in infants, with long term neurodevelopmental sequelae. GBS may be associated with poor pregnancy outcomes, including spontaneous abortion, stillbirth and preterm birth. Intrapartum antibiotic prophylaxis (IAP) is currently the only way to prevent early-onset disease (presenting at 0 to 6 days of life), although it has no impact on the disease presenting over 6 days of life and its implementation is challenging in resource poor countries. A maternal vaccine against GBS could reduce all GBS manifestations as well as improve pregnancy outcomes, even in low-income countries.

Main body: The term “PREPARE” designates an international project aimed at developing a maternal vaccination platform to test vaccines against neonatal GBS infections by maternal immunization. It is a non-profit, multi-center, interventional and experimental study (promoted by the St George University of London, [UK]) with the aim of developing a maternal vaccination platform, determining pregnancy outcomes, and defining the extent of GBS infections in children and mothers in Africa. PREPARE also aims to estimate the protective serocorrelates against the main GBS serotypes that cause diseases in Europe and Africa and to conduct two trials on candidate GBS vaccines. PREPARE consists of 6 work packages. In four European countries (Italy, UK, Netherlands, France) the recruitment of cases and controls will start in 2020 and will end in 2022. The Italian PREPARE network includes 41 centers. The Italian network aims to collect: GBS isolates from infants with invasive disease, maternal and neonatal sera (cases); cord sera and GBS strains from colonized mothers whose infants do not develop GBS infection (controls).

Short conclusion: PREPARE will contribute information on protective serocorrelates against the main GBS serotypes that cause diseases in Europe and Africa. The vaccine that will be tested by the PREPARE study could be an effective strategy to prevent GBS disease.

Keywords: Group B streptococcus, Vaccine, Newborn, Sepsis, Meningitis, Prevention
Background

Group B streptococcus (GBS or *Streptococcus agalactiae*) is a Gram-positive pathogen belonging to Lancefield group B. It is a common commensal of the gastrointestinal tract and colonizes 10–30% of pregnant women at vaginal or vaginal/rectal sites [1]. In pregnant women, GBS is a frequent causative agent in urinary tract infections, choioamnionitis and postpartum endometritis, and it is also associated with poor pregnancy outcomes, including spontaneous abortion, stillbirth and preterm birth [2].

GBS is a leading cause of sepsis, pneumonia and meningitis in infants, with long-term neurodevelopmental sequelae. Neonatal GBS infections are usually divided into Early-Onset Disease (EOD, presenting at 0 to 6 days of life) and Late-Onset Disease (LOD, presenting at 7 to 90 days of life) [3]. EOD is prevented through intrapartum antibiotic prophylaxis (IAP) in women with GBS colonization or obstetrical risk factors for GBS vertical transmission.

Main text

The term "PREPARE" designates an international project entitled “Prevention of invasive Group B Streptococcus disease in young infants: a pathway for the evaluation & licensure of an investigational maternal GBS vaccine". PREPARE is aimed at developing a vaccine against neonatal GBS infections and is promoted by the St George University of London (UK) (see https://gbsprepare.org).

This project is part of the EDCTP2 program (European & Developing Countries Clinical Trials Partnership) that funds research for prevention and treatment of poverty-related infectious diseases in sub-Saharan Africa and it is aligned with the WHO roadmap [1]. Moreover, PREPARE is supported by Horizon 2020 (European Union’s Framework Program for Research and Innovation).

Strategies implementing IAP, especially those that screen women in late pregnancy for vagino-rectal GBS colonization (regardless of presenting risk factors) has led to a dramatic decline in the incidence rates of EOD (i.e., from 0.37 to 0.22 per 1000 live births from 2006 to 2017 in USA) [4]. However, IAP coverage is incomplete even in the best of settings. Furthermore, the burden of invasive GBS disease may be high in resource poor countries such as Africa (estimated incidence of 1.12/1000 live births) where IAP implementation is challenging [5]. Concerns have arisen as to the possible negative impact of large-scale prevention, as IAP may promote the emergence of antibiotic resistance, and early exposure to antibiotics can disrupt the development of the intestinal microbiome, with consequences in adulthood [6]. Finally, IAP has no impact on LOD, stillbirths and prematurity due to GBS, as well as a limited impact on disease in pregnant women [7]. Further strategies are urgently required to decrease GBS-associated morbidity and mortality.

There are ten known GBS serotypes (Ia, Ib and II-IX), but serotype Ia, III and V are more commonly responsible for invasive GBS disease in infants under 90 days of life. Multivalent vaccines administered to pregnant women to protect their infants against GBS disease could overcome many of the outstanding issues related to IAP and could be an effective strategy for resource-poor countries. Indeed, compared to WHO European region, in WHO African region mortality rates are 7 times higher (7/1000 vs 51/1000 LBs) [8]. Therefore, the prevention of neonatal infections through maternal immunoprophylaxis is a topic that has recently aroused wide attention. The purpose of this strategy is to induce maternal protective immunity resulting in a specific transplacental IgG passage. Indeed, recent data have shown that vaccinating pregnant women does not increase adverse events or fetal risks [9]. WHO data from developing countries show a 92% decline (from the 1980s to 2000) in neonatal tetanus case fatalities following maternal vaccination with tetanus toxoid [10].

It is estimated that to detect a 75% reduction in EOD and LOD in countries with a disease incidence of more than 1/1000 births it would be necessary to enroll about 60,000 pregnant women to study the effectiveness of the vaccine, assuming that this protects from 90% of circulating serotypes [11]. Therefore, in order to facilitate the licensure of a vaccine, the study of protective serocorrelates, followed by a demonstration of a post-license efficacy, aroused interest. Although previous studies have shown an association between serotype-specific maternal IgG titers and reduction of neonatal disease risk, no study has been able to establish with certainty a protective antibody threshold value, due to different assays for determining antibody titers or inability to compare and pool the results of different studies [12]. Vaccines have been tested against serotype-specific capsular polysaccharide and against surface proteins that are expressed in different serotypes and could then protect against specific serotypes [7, 12].

PREPARE is a non-profit, multi-center, interventional and experimental study. It aims to develop a maternal vaccine platform in Uganda, determine pregnancy outcomes and to define the extent of GBS infections in children and mothers in a sub-Saharan context. It also aims to estimate the protective serocorrelates against the main GBS serotypes that cause diseases in Europe and Africa and to conduct two trials on candidate GBS vaccines. The PREPARE project involves 7 countries across the world (Malawi, Uganda, South Africa, the United Kingdom, the Netherlands, Italy and France) and aims to develop a serum biobank, in order to define
serocorrelates of protection against GBS, by using standardized antibody assays and a bacterial strains bank to study the characteristics of neonatal and maternal strains.

The overarching objectives will be achieved through 6 work packages (WPs), each with specific aims (Table 1). Italy (that belongs to WP3) is represented by a network made up of 41 centers across the country (Table 2), coordinated by the Azienda Ospedaliero-Universitaria Policlinico (Modena). The Italian network will collect at least 50 neonatal GBS invasive cases (defined as an infant with isolation of GBS from blood culture or from culture of cerebro-spinal fluid) within 2 years. Strains will be sent to the national referring center (Istituto Superiore di Sanità) for GBS typing.

The PREPARE Italian network will collect: i) isolates from infants with invasive disease (cases), together with maternal and neonatal sera collected at the time of diagnosis of infant disease; ii) cord sera and GBS strains (of the same serotype as cases) from colonized mothers whose infants do not develop GBS infection (controls). Biological materials will be used for i) determining the concentration of specific IgG anti-GBS (serotype III the most frequent cause of neonatal disease) in the cord

**Table 1** Work-Packages (WP) of the PREPARE Study: role, goals and participating countries

| Work packages | Role in the project | Goals | Participating country |
|---------------|---------------------|-------|-----------------------|
| WP1           | Project Management, Scientific Coordination and Oversight of Capacity Building. | To ensure conduct of all research activities to the highest standards, including oversight and coordination of the other WPs to ensure deliverables and milestones are met. | United Kingdom South Africa |
| WP2           | Clinical trial site development and GBS disease surveillance. | To establish the GBS disease incidence in an urban Ugandan cohort followed to 3 months of age and establish the baseline rates of common obstetric and neonatal outcomes in preparation for WP4 and WP5. | Uganda South Africa United Kingdom |
| WP3           | Developing serocorrelates of protection against GBS | To develop a biobank of prospectively collected sera from cases of GBS disease and associated GBS disease isolates from a network of African and European sites in order to define serocorrelates of protection against GBS, using standardized antibody assays. | Uganda, Malawi, South Africa, United Kingdom, Italy France, Netherlands |
| WP4           | Multivalent CPS-conjugate vaccine trial. | To conduct a phase II study of a multivalent vaccine against the GBS CPS in pregnant HIV-infected and uninfected women and to establish a platform for future trials with new GBS vaccines. | United Kingdom Uganda |
| WP5           | Minervax Alp-NN GBS vaccine trial. | To conduct a phase II study of a multivalent vaccine against the Alp and Rib proteins on the surface of GBS in pregnant HIV-infected and uninfected women and to establish a platform for future trials with new GBS vaccines. | Denmark United Kingdom South Africa |
| WP6           | Communications, networking and dissemination. | To develop a strategy for patient and public involvement, communications, capacity strengthening and stakeholder engagement. | United Kingdom |

CPS Capsular polysaccharide, GBS group B streptococcus

**Table 2** Partner of the PREPARE Consortium

| Organisation | Country | Role | H2020 type of organisation |
|--------------|---------|------|---------------------------|
| St George's Hospital Medical School (SGUL) | United Kingdom | Coordinator | Secondary or higher education establishment |
| Makerere University - Johns Hopkins University Care Ltd | Uganda | Participant | Research organisation |
| University of Liverpool | United Kingdom | Participant | Secondary or higher education establishment |
| Wits Health Consortium (PTY) LTD | South Africa | Participant | Secondary or higher education establishment |
| Assistance Publique Hopitaux de Paris (AP- HP) | France | Participant | Secondary or higher education establishment |
| Academisch Medisch Centrum bij de Universiteit van Amsterdam | The Netherlands | Participant | Secondary or higher education establishment |
| Azienda Ospedaliero- Universitaria di Modena | Italy | Participant | Secondary or higher education establishment |
| University College London (UCL) | United Kingdom | Participant | Secondary or higher education establishment |
| London School of Hygiene and Tropical Medicine (LSHTM) | United Kingdom | Participant | Secondary or higher education establishment |
| Minervax ApS | Denmark | Participant | Small or medium sized enterprise |
| Pfizer Inc. | United Kingdom | Participant | International Organisation |
serum of healthy controls and in the serum of infants (aged 0 to 90 days of life) with GBS infection ii) assessing a correlation between antibody concentration and GBS disease risk and iii) validating estimates of protective serocorrelates.

Conclusions
Despite the progress made in high-income countries in the prevention of EOD, GBS remains an important cause of morbidity and mortality in the first months of life worldwide.

A maternal GBS vaccine could reduce the burden of both EOD and LOD, maternal puerperal sepsis, stillbirth and preterm delivery. A vaccine could help to overcome the inherent limitations of IAP, and could reduce unnecessary antibiotics, as well as costs and long-term disabilities consequent to GBS infection. Finally, a vaccine could be an effective strategy for resource-poor countries, where the antenatal screening and large-scale IAP might be unfeasible. PREPARE aims to undertake clinical trials of a maternal GBS vaccine, to determine pregnancy outcomes, and to estimate the protection serocorrelates against the main GBS serotypes that cause diseases in Europe and Africa.

Acknowledgments
The Prepare Network:
Non-Italian Contributors
Dr. Merijn van Bijlsma- Academisch Medisch Centrum Bij De Universiteit Van Amsterdam
Prof. Diederik van De Beek- Academisch Medisch Centrum Bij De Universiteit Van Amsterdam
Dr. Claire Poyart- Assistance Publique-Hôpitaux De Paris
Dr. Maryke Nielsen -The University of Liverpool
Prof. Neil French- The University of Liverpool
Dr. Philippa Musoke- Mu-Jhu Care Ltd
Dr. Italia Parma
Dr. Angela Maiocchi- UO Microbiologia, Ospedale Civile, Vigevano
Dr. Giacomo Biasucci- UO di Pediatría e Neonatología, Ospedale G da Saliceto, Piacenza
Dr. Belinda Benenati - UO Pediatria, Ospedale G da Saliceto, Piacenza
Dr. Roberta Schiavo- UO Microbiologia e Virologia, Ospedale G da Saliceto, Piacenza
Dr. Giancarlo Piccinini- UO Terapia Intensiva Neonatale, Ospedale Santa Maria delle Croci, Ravenna
Dr. Rita Pulvirenti- UO Pediatria, Ospedale G.B. Morgagni- L. Piersantoni, Forlì
Dr. Vittoria Rizzo- UO Terapia Intensiva Neonatale e Pediatria, Ospedale Civile M. Bufalini, Cesena
Dr. Gina Ancora- UO Terapia Intensiva Neonatale, Ospedale Infermi, Rimini
Dr. Chiara Chini- UO Terapia Intensiva Neonatale, Ospedale Infermi, Rimini
Dr. Irene Papa- UO Terapia Intensiva Neonatale, Ospedale Infermi, Rimini
Dr. Laura Viola- UO Pediatria, Ospedale Infermi, Rimini
Dr. Maria Federica Pedna- UO Microbiologia, Laboratorio Unico Ausl della Romagna, Pievevesentina
Dr. Jenny Bua- UO Terapia Intensiva Neonatale, IRCCS "Burlo Garofolo", Trieste
Dr. Laura Travani- UO Terapia Intensiva Neonatale, IRCCS "Burlo Garofolo", Trieste
Dr. Marina Busetti- SC Microbiologia e virologia, IRCCS "Burlo Garofolo", Trieste
Dr. Daniele Santoni- SC Pediatria e Neonatología, Azienda Ospedaliera Santa Maria degli Angeli, Pordenone
Dr. Daniele Merazio- UO Terapia Intensiva Neonatale, Pediatria e Neonatología, Ospedale Valduce, Como
Dr. Angela Papa- UO Laboratorio Analisi, Ospedale Valduce, Como
Dr. Liliberta Maria Castelli- UO Terapia Intensiva Neonatale e Neonatología, Ospedale S. Filippo Neri, Roma
Dr. Cinzia Auriati- UO Terapia Intensiva Neonatale, Ospedale Pediatrico Bambino Gesù, Roma
Dr. Paola Bernaschi- UO Microbiologia, Ospedale Pediatrico Bambino Gesù, Roma
Prof. Giovanni Vento- UO Neonatología, Policlinico Universitario A. Gemelli, Roma
Dr. Lucia Giordano- UO Neonatología, Policlinico Universitario A. Gemelli, Roma
Dr. Teresa Spanu- UO Microbiologia, Policlinico Universitario A. Gemelli, Roma
Dr. Cristina Haass- UO Pediatria e Neonatología, Ospedale S. Pietro Fatebene Fratelli, Roma
Dr. Maria Carmela Margiotta- UO Microbiologia, Ospedale S. Pietro Fatebene Fratelli, Roma
Dr. Giovanna Nardella- UO Neonatologia, Azienda Ospedaliera Universitaria Ospedali Riuniti, Foggia
Dr. Rosella De Nittis- UO Microbiologia, Azienda Ospedaliera Universitaria Ospedali Riuniti, Foggia
Prof. Nicola Laforgia- UO Terapia Intensiva Neonatale e Neonatología, Ospedale Policlinico, Bari
Dr. Sabrina Loprieno- UO Terapia Intensiva Neonatale e Neonatología, Ospedale Policlinico, Bari
Dr. Durante Giuseppe- UO Terapia Intensiva Neonatale, Ospedale Generale Regionale "F. Mutili", Acquaviva delle Fonti
Dr. Angela Maria Moramarcos- UO Microbiologia, Ospedale Generale Regionale "F. Mutili", Acquaviva delle Fonti
Dr. Chrysoula Tzialia- UO Neonatología, Patologia Neonatónica y Terapia Intensiva Neonatal, Fundación IRCCS Policlinico "San Matteo", Pavía
Dr. Valeria Fasolato- UO Terapia Intensiva Neonatología, Neonatología e Nido, Ospedale Carlo Poma, Mantova
Dr. Silvia Orlandini- UO Terapia Intensiva Neonatología, Neonatología e Nido, Ospedale Carlo Poma, Mantova
Dr. Lidia Decembrino- UO Pediatria e Nido, Ospedale Civile, Vigevano
Dr. Giulia Del Campo- UO Pediatria e Nido, Ospedale Civile, Vigevano
Dr. Angela Masocchi- UO Microbiologia, Ospedale Civile, Vigevano
Authors’ contributions
AB and TC drafted the initial manuscript, reviewed, revised, and approved the final manuscript as submitted. RC, CV, SA, MS and FF designed the data collection instruments, drafted the initial manuscript, reviewed, revised, and approved the final manuscript as submitted. KLD, PH and SC conceptualized and designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Prot N° 0011051/20 del 20/04/2020.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Unità Operativa di Terapia Intensiva Neonatale, Dipartimento Integrato Materno-Infantile, Azienda Ospedaliero- Universitaria Policlinico, Via del Pozzo, 71, 41124 Modena, Italy. 2Unità Operativa di Microbiologia Clinica, Azienda Ospedaliero- Universitaria Policlinico, Modena, Italy. 3Reparto di Antibiotico Resistenza e Patogeni Speciali (AR-PS), Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy. 4Unità Operativa di Microbiologia, Azienda Ospedaliero- Universitaria Policlinico, Modena, Italy. 5Unità Operativa di Microbiologia, Azienda Ospedaliero- Universitaria Policlinico, Modena, Italy. 6Reparto di Antibiotico Resistenza e Patogeni Speciali (AR-PS), Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy. 7Unità Operativa di Microbiologia Clinica, Centro di Riferimento Regionale per le Emergenze Microbiologiche, CrREM, Policlinico S. Orsola-Malpighi, Università di Bologna, Bologna, Italy. 8Unità Operativa di Microbiologia, Azienda Ospedaliero- Universitaria S. Orsola-Malpighi, Bologna, Italy. 9Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Azienda Ospedaliero Universitaria Policlinico, Modena, Italy. 10MRC/UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda. 11Department of Clinical Research, LSHTM, London, UK. 12St George’s Vaccine Institute, Institute of Infection and Immunity, St George’s, University of London, London, UK. 13Paediatric Infectious Diseases Research Group, St George’s University of London, London, UK.

Received: 12 September 2020 Accepted: 19 October 2020
Published online: 28 October 2020

References
1. Edwards MS, Nizet V, Baker CJ. Group B streptococcal infections. In: Remington and Klein’s infectious diseases of the fetus and newborn infant. 8th ed. Philadelphia: Elsevier; 2016. p. 411–56.
2. Berardi A, Cattelani C, Creti R, Berner R, Pietrangiolillo Z, Margaret I, Maione D, Ferrari F. Group B streptococcal infections in the newborn infant and the potential value of maternal vaccination. Expert Rev Anti-Infect Ther. 2015;13(11):1387–99. https://doi.org/10.1586/14787210.2015.1079126 Epub 2015 Aug 20.
3. World Health Organisation. GBS vaccine research and development technical roadmap and WHO preferred product characteristics. Geneva: World Health Organisation; 2016.
4. Centers for Disease Control and Prevention. ABCs Report: Group B Streptococcus, 2017 https://www.cdc.gov/abcs/reports-findings/surveysreports/gbs17.html.
5. Davies HG, Carreras-Abad C, Le Doare K, Heath PT, Group B Streptococcus: Trials and Tribulations. Pediatr Infect Dis J. 2019;38(Suppl 1):S72–S76. doi: https://doi.org/10.1097/INF.0000000000023328. PMID: 31205250 Review.
6. Ficara M, Pietrella E, Spada C, et al. Changes of intestinal microbiota in early life. J Matern Fetal Neonatal Med. 2018;10:1–8.
7. Carreras-Abad C, Ramkhelawon L, Heath PT, Le Doare K, A vaccine against group B Streptococcus: recent advances. Infect Drug Resist. 2020;3:1263–72. https://doi.org/10.2147/IDR.S203454 eCollection 2020. PMID: 32425562.
8. Unicef; World Health Organization; The world Bank; United Nations. Levels and Trends in Child Mortality. Report 2019; 2019.
9. Shakib JH, Korgenski K, Sheng X, et al. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. J Pediatr. 2013;163:1422–6.
10. Munoz FM, Ferrielli P. Group B streptococcal vaccination in pregnancy: moving toward a global maternal immunization program. Vaccine. 2013;31:46–51.
11. Vekemans J, Crofts J, Baker CJ, Goldblatt D, Heath PT, Madhi SA, Le Doare K, Andrews N, Pollard AJ, Saha SK, Schrag SJ, Smith PG, Kaslow DC. The role of immune correlates of protection on the pathway to licensure, policy decision and use of group B Streptococcus vaccines for maternal immunization: considerations from World Health Organization consultations. Vaccine. 2019;37(24):3190–8. https://doi.org/10.1016/j.vaccine.2019.04.039 Epub 2019 Apr 25. PMID: 31031031.
12. Le Doare K, Kampmann B, Vekemans J, Heath PT, Goldblatt D, Nahm MH, Baker C, Edwards MS, Kwatra G, Andrews N, Madhi SA, Ter Meulen AS, Anderson AS, Consaro B, Fischer P, Goringe A. Serocorrelates of protection against infant group B streptococcus disease. Lancet Infect Dis. 2019;19(5):516–71. https://doi.org/10.1016/S1473-3099(18)30865-5 Epub 2019 Jan 22. PMID: 30683467.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.