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Jaya Chandna

Wan-Hsin Liu

Ziyaad Dangor

Shannon Leahy

Santhanam Sridhar

See next page for additional authors

Authors

Jaya Chandna, Wan-Hsin Liu, Ziyaad Dangor, Shannon Leahy, Santhanam Sridhar, Hima B. John, Humberto Mucasse, Quique Bassat, Azucena Bardaji, and Amina Abubakar

Emotional and behavioural outcomes in childhood for survivors of Group B Streptococcus invasive disease in infancy: findings from five low and middle-income countries

Jaya Chandna[1*], Wan-Hsin Liu[1,2*], Ziyaad Dangor[3], Shannon Leahy[3], Santhanam Sridhar[4], Hima B John[4], Humberto Mucasse[5], Quique Bassat[5,6,7,8,9], Azucena Bardaji[5,6], Amina Abubakar[10,11], Carophine Nasambu[10], Charles R Newton[10,12], Clara Sánchez Yanotti[13], Romina Libster[13], Kate Milner[14], Proma Paul[1,+] Joy E Lawn[1+] on behalf of the LMIC collaborative group.

1. Maternal, Adolescent, Reproductive & Child Health (MARCH) Centre, London School of Hygiene & Tropical Medicine, London, UK
2. Division of General Paediatrics, Department of Paediatrics, Taipei Veterans General Hospital, Taipei, Taiwan
3. Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
4. Neonatology Department, Christian Medical College, Vellore, India
5. Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique
6. ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain
7. ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain
8. Pediatrics Department, Hospital Sant Joan de Déu (University of Barcelona), Barcelona, Spain
9. Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
10. Neuroscience Research Group, Department of Clinical Sciences, KEMRI-Wellcome Trust, Kilifi, Kenya
11. Institute of Human Development, Aga Khan University, Nairobi, Kenya
12. Department of Psychiatry, Medical Sciences Division, University of Oxford, Oxford, UK
13. Fundación INFANT, Buenos Aires, Argentina
14. Neurodisability & Rehabilitation Research Group, Murdoch Children's Research Institute 2. Department of Paediatrics, University of Melbourne

* Authors share joint first authorship

+ Authors share senior authorship

Corresponding Author: Jaya Chandna, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT. @: jaya.chandna@lshtm.ac.uk T: 020 7636 8636

ABSTRACT

BACKGROUND: Survivors of invasive Group B streptococcus (iGBS) disease, notably meningitis, are at increased risk of neurodevelopment impairment (NDI). However, the limited studies to date have a median follow-up to 18 months and mainly focused on moderate/severe NDI, with no previous studies on emotional-behavioural problems among iGBS survivors.

METHODS: In this multi-country, matched cohort study, we included children aged 18 months to 17 years with infant iGBS sepsis and meningitis from health demographic surveillance systems, or hospital records in Argentina, India, Kenya, Mozambique and South Africa. Children without iGBS history were matched to iGBS survivors on sex and age. Our primary outcomes were emotional-behavioural problems and psychopathologies as measured with the Child Behaviour Checklist (CBCL). The CBCL was completed by the child's primary caregiver.

RESULTS: Between October 2019 and April 2021, 573 children (mean age of 7.18 years old) were assessed: 156 iGBS survivors and 417 non-iGBS comparison children. On average, we observed more total problems and more anxiety, attention and conduct problems for school-aged iGBS survivors compared with the non-iGBS group. No differences were found in the proportion of DSM-5 defined, clinically significant psychopathologies.

CONCLUSIONS: Our findings suggested that school age iGBS survivors experienced increased mild emotional behavioural problems which may impact children and families. At-risk neonates including iGBS survivors need long-term follow-up with integrated emotional-behavioural assessments and appropriate care. Scale-up will require simplified assessments that are free and culturally adapted.

Keywords: Group B Strep, neurodevelopment, neonatal sepsis, emotional behaviour

LIST OF ABBREVIATIONS

CBCL	Child Behaviour Checklist
GBS	Group B Streptococcus
iGBS	invasive Group B Streptococcus
HDSS	Health and Demographic Surveillance System
ID	Identification Number
LMIC	Low- and Middle-Income Countries
NDI	Neurodevelopmental Impairment
SDG	Sustainable Development Goals
UN	United Nations
WHO	World Health Organization

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1. WHAT IS KNOWN AND WHAT IS NEW?

There is a paucity of comparable data regarding emotional-behavioural outcomes for early-mid childhood and school-age, especially from low- and middle- income countries (LMIC). There are no studies that use a standardised, validated emotional-behavioural assessment tool such as the Child Behaviour Checklist (CBCL) which, although developed in USA, is used widely. A multi-country study of long-term outcomes for infant survivors of iGBS enabled us to address this gap.

2. WHAT DID WE DO AND WHAT DID WE FIND?

We used the CBCL, a caregiver-administrated tool, to measure outcomes from 156 survivors of infant iGBS and 417 non-iGBS children from five countries across South Asia, Sub Saharan Africa, and Latin America. We found that school-aged iGBS survivors have more total emotional-behavioural problems than the non-iGBS children, and this difference seems to be mainly driven by internalising problems (emotionally reactive, anxious/depressed, somatic complaints and withdrawn scales). However, we detected no differences between iGBS survivors and non-iGBS children for more severe clinical disorders according to DSM-5 psychopathologies. Importantly we found major differences between countries, with one country recording no social emotional problems.

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3**. WHAT NOW FOR PROGRAMMES?**

Assessment of emotional-behavioural development is important for every child and all families and countries as part of the SDGs, enabling optimal human capital worldwide. Follow up of at-risk neonates including iGBS survivors is needed and requires context-specific integration within child health programmes and education settings.

4. WHAT NEXT FOR RESEARCH

CBCL and other developmental assessment tools require cultural adaptation to varying settings in order to accurately detect true differences. Importantly there is currently no freely accessible and adaptable tool that is validated which is a crucial challenge impeding uptake.

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BACKGROUND

Despite the substantial potential impact of emotional-behavioural problems on children, their families, and human capital, there are limited data on the prevalence of emotional-behavioural problems, in particular, those with milder or non-clinical problems. Mild neurodevelopmental impairments (NDI), emotional-behavioural and specific learning difficulties tend to become apparent later, especially once children transition to primary school without intervention in low resource settings these mild problems may effect educational attainment and impact the child's life course.[1, 2] In the global burden of disease study, two mental health disorders, depression and anxiety, were among the top ten causes of global disability-adjusted life-years (DALYs) in adolescents and young adults.[3] An estimated 52·9 million children younger than 5 years had developmental disabilities in 2016, and 95% were in low-income and middle-income countries. Estimates were generated for autism disorders and ADHD, but it was also noted there were very limited data especially from Saharan Africa.[4]

Measuring emotional-behavioural problems in preschool and school-aged children allows us to assess executive functioning of the child which is predictive of long-term adult functioning. Internalizing behavioural problems (such as anxiety or depression) by their nature may be more challenging to detect without active surveillance, even at school-age, whereas externalizing behaviours (e.g. rule-breaking problems and aggressive behaviour) which are typically disruptive to others may be more readily detected by parents or teachers. [5, 6]

Group B streptococcus(GBS) is a leading pathogen causing neonatal and young infant infection,[7, 8] notably as sepsis, or meningitis or pneumonia, which is collectively known as invasive GBS (iGBS) diseases.[7, 9] Some studies have reported emotional-behavioural difficulties in around ten percent

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to one third of bacterial meningitis survivors, which can significantly impair their quality of life and activities of daily living.[2, 10] The only systematic review of NDI after iGBS reported results after meningitis, with median follow up of 18 months and focused on intellectual, motor, vision, and hearing.[11]

Major neurological sequelae such as epilepsy, mental retardation, cerebral palsy and moderate-severe sensory impairments are more readily identifiable in early life (0-3 years). [11] None of the studies specifically included emotional-behavioural problems.

A multi-country study, [9] investigating the long term outcomes for iGBS survivors provided an opportunity to evaluate the prevalence of emotional-behavioural problems amongst children from toddlers to the end of secondary school.

AIM and OBJECTIVES

This paper is part of a series of papers on GBS worldwide. The aim of this paper is to estimate the prevalence of emotional-behavioural problems in iGBS survivors aged 18 months to 17 years using data collected in Argentina, India, Kenya, Mozambique and South Africa.

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Objectives

The objectives are to:

1. Describe characteristics of iGBS survivors and non-iGBS comparison group.

2. Assess differences in emotional-behavioural problems between iGBS survivors and non iGBS comparison group using the following scales:

    a) CBCL Syndrome Scale

    b) Diagnostic and Statistical Manual of Mental Disorders (*DSM–5*) categories

3. Compare prevalence of clinical range problems using the clinical cut offs for the syndrome scale between iGBS survivors and non-iGBS comparison group

METHODS

Overall study design, setting and case definitions

This work was part of a matched, multi-country cohort study to estimate the long-term health outcomes and economic costs for children surviving from iGBS. Information regarding the research protocol and methods have been published.[9] In summary, data was collected from five low- and middle-income countries (LMICs): Kenya, Mozambique and South Africa (Africa), India (Asia) and Argentina (Latin America). Children exposed to neonatal or infant iGBS diseases were identified through hospital admission records in Argentina, India, Kenya and South Africa and by surveillance of laboratory services in Mozambique and South Africa. All the children who met the case definitions of iGBS were approached. Children without history of iGBS disease were recruited via hospital network in Argentina, India and South Africa or using the Health and Demographic Surveillance Systems

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(HDSS) in Kenya and Mozambique and matched to iGBS survivors on sex and age with a 3:1 ratio, more detail can be found for individual country recruitment (Placeholder Hima, SupPaper1; Harden, SupPaper2, Bramugy, Suppaper3). The sample size was based on detection of a 16% difference of severe-moderate NDI which was inclusive of emotional-behavior outcomes, a detailed power calculation is described in the protocol paper. [9, 12]

Case definitions for iGBS were presenting clinical signs of possible serious bacterial infection (pSBI) and detecting GBS from a normally sterile site in an infant less than 90 days old. iGBS was further categorised disease onset and clinical syndrome. Early onset disease (EOD) was defined as diseases occurring in an infant aged 0-6 days, whereas infants with iGBS 7-89 days of age have late onset disease (LOD). There are two main clinical syndromes of iGBS diseases: GBS meningitis and sepsis (Supplemental Table 2).

Trained fieldworkers scheduled a one-time health facility visit with the enrolled children and their parents/main caregivers. At the assessment visit, the parents/main caregivers provided information on health, demographic, economic, and health-related quality of life.[9] Children were assessed with a set neurodevelopmental assessments that were age and culturally appropriate.[9] All data were captured on the paper forms or through a tablet-based, customised application.

Assessment of social emotional problems using the Child Behaviour Checklist

Across all 5 study sites, the emotional and behaviour outcomes were assessed using the Child Behaviour Checklist (CBCL) tool. The CBCL, developed by the Achenbach System of Empirically Based Assessment(ASEBA), is a self-administrated questionnaire completed by caregivers to identify a broad spectrum of adaptive functioning and problems. The checklist has two versions. For children younger or equal to 6 years old, the CBCL/1.5-5 version was used, while the CBCL/6-12 version was applied to children older than 6 years old.[13, 14] The instrument has good reliability (test-retest correlation: 0.90, Cronbach α: 0.92) and has been widely validated in numerous cultural and geographical settings.[15, 16] The study staff who gave the questionnaire to the parents were not blinded to the iGBS exposure status of the children.

CBCL obtains parents' responses based on observation of their children's behaviour in the preceding 6 months. Following the instructions in ASEBA, similar items were grouped together and their scores were added up to provide raw scales for syndromes. CBCL/1.5-5 and CBCL/6-18 measure different problem scales (1.5-5 years: emotionally reactive, anxious/depressed, somatic, withdrawn, sleep problems and attention problems and aggressive behaviour; 6-18 years: anxious, depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour and aggressive behaviour), but yield results in common scales: the internalising and externalising problem scales. The total problem score is the sum of all problem items. CBCL also produces DSM-5 oriented scales, which are derived from experts' consensus on the items' consistency with the diagnostic criteria for DSM-5 disorders (Supplemental Table 3). [17] Scores were not calculated at

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the time of the assessment, however children were referred for support based on a comprehensive developmental assessment carried out by a trained clinician.

To ensure comparability between studies, raw scores were converted into age- and sex-standardised T-scores using the conversion tables provided by the ASEBA. For each scale, its T-score can be interpreted as falling in the normal, borderline, or clinical range. Clinical range are grouped in accordance with ASEBA's guidance to avoid false negatives, and children whose scales fall into the clinical ranges are of clinical significance and are suggested to receive clinical consultation.[17] For problem scales, T-scores ≥60 are classified as borderline/clinical, and T-scores <60 is normal, while the cut-off point for DSM-5 oriented scales is 65.[14, 17]

Statistical analysis

Descriptive analyses were performed to compare the baseline characteristics between iGBS survivors and non-iGBS children; we used Pearson's chi-square tests for categorical variables and two-sample T tests for continuous variables. We used linear regression to assess differences in the raw problem scores between groups, adjusting for study site and matching variables of age and sex when pooling the data. We also conducted sensitivity analysis excluding children with moderate to severe NDIs. All analyses were conducted using STATA version 15.1 software.

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RESULTS

Overall

Between October 2019 and April 2021, iGBS survivors and non-survivors were enrolled in a multi-country case cohort study from Argentina, India, Kenya, Mozambique, and Kenya. **Of the 393 iGBS survivors and 1023 non-iGBS children initially contacted, we failed to approach approximately a third of eligible children in both cohorts. 156(39.7%) survivors and 417(40.8%) comparison children were enrolled and completed the CBCL (Figure 1)**. Among the 573 children with CBCL assessment, 405 (70.7%) of the cohort completed the school-aged (>6 years old) assessment tool and the remaining 168 (29.3%) children completed the preschool-aged (≤ 6 years old) assessment (Figure 1). India and Kenya made up 73.8% of the pre-school cohort, while Mozambique and South Africa accounted for 26.6% of the school-aged cohort population. Argentina made up less than 5% of the total cohort (Table 1).

Objective 1: Characteristics among iGBS survivors and non-iGBS comparison group

There were no differences between iGBS and non iGBS cohorts for age, sex and main caregiver's educational attainment in each country. We observed that preschool-aged iGBS survivors were more likely born preterm (14.9% versus 6.0%), but the differences didn't reach statistical significance (p-value: 0.15). The trend could also be seen in school-aged cohort (11.5% versus 7.7%, p-value: 0.31). In Kenya, more iGBS survivors were preterm (17.2%) compared to non-iGBS comparison group (4.9%) and more iGBS survivors had low birth weight (34.5) than non-iGBS comparison group (9.5%)(Table 1).

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Objective 2: Emotional-Behavioural Problems: syndrome scale and DSM-5 Scale

In the school-aged cohort we observed the iGBS children had significantly higher total emotional behavioural problem scores than the non iGBS group (adjusted mean difference 3.85; 95% CI 0.33 to 7.38, p-value: 0.03). These scores were driven by both the internalizing (anxious and withdrawn syndrome subscales) and externalizing (aggressive syndrome subscale) scores (Table 2). Conversely in the preschool aged cohort we detected no differences in emotional-behavioural problem scores between the iGBS survivors and the non iGBS comparison cohort (Table 2). The results were similar when removing children with moderate-severe neurodevelopmental impairment (Supplementary Table 7). Total problems, externalizing problems and internalizing problems scores were similar between the countries, except in Mozambique, which has the lowest scores in all three categories and in Argentina where external problem score is highest (Supplementary Table 4).

For school aged children, the DSM-5 categorisation showed that iGBS survivors had higher scores for anxiety (adjMD=0.50; p=0.02), attention (adjMD=0.64; p=0.01) and conduct problem (adjMD=0.44; p=0.06) after adjustment for age, sex, and study site. Conversely the pre-school aged children showed no differences between iGBS survivors and the non-iGBS comparison group (Table 3).

Objective 3: Emotional- behavioural problems in clinical range

There were no significant differences in the proportion of children in either age group's CBCL scores in the clinical range in the iGBS and non iGBS comparison cohort (preschool children p=0.36; school aged children p=0.51; Supplementary Table 5). However, when looking between countries there was some variability between sites, of note there were no clinically significant problems detected in Mozambique in either the iGBS group or the non-iGBS comparator. (Supplementary Tables 6A, 6B)

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DISCUSSION

Our multi-country study of long-term outcomes provides the first data on emotional-behavioural problems in pre-school and school aged groups using a standard tool and training across five LMICs, and importantly with locally selected, matched children as a counterfactual. We were able to compare results between countries and also between iGBS and non-iGBS children, as well as following iGBS sepsis which has not been reported before from LMIC.

Amongst school aged children, iGBS survivors were detected as having increased numbers of total problems (in both externalising and internalising scales) and higher scores for some DSM-5 psychopathologies, including anxiety, attention, and conduct disorders. These findings align with two case-control studies after meningococcal meningitis which found that the school-age survivors had significantly more anxiety, conduct and attention problems than their controls. [12, 18] Other studies reported that school-age survivors of neonatal or childhood bacterial meningitis were more likely to be rated by their parents as having behavioral problems when compared to healthy controls. [19, 20] A systematic review suggested that adult sepsis survivors had an increased risk of long-term cognitive problems. [21] However, we also found two studies that refuted the increased behavioral problems in post-meningitis children. [1, 22] Notably all these studies were based in HIC settings and so may not be comparable to the contexts of our study.

Conversely, in pre-school children we found no differences in total number of problems, problems within a clinical range or DSM-5 oriented scores. It is recognized that at this age, social-emotional problems are more difficult to detect and may not identified by parent report scales. [23] In addition

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to this as we detected no significant differences in scores within the clinical range in either age group, it is plausible that mild social-emotional problems are only apparent later in childhood and therefore differences were only detected in the school-aged group.

Interestingly we found some variation in total problems and clinical level problems between countries, with Mozambique recording zero clinical range problems in either group and very low number of total problems cohort (Supplementary tables 6A, 6B). Hence cultural variation in measurement and reporting may be a challenge even when using the same CBCL tool [24].

A major strength of our study was that the multi-country design and the use of the same CBCL tool across all countries, including putting this in a software app and having standard training for all sites. The use of a local, matched counterfactual group is also a strength, rather than comparing to normative standards as is usual in developmental data analysis. Although the sample size was small, this is still a relatively large cohort compared to previous studies in to emotional-behavioural problems and includes data collected from a range of settings.

However our studyhighlights a weakness of the tool as although the CBCL is well validated in a number of settings, the adaptation of constructs is often overlooked in the validation process . [25]

Hence, CBCL may still not be appropriate in all settings, as evidenced in Mozambique where no clinical problems were detected.

A limitation of our study isthat although this is larger than previous studies, the sample size is small. We note that the Covid-19 pandemic posed a challenge to recruitment which resulted in lower power to detect the differences between the iGBS and non-iGBS comparison groups. Another limitation was the low participation rates. Approximately a third of eligible participants were uncontactable and this could lead to selection bias. We did not adjust for preterm or low birthweight since across most countries there were no differences between the iGBS and non iGBS comparison group. Though there is a non-significant trend that there was more preterm birth in iGBS survivors.

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However, we did adjust for study site. There was a lack of co-exposure data on neonatal risks such as multiple birth, hypoxic encephalopathy and data in this study, which meant we could not adjust for possible confounding.

Our findings show the importance of longer term follow up to school age transition where emotional-behavioral problems are likely to become apparent to prevent dual disadvantage due to potential impact on educational engagement and performance. However, more population data is needed to interpret the lack of difference for clinically significant problems between groups and the unexpectedly low prevalence of problems in Mozambique. Qualitative exploration of the potential role of cultural differences in parental reporting across settings is warranted.

Implementation research is needed to develop context specific approaches to integrate testing for at-risk newborns and children, including iGBS survivors, into routine child health programmes, and to provide health and educational support if needed. Since most problems were detected at school-age, families and school teachers should be made more aware the possibility of emotional-behavioural difficulties and the impact that these can have on school performance if not adequately addressed. Importantly, behavioural assessment tools are needed that are open access, and can be used across cultures in a standardised way.

Our findings contributed new evidence on the risk of long-term emotion-behavioural problems after iGBS. As well as important implications for monitoring children, these findings have implications for the higher potential impact of prevention of GBS, including possible gains from a GBS maternal vaccine.

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CONCLUSIONS

These findings have implications for both programmes and research. Follow up of at-risk neonates including iGBS survivors is needed and requires context-specific integration within child health programmes. There is a need for the development of culturally sensitive detection tools which consider carefully how constructs of social-emotional behaviour can be measured in different settings. To achieve equity of measurement these tools must be open access, free and useable by a wide ranges of workers. [26] Implementation research is needed to identify context specific integration of social-emotional follow up into routine child health programmes.

Assessment of emotional-behavioural development is important for every child and every family in every country as part of the SDGs, enabling optimal human capital worldwide.

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DECLARATIONS

Authors' contributions

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Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Tshepiso Nompumelelo Msibi (Medical Research Council: Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Sridhar Santhanam (Department of Neonatology, Christian Medical College, Vellore, India), Hima B. John (Department of Neonatology, Christian Medical College, Vellore, India), Asha Arumugam (Department of Neonatology, Christian Medical College, Vellore, India), Nandhini Murugesan (Department of Neonatology, Christian Medical College, Vellore, India), Nandhini Rajendraprasad (Department of Neonatology, Christian Medical College, Vellore, India), Mohana Priya (Department of Neonatology, Christian Medical College, Vellore, India), Amina Abubakar (Neuroscience Research Group, Department of Clinical Sciences, KEMRI-Wellcome Trust, Kilifi, Kenya; Institute for Human Development, Aga Khan University, Nairobi, Kenya), Carophine Nasambu (Neuroscience Research Group, Department of Clinical Sciences, KEMRI-Wellcome Trust, Kilifi, Kenya), Adam Mabrouk Adan (KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya), Patrick Vidzo Katana (KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya), Eva Mwangome (KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya), Charles R. Newton (Department of Psychiatry, Medical Sciences Division, University of Oxford, Oxford, UK; KEMRI/Wellcome Trust Research Programme), Quique Bassat (Centro de Investigaçãoem Saúde de Manhiça, Maputo, Mozambique; ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain; ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain; Pediatrics Department, Hospital Sant Joan de Déu [University of Barcelona], Barcelona, Spain; Consorcio de Investigación Biomédicaen Red de Epidemiología y SaludPública [CIBERESP], Madrid, Spain), Azucena Bardají (Centro de Investigaçãoem Saúde de Manhiça, Maputo, Mozambique; ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain), Justina Bramugy(Centro de Investigaçãoem Saúde de Manhiça, Maputo, Mozambique), Humberto Mucasse (Centro de InvestigaçãoemSaúde de Manhiça, Maputo, Mozambique), Celine Aerts (ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain), Sergio Massora (Centro de InvestigaçãoemSaúde de Manhiça, Maputo, Mozambique), Romina Libster (Fundación INFANT, Buenos Aires, Argentina), Clara Sánchez Yanotti (Fundación INFANT, Buenos Aires, Argentina), Valeria Medina (Instituto de Maternidad y Ginecología Nuestra Señora de las Mercedes, Argentina), Andrea Rojas (Instituto de Maternidad y Ginecología Nuestra Señora de las Mercedes, Argentina), Daniel Amado (Instituto de Maternidad y Ginecología Nuestra Señora de las Mercedes, Argentina), Conrado J. Llapur (Instituto de Maternidad y Ginecología Nuestra Señora de las Mercedes, Argentina), A. K. M. Tanvir Hossain (Maternal and Child Health Division, International Centre for Diarrhoeal Disease Research, Bangladesh [icddr,b], Dhaka, Bangladesh), Qazi Sadeq-ur Rahman (Maternal and Child Health Division, International Centre for Diarrhoeal Disease Research, Bangladesh [icddr,b], Dhaka, Bangladesh)

Ethics and consent to participate

The overarching protocol for this multi-country observational study was granted ethical approval at the London School of Hygiene & Tropical Medicine (approval number 16246). Institutional review boards in each of the operating countries granted ethics approval (Argentina approval number Protocol EGB-1, India approval numbers 11723 (CMC Vellore), 2019–7034 (ICMR); Kenya approval number SERU/CGMR-C/164/3882; Mozambique approval numbers 98/CNBS/2019; South Africa approval number M190241), as well as the institutional review board of the World Health Organization (approval number ERC.0003169). Written informed consent will be obtained from parents or guardians. Whenever appropriate, based on local guidelines, assent will also be obtained from children participating in the study.

Availability of data and material

Data sharing and transfer agreements were jointly developed and signed by all collaborating partners. Data will be available to request on LSHTM data compass.

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Conflict of interest

Potential conflicts of interest. Many contributors to the papers in this supplement have received funding for their research from foundations, especially the Bill & Melinda Gates Foundation, the Meningitis Research Foundation, EDCPT and others. All authors report no potential conflicts of interest, and all authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed. AA reports subawards from LSHTM to University of Oxford. AB reports subawards from

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FIGURE LEGEND

Figure 1: Participant flow of iGBS cases and non-iGBS children recruited
Out of 393 iGBS survivors contacted, 160 consented for participation and completed the assessment. Out of 1023 matched non iGBS children contacted for participation, 422 children consented and completed neurodevelopmental, vision and hearing asses

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TABLES

Table 1. Descriptive characteristics of iGBS survivors and non-iGBS comparison group from India, South Africa, Mozambique, Kenya and Argentina. Total N=573

	Preschool-aged cohort(≤ 6 years old) n=168			School-aged cohort(> 6 years old) n=405		
	iGBS survivors (n=50)	non-iGBS comparison group (n=118)	p value	iGBS survivors (n=106)	non-iGBS comparison group(n=299)	p value
Country						
India	23(46.0)	44(37.3)		10(9.4)	17(5.7)	
Kenya	13(26.0))	44(37.3)		16(15.1)	64 (21.4)	
Mozambique	8(16.0)	22(18.6)		31(29.2)	100 (33.4)	
South Africa	4 (8.0)	5(4.2)		39 (36.8	112(37.5)	
Argentina	2(4.0)	3(2.5)	0.51	10(9.4)	6(2.0)	0.01
Sex (F)	28(56.0)	66(55.9)	0.99	45(42.5)	149(49.8)	0.16
Preterm	7/47(14.9)	7/117(6.0)	0.15	11/96(11.5)	22/286(7.7)	0.31
Low birth weight	10(20.0)	16/109(14.7)	0.40	20/95(21.1)	31/214(14.5)	0.15
Birth order						
First	31(62.0)	41(34.8)		42(39.6)	106(35.5)	
Second	7(14.0)	38(32.2)		31(29.3)	65(21.7)	
Third and higher	12(24.0)	39(33.0)	0.003	33(31.1)	128(42.8)	0.09
Main caregiver's educational attainment						
College or university	35(70.0)	92(78.0)		88(83.0)	255(85.3)	
High school and below	15(30.0)	26(22.0)	0.27	18(17.0)	44(14.7)	0.58

Abbreviations: iGBS = invasive GBS disease Data presented as n/N(%)

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Table 2. Mean differences of the CBCL problem scores, stratified by preschool-aged and school-aged cohort, assessed from October 2019 to April 2021. Total n=573

	iGBS mean*	Non-GBS mean*	Adjusted mean differences^ (95% CI)	p-value
Pre-school aged children (≤ 6 years old)	N=50	N=118		
Total problems	21.48	20.90	-0.45 (-6.59, 5.68)	0.883
Externalizing problems	8.08	7.32	0.01 (02.54, 2.57)	0.992
Attention problems	1.46	1.73	-0.42 (-1.07, 0.23)	0.204
Aggressive problems	6.62	5.59	0.44 (-1.65, 2.52)	0.680
Internalizing problems	6.10	6.21	-0.13 (-2.03, 1.78)	0.896
Emotional reactive	1.18	1.22	-0.06 (-0.67, 0.55)	0.840
Anxious/depressed	1.68	2.03	-0.42 (-1.03, 0.19)	0.174
Withdrawn	1.08	1.49	-0.33 (-1.00, 0.35)	0.343
Somatic complaints	2.16	1.47		
School-aged children (> 6 years old)	N=106	N=299		
Total problems	23.49	17.51	3.85 (0.33, 7.38)	0.032
Externalizing problems	5.82	4.29	0.97 (-0.06, 2.00)	0.064
Rule breaking behaviour	1.75	1.25	0.36 (-.002, 0.73)	0.051
Aggressive	4.08	3.04	0.61 (-0.15, 1.37)	0.117
Internalizing problems	6.78	5.11	1.14 (0.02, 2.27)	0.046
Anxious/depressed	3.12	2.39	0.45 (-0.12, 1.02)	0.120
Withdrawn/depressed	1.78	1.19	0.46 (0.05, 0.86)	0.026
Somatic	1.88	1.53	0.23 (-0.24, 0.71)	0.332

*Unadjusted means for iGBS and non-GBS groups

^adjusted for study site, age and sex

Table 3. Mean differences of the DSM-5 oriented scores in the preschool-aged and school-aged cohort, assessed from October 2019 to April 2021. Total N =573.

	iGBS mean*	Non-GBS mean*	Adjusted mean differences^ (95% CI)	p-value
Pre-school aged children (≤ 6 years old)	N=50	N=118		
Depressive problem	1.14 (0.64, 1.64)	1.06 (0.77, 1.35)	0.01 (-0.54, 0.56)	0.972
Anxiety problem	2.28 (1.67, 2.89)	2.50 (2.03, 2.97)	-0.32 (-1.08, 0.45)	0.414
Attention problem	2.64 (1.92, 3.36)	2.47 (2.00, 2.95)	0.03 (-0.76, 0.82)	0.946
Oppositional problem	2.26 (1.52, 2.99)	1.91 (1.43, 2.38)	0.12 (-0.68, 0.92)	0.762
Autism problem	2.08 (1.23, 2.87)	1.93 (1.45, 2.41)	0.14 (-0.72, 1.00)	0.748
School-aged children (> 6 years old)	N=106	N=299		
Depressive problem	2.02 (1.60, 2.44)	1.45 (1.20, 1.70)	0.34 (-0.09, 0.77)	0.120
Anxiety problem	2.52 (2.09, 2.95)	1.78 (1.51, 2.04)	0.50 (0.07, 0.93)	0.023
Somatic problem	1.16 (0.82, 1.50)	1.14 (0.95, 1.33)	0.03 (-0.33, 0.39)	0.877
Attention problem	3.09 (2.52, 3.66)	2.14 (1.83, 2.45)	0.64 (0.14, 1.14)	0.012
Oppositional problem	1.48 (1.13, 1.83)	1.16 (0.97, 1.35)	0.10 (-0.23, 0.42)	0.562
Conduct problem	1.96 (1.53, 2.40)	1.40 (1.15, 1.66)	0.44 (-0.01, 0.90)	0.057

Abbreviations: DSM = the diagnostic and statistical manual of mental disorders; iGBS = invasive GBS disease; CI = confidence interval; AP = attributable proportion

Data presented as mean differences and 95% CI.

*Unadjusted means for iGBS and non-GBS groups

^adjusted for study site, age and sex

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Figure 1