South Indian children's neurodevelopmental outcomes after Group B Streptococcus invasive disease: A case cohort study

Hima B John[1], Asha Arumugam[1], Mohana Priya[1], Nandhini Murugesan[1], Nandhini Rajendraprasad[1], Grace Rebekah[2], Proma Paul[3,4], Jaya Chandna[3,4], Joy E Lawn[3,4], Sridhar Santhanam[1]

1. Department of Neonatology, Christian Medical College, Vellore
2. Department of Biostatistics, Christian Medical College, Vellore
3. Maternal, Adolescent, Reproductive & Child Health (MARCH) Centre, London School of Hygiene & Tropical Medicine, London, UK
4. Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

Corresponding Author Contact details:

Sridhar Santhanam
Department of Neonatology, Christian Medical College, Vellore, India.632004
E mail: neonat@cmcvellore.ac.in
Phone: +91-416-2283311

ABSTRACT

Introduction

This study is part of a multi- country matched cohort study designed to estimate the risk of long term neurodevelopmental of children exposed to iGBS. The specific objective of this paper is to compare NDI across domains of iGBS survivors with a matched non-GBS group in our population.

Methods

Survivors of iGBS in a south Indian hospital were identified and recruited between January 2020 and April 2021. Cases were compared with age and gender matched non-GBS children. Participants were assessed using Bayley Scales of infant and toddler development (BSID-III), Wechsler Preschool and Primary Scale of Intelligence (WPPSI- IV), Wechsler Intelligence Scale for Children (WISC- V), Child behaviour checklist (CBCL) and Bruininks- Oseretsky Test of Motor Proficiency (BOT-2) depending on age.

Results

Our cohort comprised 35 GBS exposed and 65 matched non-GBS children, aged 1- 14 years. iGBS exposed group had 17 (48.6%) children with impairment in at least one domain compared to 25 (38%) in the non-GBS group [Unadjusted OR- 1.51, 95%CI 0.65- 3.46], 9 (26%) children with 'multi domain impairment' compared to 10 (15.4%) in the non-GBS group [Unadjusted OR- 1.90, 95% CI 0.69- 5.24] and 1 (2.9%) child with moderate to severe impairment compared to 3 (4.6%) in the non-GBS group [Unadjusted OR- 0.60, 95%CI 0.06- 6.07]. In the iGBS group, more children had motor impairments compared to the non-GBS group [Unadjusted OR- 10.7, 95%CI 1.19- 95.69, p= 0.034]

Conclusion

Children with iGBS seem at higher risk of developing motor impairments compared to a non-GBS group.

Key words: neurodevelopmental impairment, Group B Streptococcus invasive disease, India, neurodevelopmental outcomes

LIST OF ABBREVIATIONS

BOT	Bruininks-Oseretsky Test
BSID	Bayley Scales of Infant and Toddler Development
CBCL	Child Behaviour Checklist
GBS	Group B Streptococcus
iGBS	invasive Group B Streptococcus
LMIC	Low- and Middle-Income Countries
NDI	Neurodevelopmental Impairment
WISC-V	Wechsler Abbreviated Scale of Intelligence V
WPSSI	Wechsler Preschool and Primary Scales of Intelligence

TEXT BOX 1: KEY FINDINGS

1. WHAT IS KNOWN and WHAT IS NEW?

There are an estimated 392,000 children worldwide with invasive Group B Streptococcal Disease (iGBS), with the highest numbers in Sub Saharan Africa and Asia. Globally there are almost no published studies of neurodevelopmental impairment (NDI) amongst iGBS survivors from low and middle-income countries (LMIC). This is the first study from Asia to examine neurodevelopment of iGBS survivors using standardised developmental assessment tools across several domains.

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

We identified 35 survivors of iGBS aged 1- 14 years and 65 matched non-GBS children, undertaking standardised assessments of NDI. The iGBS exposed children had a trend towards greater NDI, but this was not statistically significant [Unadjusted OR1.51, 95%CI 0.65- 3.46]. An important limitation of this study was that some children were not able to come due to travel restrictions during the COVID-19 pandemic, reducing the capture especially of both iGBS and non-GBS cohort.

3**. WHAT TO DO NOW IN PROGRAMMES?**

Early interventional services and follow up programs are required for survivors of iGBS to optimise neurodevelopmental outcomes.

4. WHAT NEXT IN RESEARCH?

There is a need for culturally appropriate measurement tools especially in measurement of language and cognition. Larger studies are needed to estimate the incidence of NDI in this population and to study environmental contributors to impairment.

BACKGROUND

The estimated incidence of severe neonatal infections in low and middle-income countries (LMIC) is 6.9 million. Invasive Group B Streptococcus disease (iGBS), an infection that presents as sepsis or meningitis, is a leading cause of neonatal sepsis with reported incidence of 0.49 per 1000 live births.

Intrauterine and neonatal insults, contribute to a high risk of developing long term neurodevelopmental impairment (NDI) including cognitive, motor (e.g. cerebral palsy), hearing and visual impairment domains. Bacterial meningitis especially in neonates is a notable cause of NDI, with pathophysiological disruptions such as cerebral inflammation and oedema. After neonatal meningitis, an estimate of moderate to severe NDI is 23% [95% CI: 19 – 26%]. A systematic review of NDI of GBS survivors found moderate to severe NDI in 18% of meningitis survivors, but no useable data after iGBS sepsis. This review included 18 studies from upper- and middle-income countries with paucity of data for patients older than 2 years, and recommended future studies assessed the total burden of GBS disease in older children and assessing all developmental domains using valid assessment tools. There are no published studies that assessed neurodevelopment outcomes of iGBS survivors in an Asian population.

AIM and OBJECTIVES

This paper is part of a series of 10 papers reporting a value proposition for maternal vaccines against GBS by WHO. The aim of this paper is to present data collected in India as part of a multi-country study describing neurodevelopmental outcomes of iGBS survivors by domains of cognition, language, motor skills and behaviour and comparison with a non-GBS group.

The objectives of the paper are to:

(1) Describe a cohort of iGBS survivors and a matched non-GBS cohort

(2) Evaluate the risk of NDI and categorise severity in the domains of vision, hearing, cognition, language, motor skills and behaviour in the iGBS cohort when compared to a non-GBS group.

METHODS

Setting: The study setting was a tertiary care teaching hospital in south India (Figure 1). This hospital is a referral perinatal centre catering to the population of four adjoining districts of three neighbouring states. The 75 bedded Neonatal unit with Level 3 facilities, has admissions of over 2500 infants every year. There are about 12,000-14,000 births/year and the neonatal mortality rate between 2015-2019 ranged from 2.7 to 5.6/1000 live births (Mean: 3.8/1000 live births; National

NMR in 2019- 21.7/1000 live births). The hospital has a risk based intrapartum antibiotic policy for GBS prophylaxis since 2003, with no national policy for the same. A multinational study in 2017 found the prevalence of GBS colonisation among pregnant women in the institution was 20.9 %[8]. The incidence of GBS disease between 1998 to 2010 in the institution was 0.76/1000 live births, of which incidence of early onset sepsis was 0.68/ 1000 live births [95%CI: 0.52- 0.83].

Study design: The study was a matched cohort study. Exposed were survivors of infant iGBS disease, henceforth termed as 'iGBS survivors', and unexposed were individuals with no GBS identified. This study is part of a multi-centric trial on the long-term outcomes of GBS survivors in LMICs; study protocol has already been published.

Participants: iGBS survivors born between August 2006 to July 2018, were identified from the hospital's database. As per protocol, children born < 32 weeks were excluded. Additional criterion for inclusion was knowledge of English or Tamil for administration of neurodevelopmental assessments.

Parents were contacted telephonically and via post with an invitation to attend the neurodevelopmental assessment. Home visits though initially planned, were not executed due to the COVID pandemic during the period of recruitment. Exposure to GBS disease was defined as GBS isolated in blood culture between 0-89 days of the infant's life. This study did not differentiate GBS sepsis or GBS meningitis. In our cohort, none of the babies with 'meningitis' had a positive CSF culture, which is the gold standard for diagnosis but were diagnosed based on high CSF counts or protein.

Non-GBS children were matched for gender and age of ± 2 months of the iGBS survivors. We aimed to recruit 3:1 non-GBS to exposed children. Non-GBS children were recruited by identifying and contacting case- matched children from the hospital records, via the Immunisation clinic and through distribution of posters in the community. No exclusion criteria were placed except a positive history of GBS infection in early infancy. There was a time lag between recruitment of exposed and children due to government imposed lock down measures to contain COVID infection.

Recruitment was from January 2020 to April 2021. Once the family arrived at the hospital, written informed consent and child assent were obtained. The demographic, health and economic health questionnaire, and the EQ5D questionnaire were administered to the caregiver. The children's anthropometry was measured, vision and hearing assessed and the neurodevelopmental assessments and relevant questionnaires administered. Information was collected on paper forms, then transferred using standard operating procedures to a tablet-based application for data entry.

The study assessment team consisted of 3 occupational therapists, 2 psychologists, a fieldworker and a data entry operator. All team members were trained using an 8-session training module, covering standard guidelines for assessment of anthropometry, vision and hearing, administration of questionnaires and data entry. They were also certified in the administration, interpretation and scoring of the assessment tools.

Neurodevelopmental assessments:

Children aged below 42 months: Children aged 42 months or below were assessed using the Bayley Scales of Infant and Toddler development, Third Edition (BSID-3) for cognition, language, motor skills, socio-emotional skills and adaptive behaviour. The BSID is a globally accepted goal standard in child assessment and has recently been used in a number of large studies in our population.

Children aged above 42 months: In children above 42 months, cognition was assessed using the Wechsler's Preschool and Primary Scale of Intelligence- 4th Edition (WPPSI) or the Wechsler's scale of Intelligence- 5th Edition (WISC-5), depending on the age. The WPPSI assesses cognitive abilities in children aged 2.5 to 7 years. It has 13 subtests, which yield scaled scores, standard scores and percentiles. The Wechsler's Intelligence Scale for children- 5th Edition (WISC 5), is a commonly used assessment in school aged children. Both tools render composite scores for fluid reasoning, processing speed, verbal comprehension, visual spatial and working memory and a full scale IQ. The validity of both scales have been supported for use in LMIC and the WISC-4 standardised to the Indian population.

Motor skills were assessed using the "Bruininks- Oseretsky Test of Motor Proficiency Second Edition (BOT-2)". It assesses fine and gross motor skills in children and youth aged 4 to 21 years. This study used the short form of the assessment which yields standard scores, percentile ranks and descriptive categorisation

Behavioural outcomes for all children were measured using the Child Behaviour Checklist (CBCL). The *CBCL* is a parent-report questionnaire (comprised of two versions: a younger 1 ½ - 5 years and 6-18 years) on which the *child* is rated on various *behavioural* and emotional problems. It assesses internalizing (i.e., anxious, depressive, and over controlled) and externalizing (i.e., aggressive, hyperactive, noncompliant,) *behaviours.* The questionnaire was translated and back translated into Tamil. Questions were read out to caregivers with limited literacy.

The assessors were not blinded to participant group. During a developmental or psychological assessment, it is inevitable that parents share their traumatic NICU experience and this is not discouraged since this information contributes to the holistic understanding of the child. Hence the

assessors were not blinded to the groups. Since the assessment tools have stringent guidelines on scoring and interpretation, we did not anticipate bias due to the lack of blinding. Parental concerns were addressed by the team. Children with mild NDI had an additional appointment with the Unit's Psychologist or Occupational therapist (depending on the domain of impairment). Parents were taught a home-based program and encouraged to attend regular follow up visits at 2 monthly intervals. Children with moderate to severe NDI were referred to the Institution's Developmental Paediatric Unit.

All assessments were scored according to their scoring manuals. NDI was defined based on the work by Global burden of Disease. Severity coding within each assessment was as follows (Supplementary table 2):

Mild- if 1-2 SD below standardised mean

Moderate- if 2-3 SD below standardised mean

Severe- if≥ 3 SD below standardised mean

'Any impairment': If the child had impairment in any domain (vision, hearing, cognition, language, motor or behaviour)

'Multi-domain impairment': If there were impairments in more than one domain

'Moderate to Severe impairment': If the child had moderate or severe impairment in any domain

Socioeconomic status was assessed using the "Updated Modified Kuppuswamy SES" scale for the year 2020.

Statistical Methods:

Neurodevelopmental outcomes (NDO) were assessed separately for the 2 age groups- one group with children less than 42 months (who had BSID and CBCL assessments) and one group with children 43 months and above (who had a WISC or WPPSI, BOT and CBCL assessments) and combined (Supplemental Table 2). Domains of vision, hearing, cognition, language, motor abilities and behaviour were compared between exposed and non-GBS groups using a severity classification for NDI.

Analysis was undertaken in SPSS software version 21. Descriptive statistics were reported using mean+/-SD for continuous variables; Categorical variables were reported using frequency and percentage. Association was reported using Chi Square/Fisher's exact test. Comparison of means

was reported using two independent sample t test. Binary logistic regression was performed to arrive at the risk factor analysis. The Odds Ratio was reported along with the 95% Confidence Interval. A p value <0.05 was considered statistically significant.

RESULTS

Objective 1: Description of GBS survivors and a matched non-GBS group

Out of 79 iGBS survivors contacted, 35 (44.3%) consented for participation and completed the assessment (Figure 2). Of the 35 children with iGBS, 33 (94.3%) had early onset sepsis and 2 (5.7%) had late onset sepsis. There were no significant differences in gender, prematurity, birth weight, gestational age, onset of sepsis, and rates of meningitis and chorioamnionitis between children who consented for participation and those who did not participate. Out of 158 matched non-GBS children approached for participation, 65(41.1%) children consented and completed the assessments (Figure 2). One child in the non GBS group had sepsis, not caused by GBS in the neonatal period. Initially it was planned to recruit patients from the hospital data base using sequential sampling based on closest match. We were able to recruit around one third of the sample in this way. Due to the pandemic related travel restrictions, we later used convenient sampling by offering assessments to children who came for an immunisation visit and distribution of posters in the community.

Participants were of ages 1- 14 years (M (SD) - 4.49 (3.47), Median- 3). There were no significant differences in demographic variables in exposed and non-GBS groups except in birth order (p= 0.003) (Table 1). Of the parents of children who underwent treatment for GBS sepsis in our hospital, who were contacted, none reported post discharge death.

Objective 2: Risk of NDI in the GBS cohort when compared to a non-GBS group.

Of the 35 iGBS survivors who participated in the study, all children had GBS sepsis and 4 (11%) also had meningitis. Among iGBS survivors, 17 (48.6%) children had impairment in at least one of the assessed domains as compared to 25 (38%) in the non-GBS group [Unadjusted OR- 1.51, 95%CI 0.65- 3.46]; 9 (26%) children had impairment in more than one domain compared to 10 (15.4%) in the non-GBS group [Unadjusted OR- 1.90, 95% CI 0.69- 5.24]; and 1 (2.9%) child had moderate to severe impairment compared to 3 (4.6%) in the non-GBS group [Unadjusted OR- 0.60, 95%CI 0.06- 6.07]. The iGBS group had more children with motor impairments compared to the non-GBS group [Unadjusted OR- 10.7, 95%CI 1.19- 95.69, p= 0.033]. There were no differences in impairments in vision, hearing, cognitive skills [Unadjusted OR- 1.51, 95%CI 0.65- 3.46, p= 0.857], language skills

[Unadjusted OR- 2.12, 95%CI 0.85- 5.28, p= 0.106] or behaviour [Unadjusted OR- 0.77, 95%CI 0.18-3.21, p=0.727] between the iGBS and non GBS groups (Table 2, Figure 3)).

Looking at iGBS and non GBS groups combined, among children with 'any impairment', 27 (64%) had language impairment, 20 (47%) had cognitive impairment, 6 (14%) had motor impairment, and 11 (26%) had behavioural impairment. Among children with 'multi domain impairment', 19 (100%) had language impairment, 17 (89%) had cognitive impairment, 6 (31.5%) had motor impairment, and 3 (15.7%) had behavioural impairment. Among children with 'moderate to severe impairment', 3 (75%) had language impairment, 4 (100%) had cognitive impairment, and 1 (25%) had motor impairment.

Children below 42 months: There were 17 children in the exposed group and 32 in the non GBS group below 42 months. Four children (23.5%) in the exposed group and 1(3.1%) child in the non-GBS group had "multi-domain impairment' (p= 0.043).

Children above 42 months: There were 18 children in the exposed group and 33 children in the non GBS group above 42 months. The exposed group had more children with motor impairments: 4 (23.5%) in the exposed group and 1 (3.1%) child in the non-GBS group (p= 0.042). There was a trend towards lower scores in working memory Subscale (p= 0.06) and the Fullscale IQ (p= 0.06) in the exposed group (Table 2) compared to the non-GBS group. When children with 'any impairment' were excluded from analysis, the exposed group had lower FSIQ scores than the non-GBS group (p= 0.014).

DISCUSSION

This study found that iGBS exposed children had approximately 50% higher odds of NDI but this was not statistically significant [Unadjusted OR1.51, 95%CI 0.65- 3.46]. Children in the iGBS group had more motor impairments compared to the non GBS group (p=0.033). An important limitation of this study was the small size due to COVID 19 pandemic travel restrictions, reducing the capture of both iGBS and the non-GBS cohort. This is the first published study in Asia examining NDI amongst iGBS survivors using standardized developmental assessment tools across several domains, and comparing with a matched non-GBS group.

The iGBS exposed group had 17 (48.6%) children with 'any impairment' compared to 25 (38%) in the non-GBS group, 9 (26%) children with 'multi domain impairment' compared to 10 (15.4%) in the non-GBS group and 1 (2.9%) child with 'moderate to severe impairment' in the exposed group

compared to 3 (4.6%) in the non-GBS group. The exposed group had more children with motor impairments compared to the non-GBS group. Studies from south Africa found GBS affected children to be 13 times more likely to have any abnormal neurological signs when compared to non-GBS group at 6 months [5 (7.4%) in exposed and 1 (0.4% in non-GBS)], and a 3.5 fold (95% CI: 1.23- 10.04) increased odds of NDI compared to matched controls at 1 year [11 (24.4%) in exposed and 10 (7.1%) in non-GBS] using abnormal Denver- II scores to define NDI. A study on the association of GBS disease on NDI at a median age of 14 years found an increased risk of moderate to severe NDI with risk ratios of 1.7 [95%CI 1.44-2.18] in Denmark and 2.28 [1.64-3.17] in the Netherlands. In Denmark, the proportion of children with moderate to severe NDI at 10 years was 45 (4.6%) in the exposed group and 245 (2.5%) in the non-GBS group (RR1.82 [95% CI 1.33– 2.49]). In the Netherlands, the proportion of children who received special educational support at 10 years in the exposed group was 36 (14.3%) and 157 (6.2%) in the non-GBS group. A study in the United States found 2 (16%) children with neonatal GBS to have neurological impairments at 4 years. Children with GBS meningitis showed larger proportion of NDI: A meta-analysis of GBS meningitis survivors, followed up for more than 18 months, reported 'any NDI' in 32 % (95%CI, 25- 38) of children.

There are several possibilities why the rates of moderate to severe NDI in this study were lower than in other studies. The small sample size and the possibility of selection bias (with families of children with less severe impairment more able to attend-especially during the pandemic) may have been factors. In our population, survivors of GBS disease are routinely enrolled in a follow up program post discharge, which includes an early stimulation program. Education about developmental milestones may have sensitised the parents to the child's vulnerability resulting in active interventions to compensate for the child's difficulties, so the lower rates of impairment may reflect earlier intervention. Systematic reviews have shown that while early intervention programs may not avert moderate to severe impairment, they have positive effects on cognitive development, with little influence on motor development. Another stipulation is the influence of genetic polymorphisms, such as interleukin-6 (rs1800795),which is associated with the development of cerebral palsy, that may account for racial differences in outcomes of infants seen in other studies. Additionally, there may be measurement error due to varying developmental assessment tools used. The Cognitive, Language, and Motor composites of the Bayley-III, for example, have been shown to overestimate development, resulting in lower detection rates of NDI, when compared to the DDST-II.

In this study, most children with abnormal NDI had language impairments- 64% in 'any impairment', and 75% in 'moderate to severe impairment' and 100% in 'multi-domain impairment'. This may be explained in two ways: The lack of culturally appropriate assessment tools or as inherent cultural differences in language acquisition. The mechanism of language development is proposed to be cultural than universal, implying its sensitivity to social factors and cultural context.

The non-GBS group in this study has unexpected high percentages of NDI, also reported by Harden et al [placeholder ref: Harden iGBS paper 2) in this series. This study was conducted during the COVID pandemic. The lockdown in India caused a disruption in schooling, with pre-schoolers not yet enrolled, and most children not having access to any schooling. Since the exposed children were identified and assessed first; and the non-GBS controls recruited later, the effect of the lockdown may have been more pronounced in the non-GBS. Disasters including pandemics or disease outbreaks have been shown to cause short term and lasting effects on psychological functioning, behaviour and developmental trajectory of children.

The 'recovery continuum model' postulates that a child's recovery after early brain insult falls along a continuum that depends not just on injury related factors such as nature, severity and timing of insult, but also constitutional factors such as genetic make- up, gender and cognitive capacity, and environmental factors such as social status, access to rehabilitation and intervention. A limitation of this study is that due to the small sample size, confounding factors could not be studied in detail- this can be addressed in future studies in this population.

Strengths of this study include using standardised multi-country approaches and NDI tools with trained assessors, as well as inclusion of a counterfactual with a matched non-GBS group. This study was based in a referral centre, and may therefore not be generalizable to other populations.

CONCLUSION

Children with iGBS seem at higher risk of developing motor impairments compared to a non-GBS group. Larger studies are needed in LMIC to estimate incidences of NDI in survivors of GBS and to study environmental adversities that adversely influence child development.

NOTES

Authors' contributions

The GBS study was conceptualised by JEL. All site teams contributed to the design of the study protocol and undertook data collection. SS together with HJ and AA developed the detailed research questions and overall analysis plan for this paper. Analysis was undertaken by GR. SS provided statistical oversight. The manuscript was drafted by HJ and SS. All authors reviewed and helped to revise the manuscript. All authors reviewed and agreed the final version.

Acknowledgements

We are thankful to all the children and their parents who took part in the study. We recognise the contributions of Mr. Ramesh Krishnan in managing data, Mr Selvakumar G for translation of consent forms, Ms. SujaAngelin and Ms. Archana for patient recruitment and data collection and Ms. Poongodi K for her support in data entry. We express appreciation to the GBS LMIC collaborative groupfor input on study design as part of a multi-country collaboration:

GBS LMIC collaborative group for long term outcomes: Shabir A. Madhi (Medical Research Council: Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), ZiyaadDangor (Medical Research Council: Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Shannon Leahy (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Lois Harden (Brain Function Research Group, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), AzraGhoor (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), SibongileMbatha (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Sarah Lowick (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Tamara Jaye (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Sanjay G Lala (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Pamela Sithole (Medical Research Council: Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg,

South Africa), Jacqueline Msayi (Medical Research Council: Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), NtombifuthiKumalo (Medical Research Council: Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), TshepisoNompumeleloMsibi (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), NandhiniMurugesan (Department of Neonatology, Christian Medical College, Vellore, India), NandhiniRajendraprasad (Department of Neonatology, Christian Medical College, Vellore, India), MohanaPriya (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), CarophineNasambu (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), QuiqueBassat (Centro de InvestigaçãoemSaúde de Manhiça, Maputo, Mozambique; ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain; ICREA, Pg. LluísCompanys 23, 08010 Barcelona, Spain; Pediatrics Department, Hospital Sant Joan de Déu [University of Barcelona], Barcelona, Spain; Consorcio de InvestigaciónBiomédicaen Red de Epidemiología y SaludPública [CIBERESP], Madrid, Spain), Azucena Bardají (Centro de InvestigaçãoemSaúde de Manhiça, Maputo, Mozambique; ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain), Justina Bramugy(Centro de InvestigaçãoemSaúde 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 GinecologíaNuestraSeñora de las Mercedes, Argentina), Andrea Rojas (Instituto de Maternidad y GinecologíaNuestraSeñora de las Mercedes, Argentina), Daniel Amado (Instituto de Maternidad y GinecologíaNuestraSeñora de las Mercedes, Argentina), Conrado J. Llapur (Instituto de Maternidad y GinecologíaNuestraSeñora 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), QaziSadeq-ur Rahman (Maternal and Child Health Division, International Centre for Diarrhoeal Disease Research, Bangladesh [icddr,b], Dhaka, Bangladesh)

Ethics and consent to participate

Written informed consent was obtained from parents or guardians and child assent obtained from children over 6 years of age. 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 India site granted ethics approval (India approval numbers 11723 (CMC Vellore), 2019–7034 (ICMR)), as well as the institutional review board of the World Health Organization (approval number ERC.0003169).

Availability of data and material

Data sharing and transfer agreements were jointly developed and signed by all collaborating partners. The datasets generated and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing interests

All authors completed unified competing interest forms and declare no conflicts of interest.

Funding

This work was supported by a grant (OPP1180644) from the Bill & Melinda Gates Foundation to the London School of Hygiene & Tropical Medicine (PI, Joy Lawn). SS and GR report subawards from LSHTM to Christian Medical College, Vellore. HBJ reports sub awards from LSHTM to India were received. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

Potential conflicts of interest.Many contributors to the papers supplement have received funding for their research from foundations, especially the Bill & Melinda Gates Foundation, the Meningitis Research Foundation, EDCPT and others. All (other) 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.

REFERENCES

1. Seale AC, Blencowe H, Manu AA, et al. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: a systematic review and meta-analysis. *Lancet Infect Dis*. 2014;14(8):731-741.

2. Iroh Tam P-Y, Delair SF, Obaro SK. Neonatal group B streptococcus disease in developing countries: are we ready to deploy a vaccine? *Expert Rev Vaccines*. 2015;14(11):1401-1403.

3. Madrid L, Seale AC, Kohli-Lynch M, et al. Infant group B streptococcal disease incidence and serotypes worldwide: systematic review and meta-analyses. *Clin Infect Dis*. 2017;65(suppl_2):S160-S172.

4. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *The Lancet*. 2012;379(9814):445-452.

5. Hernández MI, Sandoval CC, Tapia JL, et al. Stroke patterns in neonatal group B streptococcal meningitis. *Pediatr Neurol*. 2011;44(4):282-288.

6. Seale AC, Blencowe H, Zaidi A, et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. *Pediatr Res*. 2013;74(1):73-85.

7. Kohli-Lynch M, Russell NJ, Seale AC, et al. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: systematic review and meta-analyses. *Clin Infect Dis*. 2017;65(suppl_2):S190-S199.

8. Santhanam S, Beck M et al.Group B Streptococcus (GBS) colonization in mother-newborn dyads in India– Results from a multicentre study. In: Proceedings of the 1st International Symposium of Streptococcus agalactiae disease (ISSAD), Feb 21-23, 2018, Cape Town, South Africa

9. Sridhar S, Grace R, Nithya PJ, et al. Group B streptococcal infection in a tertiary hospital in India—1998–2010. *Pediatr Infect Dis J*. 2014;33(10):1091-1092.

10. Paul P, Procter SR, Dangor Z, et al. Quantifying long-term health and economic outcomes for survivors of group B Streptococcus invasive disease in infancy: protocol of a multi-country study in Argentina, India, Kenya, Mozambique and South Africa. *Gates Open Res*. 2020;4(138):138.

11. Upadhyay RP, Taneja S, Ranjitkar S, et al. Factors determining cognitive, motor and language scores in low birth weight infants from North India. *Plos One*. 2021;16(5):e0251387.

12. Andrew A, Attanasio O, Augsburg B, et al. Effects of a scalable home-visiting intervention on child development in slums of urban India: evidence from a randomised controlled trial. *J Child Psychol Psychiatry*. 2020;61(6):644-652.

13. Bhopal S, Roy R, Verma D, et al. Impact of adversity on early childhood growth & development in rural India: Findings from the early life stress sub-study of the SPRING cluster randomised controlled trial (SPRING-ELS). *PLoS One*. 2019;14(1):e0209122.

14. Wechsler D. Wechsler preschool and primary scale of intelligence—fourth edition. *Psychol Corp San Antonio TX*. Published online 2012.

15. Ruan-Iu L, Pendergast LL, Rasheed M, et al. Assessing early childhood fluid reasoning in low- and middle-income nations: validity of the Wechsler Preschool and Primary Scale of Intelligence across seven MAL-ED sites. *J Psychoeduc Assess*. 2020;38(2):256-262.

16. Wechsler IV D. *WISC-IV India. Wechsler Intelligence Scale for Children-Fourth (India Edition)*. New Delhi: Pearson; 2016.

17. Brown T. Structural validity of the Bruininks-Oseretsky test of motor proficiency–second edition brief form (BOT-2-BF). *Res Dev Disabil*. 2019;85:92-103.

18. Achenbach TM, Rescorla LA. *Manual for the ASEBA Preschool Forms and Profiles*. Vol 30. Burlington, VT: University of Vermont, Research center for children, youth …; 2000.

19. Achenbach TM, Rescorla L. *Manual for the ASEBA School-Age Forms & Profiles: An Integrated System of Multi-Informant Assessment*. Aseba Burlington, VT:; 2001.

20. Saleem SM. Modified Kuppuswamy socioeconomic scale updated for the year 2020. *Indian J Forensic Community Med*. 2020;7(1):1-3.

21. Dangor Z, Lala SG, Cutland CL, et al. Burden of invasive group B Streptococcus disease and early neurological sequelae in South African infants. *PloS One*. 2015;10(4):e0123014.

22. Nakwa FL, Lala SG, Madhi SA, Dangor Z. Neurodevelopmental Impairment at 1 Year of Age in Infants With Previous Invasive Group B Streptococcal Sepsis and Meningitis. *Pediatr Infect Dis J*. 2020;39(9):794-798.

23. Horváth-Puhó E, van Kassel MN, Gonçalves BP, et al. Mortality, neurodevelopmental impairments, and economic outcomes after invasive group B streptococcal disease in early infancy in Denmark and the Netherlands: a national matched cohort study. *Lancet Child Adolesc Health*. 2021;5(6):398-407.

24. Horn KA, Zimmerman RA, Knostman JD, Meyer WT. Neurological sequelae of group B streptococcal neonatal infection. *Pediatrics*. 1974;53(4):501-504.

25. Gueron-Sela N, Atzaba-Poria N, Meiri G, Marks K. The caregiving environment and developmental outcomes of preterm infants: Diathesis stress or differential susceptibility effects? *Child Dev*. 2015;86(4):1014-1030.

26. Oommen SP, Santhanam S, John H, et al. Neurodevelopmental Outcomes of Very Low Birth Weight Infants at 18–24 Months, Corrected Gestational Age in a Tertiary Health Centre: A Prospective Cohort Study. *J Trop Pediatr*. Published online 2019.

27. Spittle AJ, Morgan C. Early intervention for children with cerebral palsy. In: *Cerebral Palsy*. Springer; 2018:193-200.

28. Nelson KB, Dambrosia JM, Iovannisci DM, Cheng S, Grether JK, Lammer E. Genetic polymorphisms and cerebral palsy in very preterm infants. *Pediatr Res*. 2005;57(4):494.

29. Wu D, ZOU Y-F, XU X-Y, et al. The association of genetic polymorphisms with cerebral palsy: a meta-analysis. *Dev Med Child Neurol*. 2011;53(3):217-225.

30. Anderson PJ, Burnett A. Assessing developmental delay in early childhood—concerns with the Bayley-III scales. *Clin Neuropsychol*. 2017;31(2):371-381.

31. Jeong SU, Kim GC, Jeong HJ, et al. The Validity of the Bayley-III and DDST-II in preterm infants with neurodevelopmental impairment: a pilot study. *Ann Rehabil Med*. 2017;41(5):851.

32. Fitneva SA, Matsui T. The emergence and development of language across cultures. Published online 2015.

33. Schonfeld DJ, Demaria T. Providing psychosocial support to children and families in the aftermath of disasters and crises. *Pediatrics*. 2015;136(4):e1120-e1130.

34. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*. 2011;134(8):2197-2221.

Figure Legends:

Figure 1: Map of the multi-country iGBS long-term follow-up studies, showing details of the India site.

India was one of 5 low and middle-income countries who participated in the study.

Figure 2: Participant flow of iGBS cases and non-iGBS children recruited

Out of 79 iGBS survivors contacted, 35 consented for participation and completed the assessment. Out of 158 matched non-GBS children contacted for participation, 65 children consented and completed neurodevelopmental, vision and hearing assessments.

Figure 3: Results of NDI by domain for iGBS and non- iGBS children

Figure 3 describes impairment severity by domain in the iGBS) and non-GBS group. Unadjusted OR values are reported for no impairment versus impairment.

Table 1. Demographic and health characteristics amongst survivors of invasive Group B Streptococcal (iGBS) in infancy and comparison cohort in India

	iGBS cohort (n=35)	Non GBS cohort (n=65)	p value
Matching criteria			
Age at assessment (months), mean (SD)	62.9 (46)	56.6 (38)	0.46
Sex, n (%)			0.67
Female	19 (54)	39 (60)	
Male	16 (45)	26 (40)	
iGBS characteristics			
Clinical syndrome, n (%)			
Sepsis	35 (100)		
Meningitis	4 (11)		
GBS onset, n (%)			
Early onset (0-6 days)	33 (94)		
Late onset (7- 89 days)	2 (5)		
Birth history			
Birth weight, mean (SD)	2916 (510)	2944 (570)	0.81
Gestational age (in weeks), n (%)			0.23
≥37	31 (88)	62 (95)	
33–36	4 (11)	3 (4)	
Birth order, n (%)			<0.01
First born	30 (85)	35 (53)	
Second born or higher	5 (14)	30 (46)	
Caregiver and household characteristics			
Highest education for main caregiver, n (%)			0.23
Illiterate/ Primary/ Middle school	6 (17)	12 (18)	
High school/Intermediate	7 (20)	13 (20)	
Technical/Graduate and above	22 (62)	40 (61)	
Carer employment status, n (%)			0.02
Housework	28 (80)	41 (63)	
Income from paid employment	7 (20)	24 (36)	
Family Structure, n (%)			0.28
Joint family	11 (31)	28 (43)	
Nuclear family	24 (68)	37 (56)	
Residential classification, n (%)			0.28
Urban	18(51)	42(64)	
Rural	17(48)	23(35)	
Head of household education, n (%)			0.07
Illiterate/ Primary/ Middle school	10 (28)	15 (23)	
High school/Intermediate	8 (22)	24 (36)	
Technical/Graduate and above	17 (48)	26 (40)	

	iGBS cohort (n=35)	Non GBS cohort (n=65)	p value
Head of household occupation, n (%)			
Elementary occupation	5 (14)	13 (20)	0.59
Manual Skilled	4 (11)	3 (4)	
Sales/ Clerical	14 (40)	21 (32)	
Professionals/ Managers	12 (34)	28 (43)	
House hold monthly income, n (%)			
Less than Rs 10000	9 (25)	18 (27)	0.054
Rs. 10002-29972	16 (45)	22 (33)	
Rs. 29973-49961	9 (25)	15 (23)	
More than Rs 49962	1 (2)	10 (15)	
SES classification, n (%)			
Upper/ Upper Middle	11 (31)	27 (41)	0.29
Lower Middle	14 (40)	17 (26)	
Upper Lower/ Lower	10 (28)	21 (32)	

Table 2: Developmental outcomes amongst survivors of GBS disease and comparison cohort

	iGBS cohort (n=35)	Non GBS cohort (n=65)	p-value
Children below 42 months n (%)			
	n= 17	n= 32	
Age at assessment (months) M (SD)	28.8 (8.3)	27.3 (8.9)	0.636
Vision impairment	1 (6)	0	0.347
Hearing impairment	1 (6)	0	0.378
Bayley Scales of infant and toddler development- 3			
Cognition Composite score M (SD)	106.47 (17)	101.56 (10)	0.215
Cognition Mild impairment	0	2 (6)	0.537
Language Composite score M (SD)	99.94 (13)	104.03 (11)	0.504
Language Moderate impairment	2 (11)	1 (3)	0.124
Motor Composite score M (SD)	103.12 (7)	107.53 (10)	0.266
Motor skills Mild impairment	1 (6)	0	0.347
Socio emotional scale Composite score	105 (27)	114 (17)	0.170
Socio emotional scale interpretation Mild impairment Severe impairment	3 (17) 2 (11)	2 (6) 2 (4)	0.053
Adaptive behaviour Composite score	82 (20)	80 (10)	0.654
Adaptive behaviour scale interpretation Mild impairment	5 (29)	10 (31)	

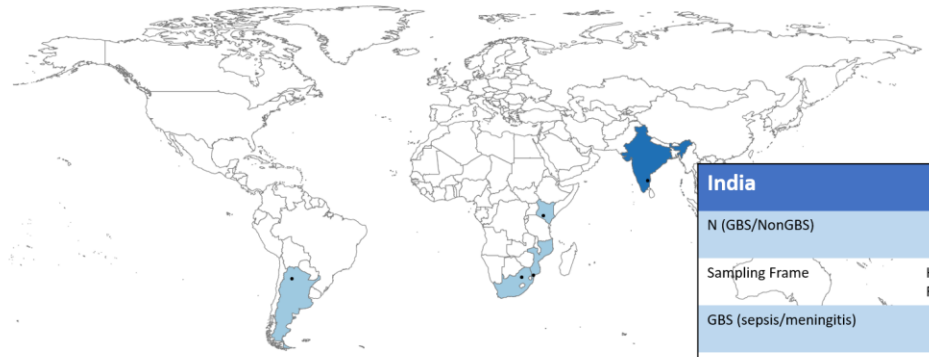
Moderate impairment Severe impairment	2 (11) 4 (23)	9 (28) 7 (22)	0.459
Child Behaviour Checklist (n=45)			
Internal interpretation n (%) Borderline Clinical range	 0 1 (6)	 2 (7) 1 (3)	 0.504
External interpretation Borderline Clinical range	 1 (6) 1 (6)	 2 (7) 4 (14)	 0.664
Total Interpretation Borderline Clinical range	 1 (6) 0	 2 (7) 3 (10)	 0.364
Any impairment	6 (35)	9 (28)	0.747
Any moderate/ severe impairment	0	1 (3)	1.000
Multi domain impairment	4 (23)	1 (3)	0.043*
Children above 42 months n (%)			
	n= 18	n=33	
Age at assessment (months) M (SD)	95.17 (43)	84.97 (34)	0.145
Vision impairment	1 (6)	2 (6)	0.718
Hearing impairment	0	0	
Wechsler's Preschool and Primary Scale of Intelligence- 4th Edition (WPPSI)/ Wechsler's scale of Intelligence- 5th Edition (WISC-5)			
Fluid reasoning Composite score M (SD)	100.19 (12.6)	107.9 (15.1)	0.553
Fluid reasoning interpretation n (%) n= 45	N=16	N=29	

Mild impairment	1 (6)	1 (3)	
Moderate impairment	1 (6)	0	0.644
Severe impairment	0	1 (3)	
Processing speed Composite score M (SD)	92.25 (13.1)	87.86 (14.0)	0.401
Processing speed interpretation n (%) n= 45			
Mild impairment	4 (25)	9 (31)	
Moderate impairment	2 (12)	6 (20)	0.710
Severe impairment	1 (6)	3 (10)	
Working memory Composite score M (SD)	100.76 (12)	107.57 (16)	0.061
Working memory interpretation n (%) n= 47			
Mild impairment	2 (12)	3 (10)	
Moderate impairment	0	3 (10)	0.697
Severe impairment	0	0	
Visual spatial Composite score M (SD)	95.12 (11.5)	95.20 (12.6)	0.461
Visual spatial interpretation n (%) n= 47			
Mild impairment	3 (17)	7 (23)	
Moderate impairment	2 (11)	1 (3)	0.790
Severe impairment	0	1 (3)	
Verbal comprehension Composite score M (SD)	89.18 (10.64)	91.93 (12.31)	0.936
Verbal comprehension interpretation n (%) n= 47	5 (29)	8 (26)	
Mild impairment	4 (23)	4 (13)	0.547
Moderate impairment	0	0	

Severe impairment			
Full scale IQ Composite score M (SD)	93.78 (10.5)	99.39 (15.2)	0.069
Full scale IQ interpretation n (%) n= 51 Mild impairment Moderate impairment Severe impairment	 3 (16) 1 (5) 0	 9 (27) 1 (3) 1 (3)	 0.714
Bruininks-Oseretsky Test of Motor Proficiency (BOT 2)			
Standard scores	48.88 (10.9)	51.9 (8.6)	0.380
Percentile rank	47.47 (30)	54.74 (25)	0.505
Interpretation n(%) n= 48 Mild impairment Moderate impairment Severe impairment	 3 (17) 0 1 (6)	 1 (3) 0 0	 0.047*
Child Behaviour Checklist			
Internal interpretation Borderline Clinical range	n= 18 1 (5) 0	n= 33 4 (12) 1 (3)	 0.768
External interpretation Borderline Clinical range	 1 (5) 1 (5)	 1 (3) 1 (3)	 1.0
Total Interpretation Borderline Clinical range	 2 (11) 0	 1 (3) 1 (3)	 0.542

Any impairment	11 (61)	16 (48)	0.558
Any Moderate/ Severe impairment	1 (5)	2 (6)	1.000
Multi domain impairment	5 (27)	9 (27)	1.0
Age groups combined n (%)			
Vision impairment	1 (5)	2 (6)	1.0
Hearing impairment	1 (2)	0	0.372
Motor skills N= 97 Mild impairment Moderate impairment Severe impairment	 4 (11) 0 1 (2)	 1 (1) 0 0	 0.033*
Cognition Mild impairment Moderate impairment Severe impairment	 6 (17) 1 (2) 0	 11 (17) 2 (3) 1 (1)	 0.908
Language Mild impairment Moderate impairment Severe impairment	 7 (20) 6 (17) 0	 9 (14) 5 (8) 0	 0.224
Behavioural impairment n (%) Mild impairment Moderate impairment	 3 (8) 0	 3 (4) 4 (6)	 0.252
Any impairment	17 (48.6)	25 (38.5)	0.397
Moderate to severe impairment	1 (2.9)	3 (4.6)	1.000
Multi domain impairment	9 (25.97)	10 (15.4)	0.285

Figure 1. Setting Description



India		
N (GBS/NonGBS)	35	65
Sampling Frame	Hospital Records	Hospital records
GBS (sepsis/meningitis)	31	4
Median Age	3 (1-14years)	
Neurodevelopmental Assessments	Bayley Scales of Infant and Toddler development, Wechsler's Preschool and Primary Scale of Intelligence, Wechsler's scale of Intelligence, Bruininks-Oseretsky Test of Motor Proficiency Second Edition	

Figure 2

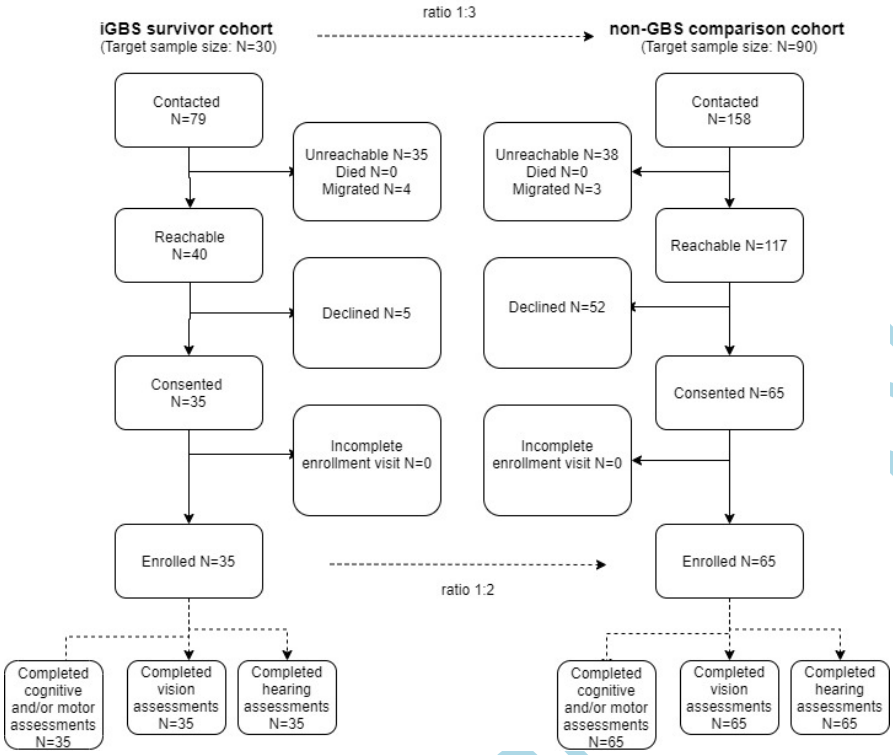


Figure 3