BMJ Open

Hospital-based sentinel surveillance for *Streptococcus pneumoniae* and other invasive bacterial diseases in India (HBSSPIBD): design and methodology

Prabu Rajkumar [iD],[1] Sukumar Bharathy,[1] C P Girish Kumar,[2]
Balaji Veeraraghavan,[3] Valsan Verghese,[4] Nivedita Gupta,[5] Boopathi Kangusamy,[1]
Muthusamy Ravi,[6] Yuvaraj Jayaraman [iD],[1] HBSSPIBD network team

For numbered affiliations see end of article.

Correspondence to
Dr Yuvaraj Jayaraman;
j_yuvan@yahoo.com

ABSTRACT

Introduction *Streptococcus pneumoniae* is one of the frequently isolated organisms and an important aetiological agent of invasive bacterial diseases (IBD) like pneumonia, meningitis and sepsis. As a measure to control the burden of IBD, the Government of India introduced Pneumoccocal Conjugate Vaccine-13 (PCV-13) in the Universal Immunization Program in high burden districts of five states in a phased manner from 2017 onwards. It is essential to understand the trend of circulating pneumococcal serotypes associated with IBD in the prevaccination and postvaccination scenarios to decide on the expansion of vaccination programmes and PCV reformulation. This manuscript describes the protocol for hospital-based sentinel surveillance for *S. pneumoniae* and other organisms causing IBD across various geographical regions in India.

Methods and analysis Hospital-based surveillance is established in selected hospitals to recruit children aged 1–59 months with symptoms of pneumonia and other IBD. Diagnostic criteria were adapted from standard WHO case definitions. Case Report Forms (CRFs) are used to collect data from the enrolled children. Blood, cerebrospinal fluid (CSF) and other normally sterile body fluids are collected and subjected to microscopy, cytology, latex agglutination, biochemistry, bacteriological culture and real-time PCR as applicable. Pneumococcal isolates are serotyped and tested for assessing antimicrobial resistance patterns. Data will be analysed by simple descriptive statistics to estimate the proportion of pneumonia and other IBD due to *S. pneumoniae*, *Hemophilus influenzae* type b and *Neisseria meningitidis*. Prevalence of bacterial infection, circulating pneumococcal serotypes, antibiotic resistance patterns, serotype variability across seasons and regions will be described in terms of percentage with 95% confidence interval.

Ethics and dissemination The institutional review boards of the coordinating centre, all sentinel sites, regional and national reference laboratories approved the project. The results will be published in peer-reviewed journals and shared with stakeholders for deciding on revising vaccination strategy appropriately.

Strengths and limitations of this study

► The current surveillance project is the largest in India being conducted after Pneumoccocal Conjugate Vaccine (PCV) introduction under Universal Immunization Program in representative geographical regions to estimate the proportion of childhood pneumonia and invasive bacterial diseases (IBDs) associated with *Streptococcus pneumoniae*, *Hemophilus influenzae* type b and *Neisseria meningitidis*.

► The burden estimates and information on circulating pneumococcal serotypes generated from this surveillance will provide necessary inputs for the policy-makers in India to make informed decisions on the need for reformulation of the existing PCV.

► This surveillance platform also assesses the impact of pentavalent vaccine on meningitis due to *Hemophilus influenzae* type b.

► This surveillance study did not include any site from North-eastern India, hence the burden of IBD from that region will not be obtained.

INTRODUCTION

Globally, *Streptococcus pneumoniae* is the most common cause of pneumonia and accounts for approximately 36% of all childhood pneumonia.[1] Besides, it is an important aetiological agent for other invasive bacterial diseases (IBD) such as meningitis, bacteraemia and sepsis.[2] The WHO estimated that 0.7 to 1 million children aged under 5 years die from pneumococcal disease every year.[3] Globally pneumococcal conjugate vaccine (PCV) immunisation significantly reduced the incidence of invasive pneumococcal diseases (IPD) in the vaccinated groups as well as in non-vaccinated groups due to herd immunity.[4] Additionally, the PCV immunisation altered the trends of circulating pneumococcal serotypes.[4] A recent review of 21 studies from various geographical regions concluded that more than 60% of IPD cases

were due to PCV serotypes with 19A (21.8%) as the most common.[5] After the introduction of higher valent PCVs, IPD due to 19A decreased (14.2%).[6] The overall contribution of IPD cases due to non-vaccine serotypes (NVT) was 42.2% but varied by region that is, 57.8% in North America, 71.9% in Europe, 45.9% in Western Pacific, 28.5% in Latin America, 42.7% in South Africa and 9.2% in Eastern Mediterranean countries.[6] Predominant NVT are 22F, 12F, 33F, 24F, 15C, 15B, 23B, 10A and 38[6] but there was little or no change in overall carriage prevalence due to replacement effects of NVT colonisation in nasopharynx.[7] On the other hand, the emergence of NVT meningitis cases was observed in several countries especially in France after PCV implementation.[8] In contrast, no increase in cases of bacteraemic pneumonia and pneumonia with pleural effusion was seen in France and England.[9 10] A small increase in the number of empyema cases was observed in Germany.[11] The serotype replacement did not show any effect in the incidence of non-invasive pneumonia and otitis media among Dutch children.[12]

India has the highest burden of pneumococcal disease (27%) with 0.35 million deaths due to pneumonia in 2010 among children under 5 years of age.[13] In 2015, 56 per 100 000 children aged 1–59 months died due to pneumococcal infection with the highest number of deaths observed in the states of Uttar Pradesh and Bihar.[14] Among the 1.6 million of severe cases with IPD, more than 97% were pneumococcal pneumonia.[14] Few multicentric studies documented the significant presence of IPD among under-five children and also generated data on prevailing serotypes of *S. pneumoniae* in various parts of the country.[15 16] However, data generated in these studies were more than a decade old and conducted before PCV introduction. Further, the differences in study methods like the choice of the study population, study design, case enrolment strategy and laboratory diagnostic methods did not adequately address the knowledge gap and were not able to provide necessary inputs for programme managers for developing appropriate pneumococcal disease control policies.[16] PCV-13 was introduced in the Universal Immunization Program (UIP) of India in 2017 in Himachal Pradesh, Bihar and Uttar Pradesh states. In 2018, PCV-13 was introduced in Madhya Pradesh and Rajasthan states with further phased expansion planned across the country.[17]

Currently implemented PCV-13 vaccine is expected to provide coverage against 74% of serotypes and also reduce antimicrobial resistance among IPD serotypes in India.[17] Penicillin resistance among meningeal isolates is a serious problem, but 75% of resistant serotypes (14, 19F, 6B, 6A and 23F) are already covered by PCV 13.[18] Therefore, it is necessary to study the trends of circulating pneumococcal serotypes associated with IBD in the prevaccination and postvaccination scenarios. Data on changes in the circulating pneumococcal serotypes and resistance pattern is required to decide the reformulation of PCV. Hence, the hospital-based sentinel surveillance for *S. pneumoniae* and other invasive bacterial diseases (HBSSPIBD) among children aged 1–59 months in India was initiated to provide

necessary inputs to the introduction of PCV across India. Phase 1 of this project was supported by the Ministry of Health and Family Welfare (MoHFW), Government of India (GoI) with funding from the Global Alliance for Vaccines and Immunizations through the United Nations Development Programme (UNDP). Indian Council of Medical Research-National Institute of Epidemiology (ICMR-NIE), Chennai coordinated the phase 1 activity which was conducted between December 2016 and June 2018. Phase 2 of the HBSSPIBD study funded by UNDP and ICMR is being conducted in 14 selected hospitals across India. Further, a grant from the Bill & Melinda Gates Foundation for meningitis surveillance strengthening enabled the establishment of regional reference laboratories (RRL) for molecular testing of CSF and provision for molecular serotyping at the National Reference Laboratory (NRL). In this manuscript, we describe the framework and protocol of the ongoing multi-site HBSSPIBD study.

METHODS AND ANALYSIS
Objectives
Primary objectives
1. To identify and type the bacteria *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Hemophilus influenzae* type b causing pneumonia, meningitis and other IBD in children aged 1–59 months attending selected hospital-based sentinel sites after introduction of PCV in the UIP in India.
2. To study the trend of pneumococcal serotype distribution and antimicrobial resistance patterns.

Secondary objectives
1. To assess the impact of the pentavalent vaccine on *H. influenzae* type b meningitis.
2. To identify the risk factors for *S. pneumoniae*, *N. meningitidis* and *H. influenzae* type b infections.

Study design
This is a cross-sectional multi-site hospital-based surveillance study being conducted for 2 years from January 2019 onwards in selected tertiary care hospitals in India. This study is coordinated by ICMR-NIE, Chennai. Sawai Man Singh (SMS) Medical College, Jaipur and ICMR-NIE are functioning as RRLs for testing the CSF samples by real-time PCR. The Department of Clinical Microbiology, Christian Medical College (CMC), Vellore serves as the NRL for the surveillance network and administers the external quality assurance (EQA) programme for the participating sentinel sites. All the sites follow the standardised study protocol for clinical and laboratory procedures.

Selection of surveillance sites
Hospital-Based Sentinel Surveillance of Bacterial Meningitis study[19] provided the required platform to set up the HBSSPIBD network across India. This project intends to build capacity in performing active sentinel surveillance

for *S. pneumoniae* in 14 hospitals across India. The sentinel sites were selected based on the following criteria:

a. Location of hospital in the representative geographical region.
b. Willingness of the study site to participate in the surveillance activity.
c. Capacity to identify all suspected cases of pneumonia and IBD including bacterial meningitis and sepsis in children aged 1–59 months.
d. Availability of facilities such as microbiological culture, digital X-ray and the patient census for the past 1 year, which was assessed using a structured checklist.

In addition to eleven new sites, three sites from phase 1 surveillance were also included in the current surveillance network namely, (1) Government Medical College, Trivandrum; (2) Lokmanya Tilak Municipal General Hospital & Medical College, Mumbai and (3) All India Institute of Medical Sciences, Jodhpur (figure 1).

Study population

Children aged 1–59 months admitted to the selected sentinel site with suspected clinical conditions for pneumonia, meningitis and sepsis are recruited after getting
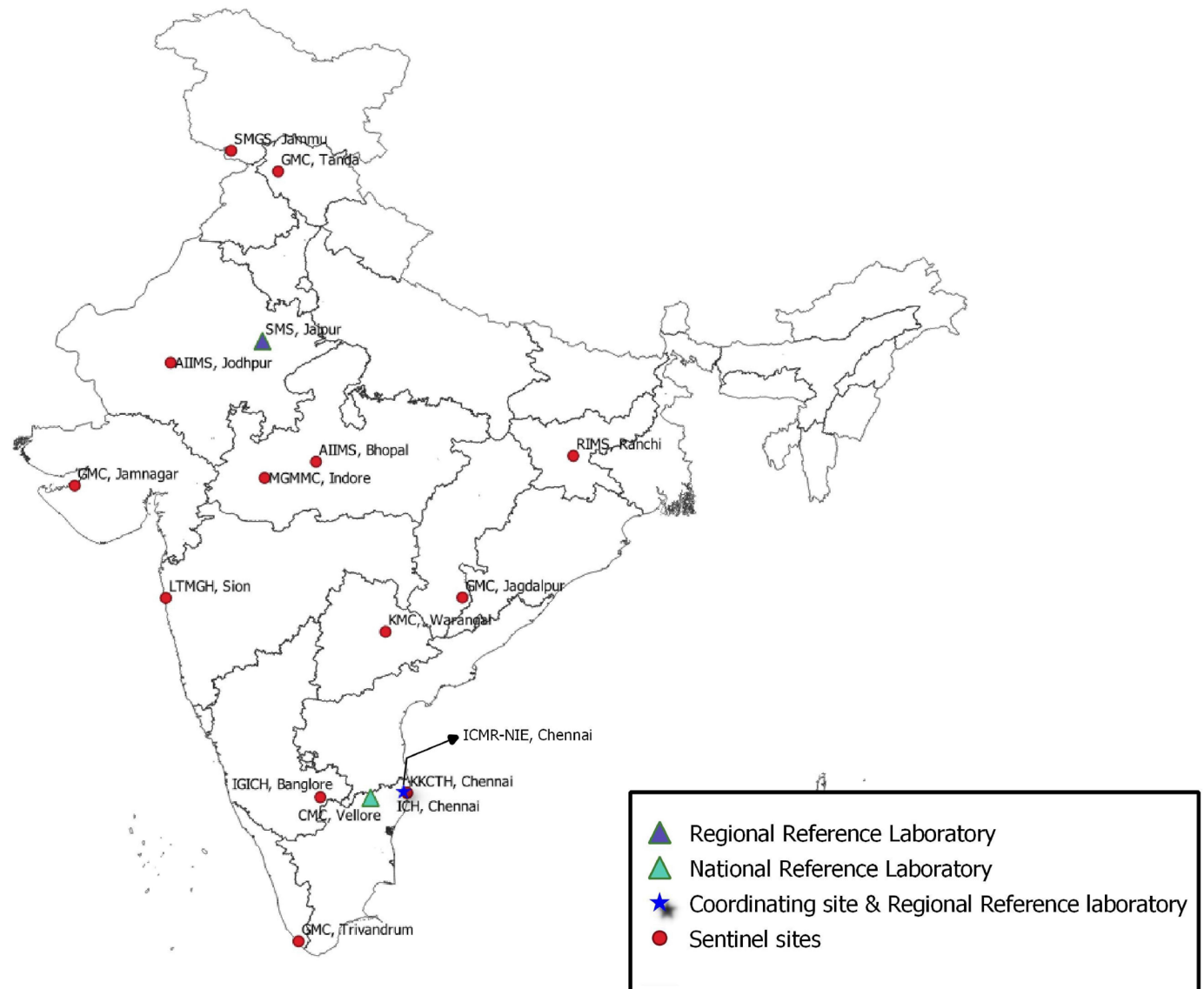
Figure 1 Hospital-based sentinel surveillance for *Streptococcus pneumoniae* and other invasive bacterial diseases (HBSSPIBD) network. (1) Government Medical College (GMC), Trivandrum; (2) Kanchi Kamakoti CHILDS trust Hospital (KKCTH), Chennai; (3) Institute of Child health and hospital for children (ICH), Chennai; (4) Indira Gandhi Institute of Child Health (IGICH), Bangalore; (5) Lokmanya Tilak Municipal General Hospital (LTMGH), Sion, Mumbai; (6) Mahatma Gandhi Memorial Medical College (MGMMC), Indore; (7) All India Institute of Medical Sciences (AIIMS), Bhopal; (8) All India Institute of Medical Sciences (AIIMS), Jodhpur; (9) Dr Rajendra Prasad Government Medical College (Dr.RPGMC), Tanda; (10) Sri Maharaja Gulab Singh (SMGS) Hospital, Jammu; (11) M. P. Shah Government Medical College, Jamnagar (GMC, Jamnagar); (12) Kakatiya Medical College, Warangal (KMC, Warangal); (13) Late Baliram Kashyap Memorial Government Medical College, Jagdalpur (GMC, Jagdalpur); (14) Rajendra Institute of Medical Sciences, Ranchi (RIMS, Ranchi).

informed consent from the parent or legally acceptable representative (LAR).

Study team

The surveillance activity was carried out by a dedicated project team consisting of a public health nurse, a laboratory technical assistant and a laboratory technician. The study team was supervised by the site investigators from paediatrics and microbiology departments.

Data collection

We use carbonless paper-based Case Report Forms (CRFs) for collecting clinical and laboratory data.

a. Clinical CRF is filled by the public health nurse under the guidance of a medical officer which includes demographic details, symptoms, clinical history, vaccination history, details of clinical examination, provisional diagnosis and patient outcome. Demographic details are obtained from the parent or LAR. The child's clinical history before admission is extracted from the case sheet of the patient or collected from the care-taker of the child for missing information. Treatment with antibiotics before hospitalisation is confirmed by verifying the receipts or records. History of vaccination is collected from immunisation cards or parent recall. The diagnosis and outcome-related information are obtained from the hospital records.

b. Laboratory CRF is filled by the laboratory technical assistant, with details regarding specimen collection, storage, transportation, laboratory test results and antibiotic resistance pattern.

c. Chest X-ray report form is filled by the public health nurse for pneumonia cases with guidance from the hospital radiologist.

d. RRL Form is used to report the results of real-time PCR testing on CSF samples.

e. NRL form is used to report results of PCR, serotyping and Minimum Inhibitory Concentration testing.

Case recruitment in the sentinel sites

On each day of surveillance, the list of children aged 1–59 months admitted with suspected pneumonia/meningitis/sepsis is obtained from the admission registry. The public health nurse screens such children admitted in the paediatrics wards and intensive care units/emergency rooms and orthopaedics wards within 24 hours of admission for assessing the eligibility for enrolment (table 1).

In addition to recruitment of cases from the wards, age-eligible children from whom *S. pneumoniae*, *H. influenzae* type b or *N. meningitidis* get isolated from normally sterile body fluids (blood, CSF, pleural fluid, bronchoalveolar lavage (BAL), joint fluid, etc) are enrolled (figure 2).

**Case definitions** (adapted from WHO guidelines[20 21]):

a. *Suspected pneumonia:* Tachypnoea (>60 breaths/min if less than 2 months of age, >50 breaths/min if 2 months to <12 months of age and >40 breaths/min if 12 months

Suspected condition	Inclusion criteria		Exclusion criteria
Suspected pneumonia	History of cough or difficulty in breathing, accompanied by increased respiratory rate* and one or more of:	1. Chest indrawing. 2. Central cyanosis. 3. Severe respiratory distress. 4. Unable to drink/breastfeed and/or vomiting everything. 5. Convulsions, lethargy or unconsciousness. 6. Stridor in a calm child.	1. Recurrent wheezing illness and meeting pneumonia case definition only by respiratory rate criteria. 2. Hospitalisation for different illness within past 10 days.
Suspected meningitis	A clinically unwell present with any of the following:	1. Neck stiffness. 2. Bulging fontanel (If the fontanel is open). 3. Altered OR reduced level of consciousness. 4. Prostration. 5. Lethargy. 6. Convulsion.	1. Post-operative or post lumbar puncture meningitis. 2. Febrile seizure or a seizure recurrence in a child with a documented seizure disorder.
Suspected sepsis	A patient with one or more of the following	1. Axillary temperature <36°C or ≥38°C. 2. Stopped feeding well (less than half of what infant usually takes). 3. Unable to drink. 4. Too weak/short of breath. 5. Incessant vomiting. 6. Lethargy. 7. Severe acute malnutrition.†	1. Hospitalisation for different illness within past 10 days.

*Increased respiratory rate for age is defined as >60 breaths/min if <2 months of age, >50 breaths/min if 2 months to <12 months age and >40 breaths/ min if 12 months to <5 years age.
†Severe acute malnutrition is defined according to the WHO definition.
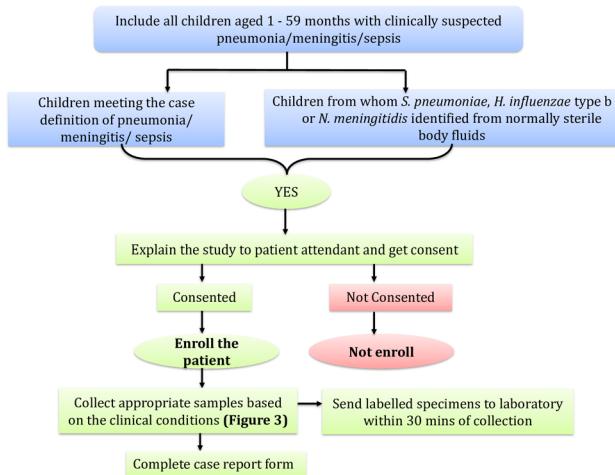
Figure 2 Case recruitment flow chart for Hospital based sentinel surveillance for *S. pneumoniae* and other invasive bacterial diseases) in India study. *H. influenzae*, *Hemophilus influenzae* type b; *N. meningitidis*, *Neisseria meningitidis*; *S. pneumoniae*, *Streptococcus pneumoniae*.

to <5 years of age) and/or cough and/or difficulty in breathing.

b. *Bacterial pneumonia:* A suspected case of pneumonia with confirmed aetiology by isolation of bacteria from a normally sterile site. For example, blood, pleural fluid or BAL and so on.

c. *Radiological pneumonia*: A suspected case of pneumonia with changes on chest X-ray that meet WHO standard criteria for endpoint consolidation.[22]

d. *Clinically suspected meningitis*: A child presenting with sudden onset of fever ≥38.5°C rectal or 38.0°C axillary with one of the following signs: neck stiffness, bulging fontanel, altered or reduced level of consciousness, prostration or lethargy, convulsions without documented seizure disorder.

e. *Clinically probable bacterial meningitis*: A child presenting with suspected meningitis and CSF examination showing the turbid appearance, leucocytes >100 cells/mm^3 or 10-100 cells/ mm^3 with either decreased glucose (<40 mg/dL) or elevated protein (>100 mg/dL) levels.

f. *Confirmed meningitis*: A confirmed case of meningitis is a suspected or probable case with *S. pneumoniae, H. influenzae* or *N. meningitidis* isolated from CSF and/or blood or detected in CSF by PCR or latex agglutination.

g. *Sepsis*: A case with a history of fever ≥38.0°C or hypothermia <36°C within the past 5 days with the presence of danger signs (inability to drink, lethargy, hypothermia, severe malnutrition, convulsions) and without any evidence of meningitis or pneumonia.

Induction training

Laboratory investigators and project laboratory staff received induction training at the NRL on laboratory procedures for sample collection, transportation, processing in the laboratory, testing and documentation and laboratory-based case recruitment.[23] Clinical investigators and public health nurses received training at

ICMR- NIE (coordinating centre) on recruitment of cases (table 1), data capture using the CRF, online data entry and management.

Sample collection and processing

Sample collection and processing framework is summarised in figure 3. Under aseptic conditions, 2–5 mL of blood samples are collected into commercial blood culture bottles and incubated at 37°C in automated BACT/Alert (BioMerieux) or BACTEC (Becton Dickinson) system for 5 days. For suspected meningitis cases, lumbar puncture (LP) is performed and 0.5 to 2 mL of CSF is collected and made into 3 aliquots. One aliquot each is used for microbiology (white cell count, Gram staining, culture and latex agglutination test) and biochemistry (protein and glucose). The third aliquot is stored at −80°C in sentinel site until shipment to RRL for real-time PCR. CSF samples from AIIM S, Jodhpur; SMGS, Jammu and Dr. RPGMC, Tanda are shipped to SMS, Jaipur whereas samples from rest of the sentinel sites are shipped to ICMR-NIE for real-time PCR testing. Positive samples from RRLs are sent to NRL for molecular serotyping. Other sterile body fluids, if collected are aliquoted (300–500 µL) and stored at −80°C for PCR testing at NRL.

CSF and other sterile body fluids are plated directly onto 5% sheep blood agar and chocolate agar plates and incubated at 35–37°C in CO_2 enriched environment for 16–18 hours. Plates are screened for growth of *S. pneumoniae, H. influenzae* and *N. meningitidi*s and suspected isolates are subjected to microbiological confirmation as per standard protocols.[23] CSF samples are subjected to real-time PCR detection of *S.pneumoniae, H. influenzae* type b and *N. meningitidis* at RRL following Centers for Disease Control and Prevention protocols.[23] All isolates and PCR-positive sterile body fluids are subjected to serotyping by Quellung/PCR protocols.

Nasopharyngeal (NP) swabs are collected in skim milk, tryptone, glucose and glycerol (STGG) medium (maintained at 4°C) and stored at −80°C until shipment to NRL. At NRL, NP swabs are culture enriched followed by real-time PCR targeting *lyt*A and sequential multiplex PCR (SMPCR) for detection of pneumococcal serotypes.[24] An aliquot of the NP-STGG specimen is stored at −80°C for future quantification studies.

Pneumococcal isolates are re-confirmed at NRL and serotyped by Quellung reaction using antisera obtained from Staten's Serum Institute (Copenhagen, Denmark) and the positive specimens are serotyped by SMPCR. Additionally, molecular serotyping of all real-time PCR positive CSF samples using TaqMan array card is performed at NRL. Antimicrobial susceptibility testing for pneumococcal isolates are done by Vitek system (Biomerieux) for penicillin, cefotaxime, levofloxacin, erythromycin, linezolid, vancomycin and co-trimoxazole as per WHO protocols and results are interpreted as per the Clinical Laboratory Standards Institute guidelines.[23 25]
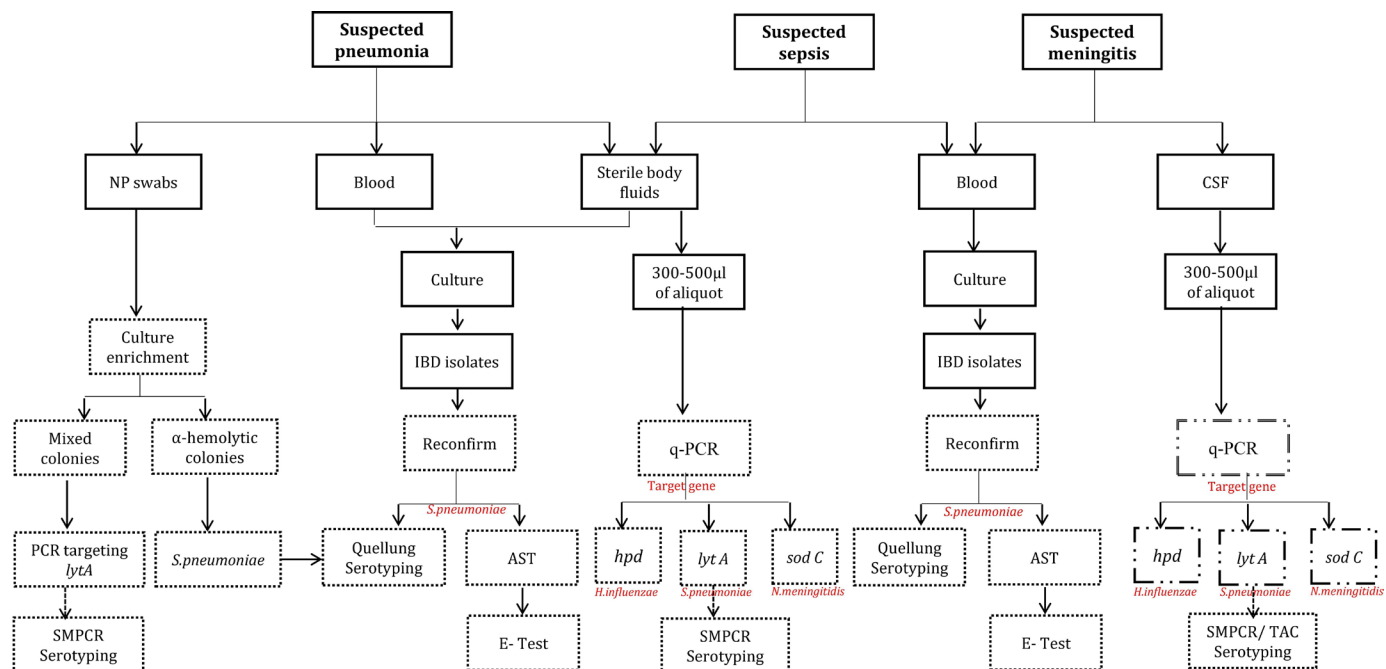
Figure 3 Algorithm for laboratory diagnosis of bacterial pneumonia and invasive bacterial disease for hospital based sentinel surveillance for *Streptococcus pneumoniae* and other invasive bacterial diseases in India study. — —Sentinel site activities; —··—··Regional Reference Laboratory activity; ……National Reference Laboratory activity. AST, antimicrobial sensitivity test; CSF, cerebrospinal fluid; *H. influenzae*, *Hemophilus influenzae* type b; IBD, invasive bacterial diseases; *N. meningitidis*, *Neisseria meningitidis*; NP, nasopharyngeal; q-PCR, real time PCR; SMPCR, sequential multiplex PCR; *S. pneumoniae*, *Streptococcus pneumoniae*; TAC, TaqMan array card.

Quality control and assurance
Before initiation
Standard operating procedures (SOP) for all the components are available at each site. The site investigators and respective project staff were trained on SOPs for uniform execution of the project. The training and certification activities were supervised by the coordinating centre for assuring the quality of the process.

After study initiation
a. *Monitoring and evaluation visits*: The investigators/designated officers visit each site once in 6 months and assess compliance with the study protocols using a standard checklist. Deviations/shortfalls if any are noted and appropriate recommendations are given to the investigators for corrective action.
b. Quality assurance for laboratory procedures: CMC, Vellore, a WHO RRL is conducting the External Quality Assurance System (EQAS) for this surveillance. Each laboratory participating in the EQAS receives four sets of EQA samples (one in each quarter) and feedback on their performance is provided.
c. Quality Assurance for X-ray diagnosis: The digital X-ray is read and reported by two independent physicians/radiologists. In case of any disagreement, umpire reading by a senior radiologist is done. The decision of the umpire reading is final.

Data management
ICMR-NIE is the central data management centre for this project. Completed CRFs are reviewed by the site investigators and entered in the eCRF developed using REDCap[26] and hosted at ICMR-NIE server. In addition, the original paper-based CRFs are received at ICMR-NIE for double data entry and quality checks. Discrepancies if any, are resolved in consultation with the respective sites. A validated dataset is used for analysis.

Data analysis
Descriptive analyses will be performed to describe demographic (age group, gender, state), clinical (duration of illness, signs and symptoms), treatment information and outcome of the children enrolled in this surveillance.

Analysis plan for primary objectives
Prevalence and type of bacterial infections (pneumonia, meningitis and sepsis) due to *S. pneumoniae*, *H. influenzae* type b and *N. meningitidis* will be presented as a percentage with 95% CI.

The trend of pneumococcal serotype distribution across seasons and regions will be analysed and presented as a percentage with 95% CI. Pneumococcal serotypes will be categorised as a vaccine (serotypes included in PCV7, PCV 10 and PCV 13) and NVT. Trends of antimicrobial resistance patterns of meningeal and non-meningeal pneumococcal isolates will be presented as a percentage with 95% CI.

Analysis plan for secondary objectives
Vaccine effectiveness (VE) will be measured by calculating the risk of disease among the vaccinated and unvaccinated persons and determining the percentage reduction

in risk of disease among the vaccinated persons relative to unvaccinated persons. The basic formula is

$$VE = \frac{Risk\,among\,unvaccinated\,group - risk\,among\,vaccinated\,group}{Risk\,among\,unvaccinated\,group}$$

The number of bacterial infections among the exposed and unexposed to risk factors will be analysed by Chi-Square test to identify any association. Further, prevalence odds ratio will be calculated to measure the risk.

Expected outcomes
Primary outcomes
1. Proportion and type of *S. pneumoniae, H. influenzae* type b and *N. meningitidis* among the suspected children admitted with pneumonia, meningitis and other IBD in children aged between 1 and 59 months in the selected sentinel sites.
2. Current trend of circulating pneumococcal serotypes and antimicrobial resistance patterns.

Secondary outcomes
1. Proportion of children with *H. influenzae* type b meningitis and their pentavalent vaccination status.
2. Risk factors associated (age group, duration of illness, clinical signs and symptoms, etc) with *S. pneumoniae, H. influenzae* type b and *N. meningitidis* infections.

Patient and public involvement
The patients/public were not involved during the development of the protocol.

Ethics and dissemination
The final study protocol, including the final version of other essential documents were peer-reviewed and approved by the following ethics committees: Institutional Human Ethics Committee of ICMR-NIE (NIE/IHEC/2 01 607–01 dated 22.5.2018); Institutional Review Board (IRB) of Christian Medical College, Vellore (IRB:11 477 (OBSERVE) dated:22.8.2018); Institutional Human Ethics Committee of AIIMS, Jodhpur (AIIMS/IEC/2018/600 dated 29.8.2019); Institutional Human Ethics Committee of AIIMS, Bhopal (IHEC-LOP/2018/EF0089 dated 10.7.2018); Ethics and Scientific Review Committee of M.G.M. Medical College & M.Y. Hospital, Indore dated 2.01.2019; Institutional Ethics Committee Human Research of Lokmanya Tilak Municipal Medical College & General Hospital, Sion, Mumbai dated 23.10.2018; Human Ethics Committee of Government Medical College, Trivandrum (HEC.No.11/74/2018/MCT dated 11.9.2018); Institutional Ethics Committee of Dr. Rajendra Prasad Government Medical College, Kangra at Tanda (IEC/2019–93 dated 10.1.2019); Institutional Ethical Committee of Indira Gandhi Institute of Child Health, Bangalore (IGICH/ACA/EC/06/2018–19 dated 13.11.2018); Institutional Ethics Committee of Government Medical College, Jammu (IEC/2019/723 dated 25.4.2019); Institutional Review Board (IRB) Ethics committee of Kanchi Kamakoti CHILDS Trust Hospital & The CHILDS Trust Medical Research Foundation dated 9.10.2018; Institutional Ethics Committee of Madras Medical College, Chennai dated 5.6.2018. Institutional Ethics Committee of Late Baliram Kashyap memorial Government Medical College, Jagdalpur (Lt.No.1214/G.M.C.J/Esstt/19 dated 22.02.2019); Kakatiya Institutional Ethics Committee of Kakatiya Medical College, Warangal (KIEC/KMC/2016/006 dated 15.05.2019); Institutional Ethics Committee of M. P. Shah Government Medical College, Jamnagar (IEC/Certi/65/02/2019 dated 11.04.2019); Institutional Ethics Committee of Rajendra Institute of Medical Sciences, Ranchi dated 21.12.2019; Institutional Ethics Committee of S.M.S. Medical College, Jaipur (Lt.No.3954 MC/EC/2018 dated 1.8.2018).

The study does not envisage the collection of extra information/biological samples. Test like latex agglutination is not routinely done at some sites, hence this study strengthens the capacity of the participating institutions by establishing the testing facilities. The test results are shared with the treating physicians for appropriate diagnosis and case management. Treatment of all patients is provided as part of routine care of the participating institutions and no intervention is planned as part of this project.

Privacy of the participants and confidentiality of the data are being ensured according to the national guidelines. Written informed consent is obtained from the LAR for participation of their children and for using leftover samples for future tests.

We will disseminate the study findings by publishing manuscripts in peer-reviewed scientific journals. Due to the interdisciplinary nature of the study findings, we will also present in the national and international conferences, which will attract other researches in the field for collaboration. The study findings will be submitted to the MoHFW (GoI), which will help them in deciding the expansion strategy for PCV roll out in India as a part of the UIP.

DISCUSSION
India has the highest burden of pneumococcal disease worldwide. But there is a huge gap in the epidemiological knowledge of IBD burden and pneumococcal serotype distribution among children in India, which needs to be addressed for successful implementation of vaccine policy in the county.[17] The current study will estimate the burden of pneumonia and IBD among children aged 1–59 months and document the circulating pneumococcal serotypes including emerging serotypes. Hence, the study findings will provide critical information for informing the immunisation policy including the decision on a reformulation of PCV.

We established the study sites both in PCV-introduced states, such as Himachal Pradesh, Madhya Pradesh and Rajasthan, and yet to be introduced states, which will help us to compare the burden of pneumococcal disease and serotype distribution in the two settings. Additionally,

laboratory capacity for diagnosis of pneumococcal diseases will be strengthened in the study sites. This study is a good example of different stakeholders joining hands to work with a unified approach to generate meaningful data that will be useful for the country's immunisation policy.

Our study has certain limitations. Being a hospital-based study, the burden might underestimate the problem in the community. Thirteen out of the fourteen study sites are government institutions and the healthcare is provided free of cost to the patients. However, private clinics in the study area also treat some proportion of infected children, who do not get captured as part of this study. Further, healthcare - seeking behaviour in the population and referral practices to the study hospitals from primary and secondary healthcare settings in each state may influence caseload in surveillance.[27] Though we attempted to include study sites representing various regions, the North-Eastern region of India is not represented. A major proportion of the children are admitted with prior antibiotic treatment, which may influence the culture yield. Hence, we planned to lay more emphasis on molecular diagnosis in surveillance.

Despite the above-mentioned limitations, the use of common definitions, standard protocol and data reporting forms will ensure data collection in a uniform fashion and enable comparison and interpretation of results across the sites.

CONCLUSION

This project represents the largest surveillance activity after the introduction of PCV to estimate the burden of *S. pneumoniae* and other infections causing pneumonia and other IBDs in India. The sustainability of PCV vaccination in India will depend on the demonstrable effect of PCV in reducing childhood morbidity and mortality. Hence it is important to measure the prevalence of pneumococcal diseases and serotypes before and following the PCV roll-out in India. The results from more representative areas in the country will also help to make decisions on vaccine reformulation. Continuous monitoring is required to assess the impact of pneumococcal vaccination in India.

Author affiliations
[1]Health Systems Research, ICMR-National Institute of Epidemiology, Chennai, India
[2]Laboratory Division, ICMR-National Institute of Epidemiology, Chennai, India
[3]Department of Clinical Microbiology, Christian Medical College, Vellore, Tamil Nadu, India
[4]Department of Child Health, Christian Medical College and Hospital Vellore, Vellore, Tamil Nadu, India
[5]Epidemiology and Communicable Diseases, Indian Council of Medical Research, New Delhi, India
[6]Computing and Information Science, ICMR-National Institute of Epidemiology, Chennai, India

ORCID iDs
Prabu Rajkumar http://orcid.org/0000-0001-9839-800X
Yuvaraj Jayaraman http://orcid.org/0000-0003-4017-8404

REFERENCES

1 Fletcher MA, Schmitt H-J, Syrochkina M, *et al*. Pneumococcal empyema and complicated pneumonias: global trends in incidence, prevalence, and serotype epidemiology. *Eur J Clin Microbiol Infect Dis* 2014;33:879–910.

2 Mook-Kanamori BB, Geldhoff M, van der Poll T, *et al*. Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev* 2011;24:557–91.

3 Ceyhan M, Ozsurekci Y, Aykac K, *et al*. Economic burden of pneumococcal infections in children under 5 years of age. *Hum Vaccin Immunother* 2018;14:106–10.

4 Choi YH, Andrews N, Miller E. Estimated impact of revising the 13-valent pneumococcal conjugate vaccine schedule from 2+1 to 1+1 in England and Wales: a modelling study. *PLoS Med* 2019;16:e1002845.

5 Cui YA, Patel H, O'Neil WM, *et al*. Pneumococcal serotype distribution: a snapshot of recent data in pediatric and adult populations around the world. *Hum Vaccin Immunother* 2017;13:1229–41.

6   Balsells E, Guillot L, Nair H, *et al*. Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis. *PLoS One* 2017;12:e0177113.

7   Le Polain De Waroux O, Edmunds WJ, Takahashi K, *et al*. Predicting the impact of pneumococcal conjugate vaccine programme options in Vietnam. *Hum Vaccin Immunother* 2018;14:1939–47.

8   Ouldali N, Levy C, Varon E, *et al*. Incidence of paediatric pneumococcal meningitis and emergence of new serotypes: a time-series analysis of a 16-year French national survey. *Lancet Infect Dis* 2018;18:983–91.

9   Ouldali N, Levy C, Minodier P, *et al*. Long-Term association of 13-valent pneumococcal conjugate vaccine implementation with rates of community-acquired pneumonia in children. *JAMA Pediatr* 2019;173:362.

10 Thorrington D, Andrews N, Stowe J, *et al*. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. *BMC Med* 2018;16:13.

11 Liese JG, Schoen C, van der Linden M, *et al*. Changes in the incidence and bacterial aetiology of paediatric parapneumonic pleural effusions/empyema in Germany, 2010-2017: a nationwide surveillance study. *Clin Microbiol Infect* 2019;25:857–64.

12 Fortanier AC, Venekamp RP, Hoes AW, *et al*. Does pneumococcal conjugate vaccination affect onset and risk of first acute otitis media and recurrences? a primary care-based cohort study. *Vaccine* 2019;37:1528–32.

13 Farooqui H, Jit M, Heymann DL, *et al*. Burden of severe pneumonia, pneumococcal pneumonia and pneumonia deaths in Indian states: modelling based estimates. *PLoS One* 2015;10:e0129191.

14 Wahl B, O'Brien KL, Greenbaum A, *et al*. Burden of Streptococcus pneumoniae and Haemophilus influenzae type B disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. *Lancet Glob Health* 2018;6:e744–57.

15 Thomas K. Prospective multicentre hospital surveillance of *Streptococcus pneumoniae* disease in India. *Lancet* 1999;353:1216–21.

16 Bravo LC, Asian Strategic Alliance for Pneumococcal Disease Prevention (ASAP). Overview of the disease burden of invasive pneumococcal disease in Asia. *Vaccine* 2009;27:7282–91.

17 Manoharan A, Manchanda V, Balasubramanian S, *et al*. Invasive pneumococcal disease in children aged younger than 5 years in India: a surveillance study. *Lancet Infect Dis* 2017;17:305–12.

18 Verghese VP, Veeraraghavan B, Jayaraman R, *et al*. Increasing incidence of penicillin- and cefotaxime-resistant *Streptococcus pneumoniae* causing meningitis in India: Time for revision of treatment guidelines? *Indian J Med Microbiol* 2017;35:228.

19 Jayaraman Y, Veeraraghavan B, Chethrapilly Purushothaman GK, *et al*. Burden of bacterial meningitis in India: preliminary data from a hospital based sentinel surveillance network. *PLoS One* 2018;13:e0197198.

20 WHO. Acute respiratory infections in children: case management in small hospitals in developing countries. In: *A manual for doctors and other senior health workers*. Geneva: World Health Organization, 1990.

21 World Health Organization. (who) recommended surveillance standards for surveillance of selected vaccine-preventable diseases, 1999. Available: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/sentinel/meningitis_surveillance/en/ [Accessed 20 Sep 2019].

22 Cherian T, Mulholland EK, Carlin JB, *et al*. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bull World Health Organ* 2005;83:353–9.

23 WHO. *Laboratory Methods for the Diagnosis of Meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenza, WHO manual*. 2nd edn. Geneva: World Health Organization, 2011.

24 da Gloria Carvalho M, Pimenta FC, Jackson D, *et al*. Revisiting pneumococcal carriage by use of broth enrichment and PCR techniques for enhanced detection of carriage and serotypes. *J Clin Microbiol* 2010;48:1611–8.

25 Clinical and Laboratory Standards Institute (CLSI). *Performance standards for antimicrobial susceptibility testing; 23rd informational supplement CLSI document M100-S23*. Wayne, PA: CLSI, 2013.

26 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.

27 Knoll MD, Moïsi JC, Muhib FB, *et al*. Standardizing surveillance of pneumococcal disease. *Clin Infect Dis* 2009;48:S37–48.