

The Remaining Challenges to Laboratory-based Surveillance of Invasive Pneumococcal Disease

Microbiologist's Perspective

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Limited information is available on the outline of invasive diseases caused by *Streptococcus pneumoniae* among the underprivileged children in India. Estimation of Invasive Pneumococcal Disease (IPD) and Pneumonia depends mainly on hospital-based clinical surveillance data. Data on serotype prevalence and antimicrobial resistance of IPD have been documented in some studies in India [1-4]. Due to national inaccessibility of a central surveillance system and appropriate laboratory facilities, the estimate of the disease burden is more intriguing.

The challenges in the laboratory isolation of *S. pneumoniae* include the scarcity of standard culture media and improper sampling [5]. In addition, its isolation by conventional culture methods is often hindered by prior antibiotic intake [6]. Isolation of fastidious *S. pneumoniae* requires suitable culture media enriched with sheep blood, but many laboratories use human blood – that has passed its date of expiry – which does not support the growth of pneumococci, leading to lower isolation rates. Minimum transportation time for culture sample has a direct effect on the yield of the pathogen in diseased conditions. Cerebro spinal fluid (CSF) and blood should be transported to the laboratory preferably within 1-2 hours of drawing the sample. Published reports state fewer than 10% of patients with clinical diagnosis of pneumonia yield a positive blood culture [5,7,8].

Presence of more than 1000 colony forming units/mL of the organism in a sample is required for a positive antigen detection test such as latex agglutination or counter immune electrophoresis; therefore such assays are of limited value in detecting pneumococci in culture negative samples [6]. In the current issue of *Indian Pediatrics*, Nisarga, *et al.* [9] found that 56 culture negative samples were positive for *S. pneumoniae* by polymerase chain reaction (PCR) using *lytA* as target gene. Serotyping information of these 56 PCR positive and

culture negative samples would have provided additional information. It should be noted that various targets have been recommended for identification of pneumococci from cultures isolates, but these have not been tested directly on culture negative specimens [10]. Amplification of *lytA* gene has been evaluated and expected to be present in all the virulent isolates while few studies have demonstrated the presence of *lytA* and *ply* gene in members of the *S. mitis* group [10]. Therefore, the presence of these genes seems to be non-specific, and it cannot be presumed that the other members of the *S. mitis* group do not possess it or may have a facsimile of gene. Hence, *lytA* and *ply*-based PCR does not appear to be clinically useful and should be used cautiously to eliminate false positives from blood and fluid samples [10,11]. Among the culture positive specimens, only 11 were tested by PCR; of these six showed the presence of *lytA* gene. It would have been desirable that all the culture positive clinical samples were tested for *lytA* gene in this study. Nucleic acid amplification tests such as PCR do not require viable bacteria for a positive assay, and are generally considered to be highly sensitive in comparison to culture. However, the presence of PCR inhibitors in clinical specimens can compromise the sensitivity [12], and might explain the reason for five negative PCR among culture positives in this study. In this study, 44 % isolates of *S. pneumoniae* (16/36) were resistant to trimethoprim/sulfamethoxazole; this number is quite less compared to 87% as reported in a recent article from India [4]. It is to be mentioned here that a study at Christian Medical College and Hospital (CMC) in Vellore, India, has documented the presence of serotypes 3, 6A, and 19A during 2007-2011 [4]. Inclusion of molecular serotyping by sequential multiplex PCR in addition to conventional antisera-based Quellung reaction would afford a reliable and inexpensive way to serotype four isolates and 56 clinical samples which could not be typed in this study. It is far most important to know serotype of all *S. pneumoniae* strains for

implementation of pneumococcal conjugate vaccines, and to monitor circulating strains to consider vaccine effectiveness and subsequent substitution of serotypes.

This study over two years has rendered useful information on the incidence, clinical spectrum and serogroups of IPD in children. Pneumococcal meningitis still remains to be a serious problem globally in spite of potent antibiotic usage and adjunct therapy. This study can serve as a touchstone for successful surveillance in India since further amelioration in therapy might be futile.

Funding: None; *Competing interests:* None stated.

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Invasive Pneumococcal Disease and India

Pediatrician's Perspective

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In this issue of *Indian Pediatrics*, Nisarga and colleagues have surveyed for the pneumococcal disease in Bangalore through the Pneumonet Programme [1], and have attempted to curtail the knowledge gap regarding the burden of invasive pneumococcal disease and distribution of pneumococcal serotypes in India. Many

other surveillance programmes like SAPNA, INCLIN, IBIS and ASAP are also working to assess the invasive pneumococcal disease burden in India. Knowing disease burden is important to make decisions regarding the introduction of pneumococcal vaccine in National immunization program. Many multi-centric [2] and

single-site studies [3,4] have previously shown the significant presence of invasive pneumococcal diseases amongst Indian children, but these are now more than a decade old. The changes, which have occurred during these years, are not fully known. Skimpy data hinder the decision regarding introduction of vaccine. The Pneumonet study published in Indian Pediatrics is a two-year multi-centric hospital-based surveillance for pneumonia and invasive pneumococcal diseases in children under five years of age. Though it is a multi-centric study, the representation is for Bangalore only. It is difficult to generalize the findings but the study has tried to demonstrate every aspect of the disease. The investigators have worked on the isolation, identification, serotyping and antibiotic resistance patterns of pneumococcus.

The surveillance of over 9000 children from Bangalore has found 40 confirmed cases of invasive pneumococcal disease and shows the presence of non-vaccine serotypes. Albeit, the serotyping was not performed for all the isolates, it still can pinpoint the change occurring in serotype distribution and hint towards the potential of non-vaccine pneumococcal serotypes causing severe invasive diseases. According to Nisarga and colleagues [1], serotype 6A is the most commonly encountered serotype, which is in contrast with the findings of a systematic review of surveillance studies [5], where it was found that the most prevalent vaccine serotypes were 14, 5, 1, 19F and 6B. This finding also highlights the changing trends of the serotypes over the years.

Nisarga, *et al.* found pneumococcus being most resistant against the antibiotic trimethoprim/sulphamethoxazole that is similar to the findings of a recent systematic review [5,6]. The study's selective preference for using non-culture methods like polymerase chain reaction (PCR) and antigen testing is another shortcoming. Obtaining positive cultures in a pediatric population is difficult, and if prior antibiotic has been administered it is even more difficult to isolate the organism. The study population was children under five years of age of which 20% had received prior antibiotics which affects the isolation rate. The study has not used the latex agglutination test and has made limited use of PCR for identifying the organisms.

The current study also lacks in updating the information on economic burden for invasive pneumococcal disease, which is an important factor for determining the disease burden and deciding upon the

policy decisions regarding future actions. Nisarga, *et al.* demonstrated the highest serotype coverage by the 13-valent pneumococcal vaccine which is consistent with the findings of the systematic review [5], and an earlier study from CMC, Vellore [7]. Though the later has shown that a new 15-valent vaccine will cover most of the disease causing serotypes but the vaccine is not yet available.

The current surveillance is a positive attempt towards answering the question on having or not having pneumococcal conjugate vaccines in Indian National immunization schedule? India hopes to see more of these surveys performed on a large-scale, community-based studies from different regions so as to have most precise estimate of the disease to plan the strategy against it. This has rightly been called for by the authors. A countrywide population-based prospective study to understand the disease burden, epidemiology, serotype distribution and also economic burden will more closely aid in recommending a country-specific vaccine.

Funding: None; *Competing interests:* None stated.

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Stress: A Modifiable Factor in the Etiology of Adolescent Depression

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In India, 50% of the population belongs to the age group of 0-25 years [1]. The prevalence rate of depression in youth is roughly 15% to 20% [2]. World Health Organization (WHO) projects depression to be the second leading cause of disability by the year 2020 [3]. Stress plays a significant role in the etiology of depression along with the genetic factors [4].

Neuroimaging studies have helped us to understand neurobiology of stress and depression in the living brain in a noninvasive manner. Early life stressors are found to be associated with reduced fractional anisotropy values in the genu of the corpus callosum despite the absence of clinically significant psychiatric symptoms [5]. Fractional anisotropy, a useful measure on the Diffusion tensor Imaging (DTI) of the structural integrity of white fiber tracts, helps us to study human brain *in vivo*. White matter micro-structural abnormalities are reported in fronto-limbic neural pathways in adolescents with Major Depressive Disorders [6].

The huge population of children and adolescents in a developing country like India are subjected to stressors. Several risk factors identified in Indian adolescents are female gender, academic difficulties, parental fights, strained familial relationships, school absenteeism, school dropout, and other school related factors that contribute to psychiatric morbidity [7]. With the limited resources, the focus should be to identify the children and adolescents who are at risk from depression and provide primary, secondary and tertiary level interventions.

In this current issue of *Indian Pediatrics*, Jayanthi, *et al.* [8] reported a positive correlation between the academic stress score and depression scores. Stress is an environmental risk factor for depression which can be modified [9]. It has been observed that cases of depression in school and college students increase when examinations are approaching. Notably, the stress-related mental disorders like acute stress reaction, post-traumatic stress symptoms, adjustment disorders, panic attacks, acute transient psychotic disorders, dissociative disorders, suicide and deliberate self harm, and substance use disorders have been observed in clinical experience in Indian student population.

Interventions to reduce stress need to be carried out at several levels. At the level of government, currently

board examination of the tenth standard school has been replaced by a grading system which is based on the performance throughout the year in the form of formative and summative assessments carried out at school level. Another unique initiative is carrying out stress management workshops for students/parents/teachers at regular intervals.

Measures like setting realistic goals and priorities, time management, adequate relaxation techniques including yoga, walking, jogging, and recreation breaks while preparing for examinations, can help students cope with the mounting academic pressures [10].

It is equally important that parents help children and adolescents through motivation, confidence building, ensuring adequate sleep, fresh short meals, and avoiding caffeinated drinks or substance use. Parents should not compare their children with other high achievers, and should have realistic expectations. It is important to keep home environment conducive for studies. Any form of emotional abuse of child or adolescent in the form of insults, derogatory comments or physical abuse in the form of slapping, etc. should not be done by the parents/caregivers. Individuals with social supports cope up better than the children in the isolated families.

There is a pivotal role to be played by teachers as well. Teachers need to ensure timely completion of the syllabus so that there is ample time for revision, clarifying individual doubts, and mock evaluations. Teachers need to emphasize on 'must read' topics, regular assignments and evaluations. There is a need to develop a good rapport between teachers and students so that they feel comfortable and share their thoughts. Training of teachers for picking up early symptoms of stress and depression in the form of crying, sitting alone, irritable, eating excessively, self harm, substance ingestion, falling grades, inattentiveness, and behavioral oddities can prevent disastrous consequences. Counselors in the school can assist in early identification of at risk students.

Regular counseling sessions for depressed and stressed out students are provided in government run psychiatric set-ups apart from several other non-governmental organizations and private clinics. Pharmacological interventions are effective for managing depression, anxiety and other stress-related psychiatric

disorders. Psychiatric emergencies in the form of suicidal ideation or acts of self harm, and substance ingestion or intoxication should be brought for immediate care at inpatient psychiatric setting.

Funding: None; *Competing interests:* None stated.

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