Effectiveness of *Haemophilus influenzae* Type b Conjugate Vaccine on Radiologically-Confirmed Pneumonia in Young Children in Pakistan

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Objective The effectiveness of *Haemophilus influenzae* type b (Hib) vaccine in preventing severe pneumonia in Asian children has been questioned, and many large Asian countries yet to introduce Hib conjugate vaccine in immunization programs. The primary objective of this study was to assess Hib conjugate vaccine effectiveness (VE) on radiologically-confirmed pneumonia in children born after introduction of Hib conjugate vaccine in Pakistan.

Study design A matched case-control study enrolled cases of radiologically-confirmed pneumonia in several hospitals serving low-income populations during 2009-2011. Cases were matched by age and season with 3 hospital and 5 neighborhood controls. Pneumonia was diagnosed using standardized World Health Organization criteria for chest radiograph interpretation. Matched OR were estimated for VE.

Results A total of 1027 children with radiologically-confirmed pneumonia were enrolled; 975 cases, 2925 hospital controls, and 4875 neighborhood controls were analyzed. The coverage for 3 doses of diphtheria-tetanus-pertussis-hepatitis B-Hib conjugate vaccine was 13.7%, 18%, and 22.7% in cases, hospital controls and neighborhood controls, respectively. Estimated Hib VE for radiologically-confirmed pneumonia was 62% with 3 doses of vaccine using hospital controls and 70% using neighborhood controls.

Conclusions Hib conjugate vaccine prevented a significant fraction of radiologically-confirmed pneumonia in children in Pakistan. Maximizing impact on child survival needs improved immunization coverage. *(J Pediatr 2013;163:S79-85)*.

Childhood pneumonia remains the leading cause of child mortality in developing countries, including Pakistan.[1-3] It is estimated that of all cases of pneumonia, 7%-13% are severe, requiring hospitalization and may lead to death in the absence of appropriate management.[4,5] Two major etiologic agents of severe pneumonia in children are *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*, both effectively preventable through vaccines.[6,7] However, determining bacterial pneumonia etiology by traditional microbiology has been challenging because of insensitive methods, resulting in a serious underestimation of disease burden, particularly in Asia where high antimicrobial use prior to tertiary care health facility presentation is frequently noted, rendering cultures sterile.[8] The combination of insensitive surveillance methods for invasive Hib disease and the equivocal findings from a large cluster-randomized Hib conjugate vaccine-probe study in Indonesia[9] has resulted in large Asian countries including China and India delaying the introduction of Hib conjugate vaccine in routine childhood immunization programs.[8]

Carefully conducted acute bacterial meningitis surveillance studies using nonculture methods for etiologic diagnosis documented a substantial burden of invasive Hib and pneumococcal disease in Pakistan,[10-12] and it is likely that Hib, therefore, also causes a substantial burden of pneumonia in Pakistan.[6] In

AKUH	Aga Khan University Hospital
DTP	Diphtheria-tetanus-pertussis
EPI	Expanded Program on Immunization
Hep B	Hepatitis B
Hib	*Haemophilus influenzae* type b
VE	Vaccine effectiveness

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2000, Pakistan was estimated to have 410 478 cases of Hib pneumonia in children aged <5 years.[7] The availability of financing by the GAVI Alliance led to a decision by the Government of Pakistan to introduce the pentavalent (diphtheria-tetanus-pertussis-hepatitis B-Hib [DTP-Hep B-Hib]) vaccine in the country's Expanded Program on Immunization (EPI) in 2009. Pentavalent vaccine in routine EPI is scheduled for children at the age of 6, 10, and 14 weeks, respectively. The primary objective of this study was to assess the impact of introduction of Hib conjugate vaccine in Pakistan by measuring vaccine effectiveness (VE) against prevention of radiologically-confirmed pneumonia in children born after the introduction of Pentavalent vaccine in the country's EPI. We also aimed to identify risk factors for radiologically-confirmed pneumonia in children in Pakistan.

Methods

A matched case-control study began immediately following the introduction of pentavalent vaccine in the Pakistan national EPI in January 2009. Sentinel surveillance was established at several public and private secondary and tertiary level health facilities serving low-income populations in 3 districts (Matiari-Sindh, Hyderabad-Sindh, and Jhelum-Punjab) and in the mega-city of Karachi, in Sindh in southern Pakistan. A total of 22 health facilities (9 public and 13 private) were included in this study based on: (1) parental/caregivers' health seeking preferences/utilization assessed on baseline cross-sectional survey in the study areas; (2) more than 20 pediatric admissions weekly at the hospital; (3) availability of chest radiography (either digital or manual with at least a 100 mA machine); and (4) willingness of hospital administration to participate in the proposed evaluation. Screening for eligible cases was conducted in outpatient and inpatient areas at each sentinel site for children aged <5 years by a research officer. Children presenting with signs of acute respiratory infection were classified as suspected pneumonia if they presented with fast respiratory rate (>50/minutes) and fever (>101°F).[13,14] Among these, parents/guardians of children who had chest indrawing as a sign of severe pneumonia,[14] who were age-eligible to have received at least 1 dose of pentavalent vaccine, and were resident in the predefined catchment population were invited to participate in the study by a study physician. Children were excluded if they were previously enrolled as a case, if there was parental refusal, or if they lived outside the catchment area from which neighborhood controls could be enrolled. Death of the child did not exclude a case. A case report form recording baseline characteristics was completed if the parent/guardian provided informed consent. Chest radiographs of study-eligible children were obtained within 24 hours of hospital admission, and interpreted at first by the onsite study physician. Digitized images of chest radiographs were made using a VIDAR scanner[15] (VIDAR Systems Corporation, 365 Herndon Parkway Herndon, VA 20170) for all radiographs read as pneumonia, and every tenth radiograph (sequentially) read by the study physician as "no pneumonia." The digitized images were separately sent to 2 pediatric radiologists who were trained in the interpretation of chest radiographs with a diagnosis of radiologically-confirmed pneumonia according to World Health Organization case definition of presence of substantial alveolar consolidation[16,17] for second level interpretation at Aga Khan University Hospital (AKUH), in Karachi, Pakistan, on the same day. These 2 radiologists were not given any clinical information about the child and were blinded to each other's interpretations. A senior pediatric radiologist (also trained in World Health Organization standardized interpretation of chest radiographs)[16] served as arbiter for discordant chest radiograph interpretations. A case of radiologically-confirmed pneumonia was diagnosed based on the agreement of the 2 blinded radiologists at AKUH, or diagnosis by the senior radiologist if the AKUH radiologists were discordant.

Selection of Hospitals and Neighborhood Controls

For each case of radiologically-confirmed pneumonia, 3 age-matched hospital controls were enrolled from the same hospital, and 5 neighborhood controls were enrolled from the community in which the case child lived. Controls were eligible if the child was age matched (±4 weeks for case children <12 months; and ±8 weeks of age for case children ≥12 months), age eligible (at least 6 weeks) to receive the first dose of pentavalent vaccine, and a resident of study catchment areas. Children (controls) were excluded if child had been previously enrolled as a case of severe pneumonia or meningitis in the previous 8 weeks, was a sibling of a previously recruited case/control who lived in the same household, or had a current severe illness possibly due to Hib. For identification of hospital controls, the study staff generated a list of all eligible children at the hospital from patient triage records (−7 to 30 days) based on the date of admission of case child, and 3 hospital controls were randomly selected and recruited after obtaining written parental consent. For identification of neighborhood controls, the project research assistants and community health workers visited the geographic area of the case child. A random direction was established by means of rotating a bottle, and the first household was approached to determine child's eligibility. Upon identification of the first household with an age eligible child, study staff invited the parents to participate in the study and obtained written parental consent. Subsequently, staff approached households using a systematic sampling technique with a skip pattern of 3 households after each eligible household, and continued in this fashion until 5 matched neighborhood controls were enrolled. The recruitment of hospital or neighborhood controls was made within 30 days from the hospital admission date of the case to account for seasonality of exposure.

Sample Size

The sample size was calculated using the NCSS PASS v. 11 software[18] (Dr. Jerry L. Hintze and NCSS, East Kaysville, Utah) for matched case- control study design. This study was designed to detect a VE of 20% for radiologically-confirmed pneumonia with 2 or more doses of Hib conjugate