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Review Article

CAUSES AND EPIDEMIOLOGY OF VACCINE PREVENTABLE INFECTIOUS BACTERIAL DISEASE: THE PROSPECT AND SHORT OUT COMING OF VACCINE

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ABSTRACT

Emerging infectious bacterial diseases are an imperishable threat to the improve health and sustainability of the Indian citizens. Vaccination is a cost-efficient and safe method practiced to prevent the infectious diseases spread in India and worldwide. The three major pathogens causing meningitis *N. meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae* type b (Hib) are vaccine preventable bacterial disease. Monitoring the effectiveness of *pneumococcal* polysaccharide-protein conjugate vaccines and Hib-conjugate vaccines is crucial prior to vaccine implementation. Recognition of the possible potential pathogen in hospital settings in many developing countries is challenged due to the inadequate resources and clear operational procedures. Thus, because of poor recognition, improper infrastructure and surveillance systems, developing a novel conjugate vaccines for *pneumococci* and *Haemophilus* is unlikely. In spite of global importance, the problems and difficulties in diagnosis impedes the capacity to obtain accurate information on disease burden and assessment of the potential of vaccination. International and national efforts are made and still continue for the introduction of vaccine and studies indicates the efficacy of vaccine in eradication of the. Accurate evaluations of the infectious disease and the economic needs to prevent these infections have to be calculated since their global nature presents a danger to the health of people and also paralyze the economy of nation.

INTRODUCTION

Emerging infectious diseases are an imperishable threat to the fine health and sustainability of the Indian citizens. Numerous factors contributes to the disease burden including geography, seasonal patterns, crowding, nutritional status, travel to and from other countries, and also genetic differences affects severity of the disease [1]. Therefore these infectious diseases necessitate regular regional wise surveillance including prompt identification and development of critical prevention strategies to control the rapid dissemination globally.

Role of Vaccine in Prevention of Disease

Being cost-efficient and safe, vaccination is an efficient method practiced to prevent the infectious diseases spread in India and worldwide [2]. Vaccines have reduced or eliminated many infectious diseases that once routinely killed or harmed many infants, children, and adults. As a paradigm, vaccine against mumps, rubeola, measles, tuberculosis, diphtheria, pertussis and oliomyelitis minimize the burden of these contagious diseases [3].

Numerous observational studies have evaluated the efficacy of vaccine in eliminating and preventing infections and also its ability in controlling the disease and minimising the socio- economic cost of the nation is certain [4]. Most childhood cases of bacterial meningitis and *pneumonia* are preventable through infant immunization. However, disease and death still exist caused by bacteria that are vaccine-preventable and can be spread on to people who are not protected by vaccines [3].

Vaccine Preventable Infectious Bacterial Disease

Among vaccine preventable Infectious bacterial disease the three major pathogens causing meningitis are *N. meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae* type b (Hib). Implementation of novel vaccines against *pneumococcal, meningococcal* and *Haemophilus* infections can reduce the mortality associated with these diseases caused by them [5, 6].

Hib is one of the most common causes of pediatric bacterial meningitis, along with *Pneumococcus* and *Meningococcus*. *Haemophilus influenza type* b (Hib) leads to substantial mortality in young children causing meningitis, pneumonia, otitis media, sinusitis, bronchitis and septicemia. Newer vaccines against the established childhood diseases caused by *Pneumococci* and *Haemophilus* will drive shifts in the case-fatality rates of these infectious agents [5, 6, 7]. *Streptococcus pneumoniae*, the etiological agent of bacteremia, meningitis, bacterial pneumonia and otitis media, causes Invasive pneumococcal disease in young children and adults suffering from chronic conditions and immune deficiencies which leads to global mortality and morbidity [8]. In developing countries, case-fatality rates among children are often over 10%, and as high as 60% among infants under 6 months of age [7].

Acquired invasive Pneumococcal disease and Haemophilus influenza b invasions in children and elderly (eg. in persons with congenital or acquired immune deficiencies, sickle cell disease, functional or anatomic asplenia) cause severe health problems in developing countries.

Problems in Vaccine Implementation

The dynamic nature of the vaccine preventable infectious bacterial disease and their unpredictable effect endanger the health prosperity and security of the nations. Effective prevention and extenuate strategies predicts the impact of infectious diseases, surveillance and decisive responses in preparing and responding for bacterial meningitis and pneumonia.

Prior to vaccine implementation, monitoring the effectiveness of pneumococcal polysaccharide-protein conjugate vaccines and Hib-conjugate vaccines is crucial. Vaccine developments have incited appropriate identification and laboratory confirmation of the infectious agents microbiologically. Furthermore, the emergence of multidrug-resistant strains increases the need for enhanced diagnostic methods for the isolation of pneumococci and Haemophilus.

Poor surveillance and infrastructure

Surveillance systems for Invasive Pneumococcal Disease (IPD) and Haemophilus invasive disease burden are inadequate in developing countries due to several reasons. The expenses of the surveillance systems and poor infrastructure refrains these countries to overcome hurdles and implement the potential vaccines. Furthermore, vaccines are more expensive than those currently available for routine immunization; hence developing countries must document the burden and etiologic agents of these infectious diseases through surveillance studies in order to determine the cost-efficient vaccine introduction strategies for their countries.

Possibilities of recognition of the potential pathogen in hospital settings in many countries are challenged due to the ineffective resources and clear operational procedures. Thus, poor recognition and infrastructure impedes proper surveillance systems and

adoption of novel conjugate vaccines for pneumococci and Haemophilus is unlikely. Appropriate allocation of financial resources can help the developing countries to surmount the barriers and to conduct proper surveillances in order to demonstrate the disease burden and associated economic-burden.

Problems in identification

Traditional laboratory diagnostic methods of culture for the identification of bacterial meningitis pathogens take up to 36 h or more. Moreover, it has been observed that the increased practice of initiating therapy prior to sampling has decreased the efficacy of identification and confirmation of the pathogenic microorganisms of bacterial meningitis and septicaemia [9].

In spite of global importance, the problems and difficulties in diagnosis impedes the capacity to obtain accurate information on disease burden and assessment of the potential of vaccination. The ramifications of molecular methods have recently overcome the complications with diagnosis but still microbiological culture and isolation of the infectious agent from CSF and blood provides conclusive evidence of the disease [10].

CSF examination

Performing Gram stain and bacterial culture of CSF is vital for confirmation of pathogen in the sample. Processing a CSF sample as soon as possible is essential because bacterial viability is lost over time [10].

Nucleic Acid Amplification Tests

Molecular diagnostic tools for IPD and Haemophilus invasive disease have gained immense importance in a microbiological diagnostic laboratory. PCR can detect even minute amounts of nucleic acid in no time but do not depend on viability of the pathogen. Detection and diagnosis using advance technology will enhance the results in under-resourced countries since it is easy, cheap and rapid in recognizing and characterizing the pathogen for surveillance purpose compared to the conventional co agglutination and culture techniques for Pneumococci and Haemophilus identification.

Molecular identification is highly sensitive and specific that it shows capability to identify the organism directly from samples of culture-negative cases. Previous studies have revealed many positive cases among available culture-negative specimens, which is equivalent of the culture-positive cases accumulated in the past months. Isolation and identification of serotype by conventional methods may take few additional months of surveillance; this is a substantial savings of time and money [11].

Disease Burden Incident

Establishing this data is important because safe and effective vaccines against all three bacterial pathogens are available. The World Health Organization estimates that ~1.6 million people, including up to 1 million children aged <5 years, die of IPD every year [12], with developing countries bearing the greatest burden (WHO position paper 2007). Invasive pneumococcal disease (IPD) is caused by >91 serotypes of streptococci worldwide, but only few among these serotypes are involved in actual invasive pneumococcal disease (IPD) are 6A, 6B, 9V, 14, 19A, 19F and 23 F [13]. The predominant pneumococcal capsular serotypes identified in the IBIS study were types 1, 4, 5, 6, 16, and 19. Type 1 and 5 accounts for 25% of infections in India but hardly identified in developed countries, evidencing the importance of these serotypes be included in the conjugate vaccine for India [14].

H. influenzae is the most common cause of childhood bacterial meningitis in India causing 30-40% of culture positive cases, and associated with 20% mortality. Studies has also shown that type b Haemophilus influenzae accounts 97% of all invasive Haemophilus disease in India therefore suggesting the use of Hib vaccine to prevent the disease in health systems [15].

Available Vaccine

Antibodies to the polysaccharide capsule are highly immunogenic, providing protection against the pneumococcal infections; these capsular antigens are used in the development of vaccines. PCV (Pneumococcal Conjugate Vaccine) was developed for the prevention of IPD caused by different prevalent serotypes of Streptococcus pneumonia [16]. PCV (Pneumococcal Conjugate Vaccine) was developed for the prevention of IPD caused by different prevalent serotypes of Streptococcus pneumoniae. Several pneumococcal conjugate vaccines have been developed and licensed abroad namely PCV 7, PCV 13, and PCV 23. Currently available vaccine to protect against prevalent strains of Streptococcus pneumoniae includes [17].

- Prevenar (PCV-7) serotypes (4, 6B, 9V, 14, 18C, 19F, 23F)
- Prevenar(PCV-13) related serotypes (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C,23A, 23B)
- Pneumovax (PPV-23) serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F)

The seven-valent pneumococcal conjugate vaccine was licensed in 2000. At the time of licensure, PCV-7 showed potency to cover 80% of infections caused by these serotypes that are most often associated with invasive disease in the US and European countries[18], but in India PCV-7 is found to have a protective coverage of only 40% due to differences in the prevalent serotypes [14].

The 23-valent Pneumococcal vaccine can prevent pneumonia and other infections caused by 23 types of the Streptococcus pneumoniae strains. These 23 serotypes account for approximately nine out of 10 cases of pneumococcal disease. The vaccine protects about 50 to 80 per cent of people against pneumococcal infection. The pneumococcal polysaccharide vaccine licensed in Canada targets about 23 types of pneumococci that accounts for 85 to 90% of IPD in the younger and older age groups [19].

Recently, PCV-10 and PCV-13 have been licensed for use in India, as optional vaccines under the Indian Academy of Paediatrics (IAP) immunisation schedule. At present, the National Immunisation Program does not include PCV-7 in routine immunisation, but it is expected to be implemented soon.

The Prospect and Short Out Coming of Vaccine

A few studies have demonstrated a significant decrease in the vaccine serotypes and an increase in the non-vaccine serotypes in post vaccine era. These replacement phenomenon or so called "replacement disease" is a matter of concern which reduce the efficacy of present vaccine due to the emergence of serotypes not included. Therefore this inadequate coverage of serotypes vaccine, newer vaccine containing additional prevalent serotypes has been developed. However, the decrease in the incidence of the vaccine serotypes was associated with an increase in the incidence of non-vaccine serotypes.

In USA, introduction of the Pneumococcal conjugate vaccines with long lasting immunity have supported significant elimination of the burden of disease in children aged less than 5 years, thereby, potentially minimising (95% reduction) the incidence of IPD and invasive Haemophilus influenzae type b disease[20]. Hib conjugate vaccines have been shown to be universally effective against all invasion caused by Haemophilus influenzae type b [21].

Certainly, immunisation of infants with the Hib vaccine has led to a prompt decline in the incidence of Haemophilus invasive disease among children. Studies conducted proved the potency of the Hib vaccine could save thousands of children from the deadly meningitis and pneumonia preventing approximately 90% of infections [22]. Nevertheless, in developing countries lack of routine immunisation, pneumococci and Hib vaccine still remains to be a major cause of invasive meningitis and lower respiratory infections in infants and children.

Current Surveillance

In India, and throughout the developing world, pneumonia and acute respiratory infections are the most frequently documented illness in children under five years of age. Each year, around the world, more than four million children under five die from respiratory infections, many of which are caused by these two bacteria [23].

The IndiaCLEN Invasive Bacterial Infection Surveillance (IBIS) study, a multicenter project funded by the International Clinical Epidemiology Network (INCLEN) and the United States Agency for International Development (USAID) in India, generated the proximal data for India regarding the significance of Pneumococcal disease in adults and children and Haemophilus influenzae disease in children. This surveillance study conducted in cooperation with Johns Hopkins University and six teaching hospitals in India: All India Institute of Medical Sciences, New Delhi; Christian Medical College and Hospital, Vellore; Government Medical College, Nagpur; King George's Medical College, Lucknow; Madras Medical College, Madras; and Trivandrum Medical College, Trivandrum render information on disease burden caused by the vaccine preventable diseases and also on the anti biotyping patterns of these organisms causing invasive bacterial infections in India.

Active Bacterial Core Surveillance (ABCs): Active population-based laboratory surveillance for invasive bacterial disease includes pathogens: groups A and B Streptococcus, Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae, and methicillin-resistant Staphylococcus aureus. Active, population-based surveillance is conducted in nine states (total population: 25 million). Pneumococcal isolates from this surveillance study were collected and sent to reference laboratories for susceptibility testing using CLSI methods and serotyping. Rates of invasive pneumococcal disease were calculated using population estimates for each year

International Effort

Implementation of vaccine against Streptococcus pneumoniae and Haemophilus influenzae type b, prevalent in developing countries, would unquestionably minimise the impact of these infectious disease. The socioeconomic status of these low-income countries hampered the immunisation programs which could be overcome by providing vaccines through substantial resources.

Internationally, the Global Alliance on Vaccines and Immunization (GAVI) campaigning effort made by WHO, UNICEF, the World Bank, governments of seven donor countries, governments of developing countries, philanthropy, and private industry inorder to provide increased access to pneumococcal, Hib, HBV and yellow fever vaccines in developing countries. The GAVI alliance was organized in 2000 principally to speed up the introduction of vaccine in these countries. Additionally, financial supports are provided by European Commission, the Bill & Melinda Gates Foundation, and other private donors. If GAVI can implement vaccines that provide protection against Hib disease and IPD, certainly, it will save more than millions of lives in more than 72 low-income countries. Minimizing the cost of vaccine and stable supply is the promising motive of the GAVI campaign. It uses International finance facility for immunization and Advance market Commitment for its financing whereby contracts are made that warranties low pricing of vaccines from drug companies. For example, the cost of Pneumococcal vaccine in developing countries is US$3.50 whereas it is US$70 in wealthier nations. GAVI vaccine fund provides supports to poor countries to improvise their health services and to implement vaccines but the sustainability demands the involvement of the countries in immunization goals.

The Global Immunization Vision and Strategy (GIVS), developed by WHO, UNICEF, and partners, has among its aims "strengthening the current immunization system so that it can maximally deliver currently available vaccines as well as under-utilized vaccines," including Hib. The GIVS also incorporates the GAVI goal of "50% of the poorest countries with high disease burdens and adequate delivery systems will have introduced Hib vaccine by 2005".China

Limitation

The capsular serotypes in the 7-valent pneumococcal vaccine can contain <80% of serotypes involved in IPD. Currently available conjugate pneumococcal polysaccharide vaccine targets only 23 serotypes of Pneumococci but does protect against many other capsular serotypes. Serotypes causing IPD vary geographically and the serotype distribution also varies periodically due to serotype replacement. The currently available 23-valent pneumococcal polysaccharide vaccine is not recommended for children under 2 years of age, in whom most IPD occurs.

Haemophilus influenzae type b (Hib) vaccine is a conjugate polysaccharide-protein vaccine targeting on type b strain of Haemophilus and not effective against non-type B Haemophilus influenzae. Moreover, the vaccine has also been shown to be immunogenic in patients at high risk of invasive disease. Moreover, imprudent use of antibiotics contributes to emerging drug resistance among the strains questioning the long term efficacy of the vaccine. The conjugate vaccine available differs in their immunogenicity among infants and children, necessitating the booster dose administration, which may be emphatically expensive.

CONCLUSION

International and national efforts made for the introduction of vaccine indicates the efficacy of vaccine in eradication of the disease although several factors hinder their use including high cost, limited knowledge and data available and distribution of vaccines in developing countries. Accurate evaluations of the infectious disease and the economic needs to prevent these infections have to be calculated since their global nature jeopardizes the health of people and also paralyze the economy of nation. Hence, strategies to implement vaccine have to be unveiled and necessary efforts have to be put forth to assist the countries financially and technically therefore ameliorating opportunities for vaccine development and immunization programs in developing countries.

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