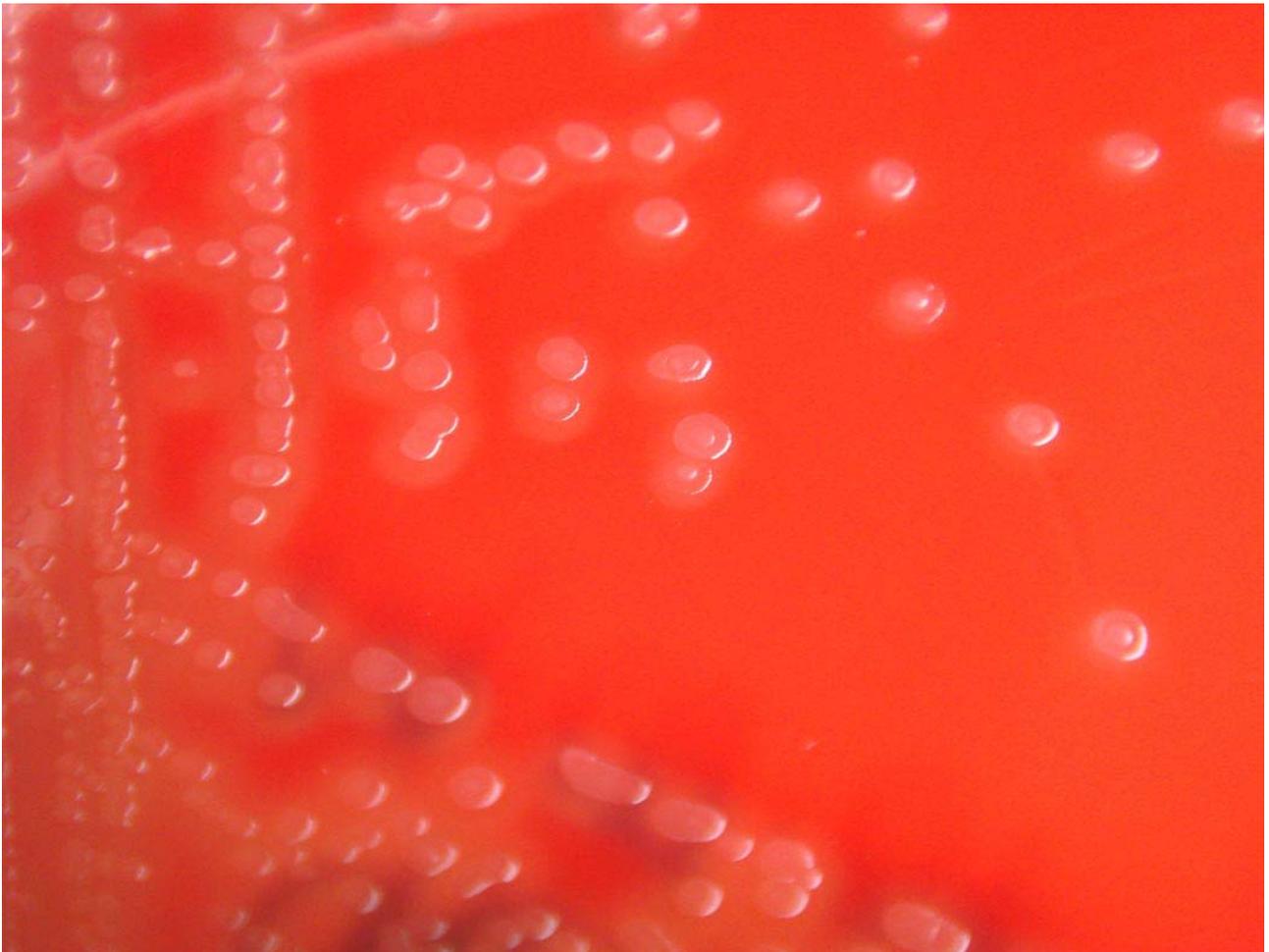


The long-escaped killer

*Pneumococcus kills over 800,000 children every year.
It can be prevented!*



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Pneumococcal disease burden in the developing world

When the mother rushed her only child into the largest paediatric hospital of Bangladesh, Dhaka Shishu Hospital (DSH), she did not have the slightest clue what had happened to her daughter. In the crowded Out Patient Department (OPD) she tried to locate a doctor, but all of them were dealing with hundreds of other patients. Finally, after lining up for more than one hour she was lucky enough to be able to talk to a doctor who immediately knew that her daughter was a dreadful case of meningitis. He, like for every other similar case, immediately got the child admitted to the hospital and sent for the necessary diagnostic tests to the next-door Microbiology Department. The results were back the next morning, but by that time the heart of the mother's only child had stopped beating. The mother went back home alone.

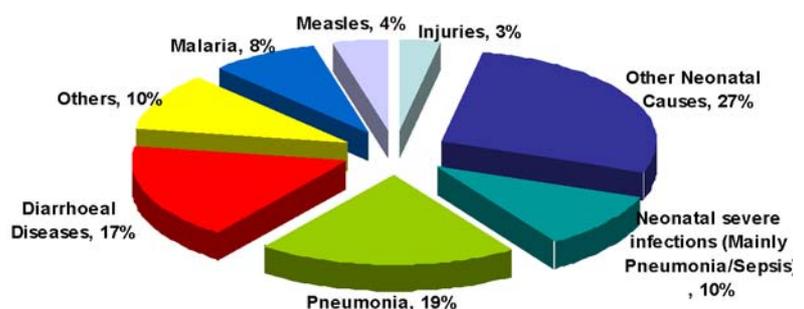
However heartbreaking the above story seems, this is a very common case in every paediatric hospital of any developing country. Across the world, every day, a huge number of patients arrive into the hospitals with severe cases of meningitis or pneumonia and many more die either at home, or on their way to the hospital, and most of these cases are due to infections by the deadly *Streptococcus pneumoniae*, popularly known as pneumococcus.

Prevalence

Meningitis occupies only a small portion of the spectrum of diseases caused by pneumococcus. The organism has positioned itself as the leading cause of mortality in under-five children in developing countries, mainly by causing pneumonia, a silent killer of third world children.

World Health Organization (WHO) calculates that the organism, as a whole, by causing pneumonia, meningitis, sepsis and other diseases, kills more than 800,000 under-five children world wide^{1,2} and 90% of them are in the developing part of the world³.

However, most cases go undetected because blood culture lacks sensitivity for detecting the organism as most of the patients with pneumonia are not bacteremic⁴. The problem is further augmented, especially in the developing part of the world, by the lack of facilities to isolate this fastidious organism and the poverty of affected people. This in turn discourages clinicians to advise for blood and cerebrospinal fluid (CSF) cultures of pneumonia and meningitis cases.

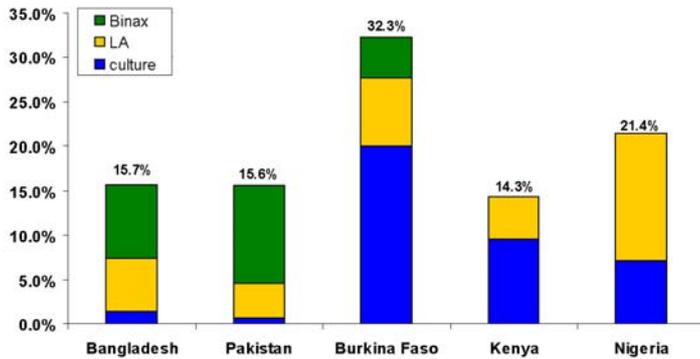


Under-5 deaths from pneumonia, excluding neonatal period

All these lead to an underestimation of pneumococcal diseases, although pneumonia is the predominant (29%) cause of death in under five children in the third world⁵. There is also strong evidence that most of the severe pneumonia cases are indeed bacterial and predominantly pneumococcal⁶.

"Robust disease burden data are essential for introducing a new vaccine. PneumoADIP is gaining the advantage by gathering this evidence to aid the decision to introduce pneumococcal vaccines."

Hanna Nohynek, National Public Health Institute, Finland.



Proportion of CSF specimens positive for *S. pneumoniae* by culture, latex or Binax

Diagnosis

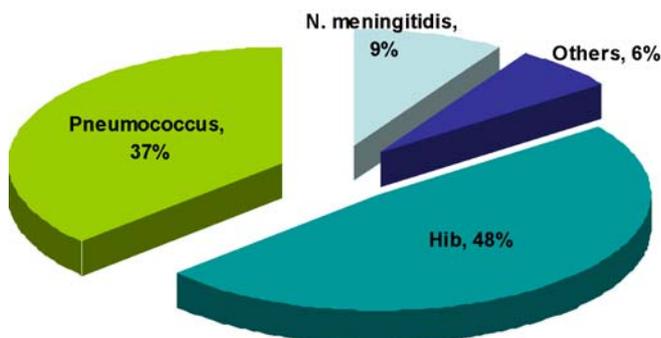
The role of *S. pneumoniae* has been made more conspicuous by the recent innovative studies where pneumococcal vaccine was used as a probe to show the proportion of pneumonia prevented in the vaccine group compared to the group without vaccine. In addition to prevention of pneumonia cases, the vaccine also showed an overall reduction (not only for pneumonia) in hospital admissions,^{7,8} indicating that many pneumococcal cases among the sick children were actually being misdiagnosed as other diseases rather than pneumococcal.

Pneumococcal meningitis, as we have seen at DSH, is a devastating disease with approximately 50% estimated case fatality rate in developing countries, higher than any other form of meningitis⁹. However, most affected children that reach the hospitals receive empirical antibiotic therapy prior to coming to the hospitals, thus rendering blood and CSF cultures sterile and non-diagnostic.

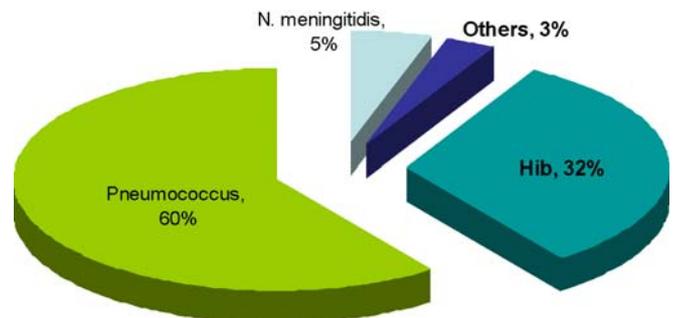
Recent availability of a diagnostic test, named Binax, with 100% sensitivity and specificity diagnostic test for pneumococcal meningitis clearly demonstrated that most of the pneumococcal meningitis cases had previously gone undetected, especially in Asia. Routine use of this test has changed the overall scenario of bacterial etiology of meningitis, and pneumococcus has manifested itself as the number one cause of meningitis.

In addition to acute disease, pneumococcal meningitis commonly leaves the victim with permanent sequelae that have substantial direct and indirect costs¹⁰.

Prevalence of pneumococcal meningitis in Bangladesh



Prior to Binax 1993-2003 (N=2410) Meningitis cases



Post Binax 2004-2007 (N=464) Meningitis cases

Disabilities and social impact

Prospective neurodevelopmental assessments of pneumococcal meningitis patients in Bangladesh, 3-4 months and 12-24 months after discharge from the hospital, revealed that about 65% and 49% of cases survived with one or more impairments and permanent disabilities respectively, including deafness, vision loss, mental shortfall, and psychomotor deficits. Other studies in India¹¹, Pakistan¹², Sudan¹³, and Vanuatu¹⁴ have shown similar results.

This high prevalence of disability from pyogenic meningitis cases can be attributed to poor care-seeking behavior, and delay in diagnosis and treatment of meningitis^{13,16}.

These disabilities not only have a huge impact on the affected child but also have significant consequences for the entire family and society, again, specifically in the developing countries. In contrast to developed countries, disabled children of developing countries do not have access to the basic facilities and services to lead a normal life, in order to be a part of the society. For example, there are no special signs or arrangements for the disabled at any of the public places to facilitate their activities – there are no ramps for wheel chairs, no special toilets and of course there are almost no special schools for disabled children. In other words, a disabled child in a developing country setting remains non-functional and survives as a handicapped person all throughout his or her life and becomes a burden for the family and the society.

	Neuro-developmental Impairments				Uneventful
	Hearing	Vision	Mental	Psychomotor	
Short term (n=51)	17 (33%)	4 (8%)	21 (41%)	25 (49%)	18 (35%)
Long term (n=51)	9 (18%)	2 (4%)	21 (41%)	18 (35%)	26 (51%)
Control (n=50)	0	0	1 (2%)	1 (2%)	49 (98%)

Short and long-term neurological outcome of pneumococcal meningitis in Bangladeshi children

Qualitative assessment of families in Bangladesh revealed that the families with a basic income of less than \$25 /person/month, struggled to pay an average of \$300 for the treatment of a meningitis case. Furthermore, after the treatment with appropriate antibiotics and care at a tertiary level hospital, the overall impact of this devastating disease on the family and society is huge.

Only a few obvious ones are mentioned below:

1. Social:

Separation between parents – it was often seen that the man abandoned the family and got married again, sometimes while the mother was still in the hospital with the disabled child.

2. Educational:

Disability not only hampers the education of the child who suffers from pneumococcal meningitis, but also the other siblings.

3. Economic:

a) Taking a loan with interest, which is at times as high as 80% - 120% per year

b) Selling the land, cattle and house hold goods to raise money for treatment and care; and

c) Losing jobs – patients, especially the women, may lose their job as they cannot attend the work while the child is in the hospital, or when the disabled child needs care at home.

However, the effects of meningitis in the developed world are much less. The patients suffer from lower rates of disabilities, for example, hearing loss has been reported to be 7% in The Netherlands¹⁵ and only 2% in UK¹⁶. This is possibly due to better care seeking behaviour and health services.

Human face of pneumococcal meningitis

The horrific effects of pneumococcal meningitis is illustrated by the story of the ‘contrasting’ twins (Nayeem and Monica) who grew up in the identical environment - one of whom, Nayeem, contacted pneumococcal meningitis and survived with devastating consequences while the other lived a normal life.

Nayeem at the age of five months, was admitted to DSH after having a high fever and seizures. On the day of his admission, he was diagnosed with pneumococcal meningitis and the doctor quickly explained what had happened to the bewildered parents.

Over next few days Nayeem’s fever did go down. However, there was little pleasure taken from that improvement as it was traded for life-long complete paralysis. As there was no sign of improvement and they could no longer keep up with the rising medical expenses, Nayeem’s parents decided to take their son home firmly believing that their son’s condition would improve with proper care at home. During this time, Nayeem’s father had sold off the little property that he had inherited, to pay the hospital bills.

Eighteen months later Nayeem was still paralyzed, lying in the bed, staring at the ceiling; unable to see, hear, talk, sit or do anything. On the contrary, Nayeem’s twin sister, Monica, was spending her days crawling around the house, learning to speak and fighting with their older brother.



Nayeem, a human face of pneumococcal meningitis with his twin sister, Monica.

Finally, Nayeem died of the consequences of disability due to pneumococcal meningitis before he reached his second birthday.

The episode of the disease devastated his family and shattered them both economically and emotionally. Nayeem's elder brother could not attend the school as his father could not afford to buy the necessary school supplies.

This is just one of the many stories of disability from pneumococcal meningitis. Imagine what it would have been like for everyone of the family if this episode of disease had been prevented.

*Options to prevent death and disability caused by *Pneumococcus**

All in all, pneumococcal disease contributes to the vicious cycle of poverty and ill health¹⁷.

There are two ways to break this vicious cycle and save these children from death or disability – either by preventing the disease through immunization with appropriate vaccine or by treating the patients with proper antibiotics at an early stage of disease.

However, treatment is a difficult option in developing countries where care seeking is poor as evidenced by the fact that only about 50% of the children with pneumonia cases get medical care and only one in five receive appropriate antibiotic therapy¹⁸.

Moreover, like any other antibiotic treatment in the world, treatment success is threatened by the rapid emergence of antibiotic resistant strains of pneumococcus. On the other hand, immunization programme in most of the developing countries have shown success with more than 80% coverage for complete immunization with 3 doses of DPT¹⁹.

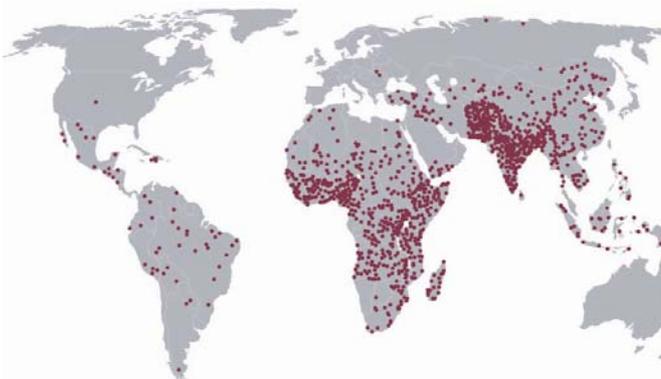
Financial factors involved with the vaccine introduction

Success of immunization can easily be witnessed by its dramatic impact on child survival in developing countries. Devastating diseases like tetanus, diphtheria, polio, etc. have either been eradicated or are near to eradication from most developing countries.

For instance, Bangladesh, one of the poorest countries in the world, mostly known for poor care seeking behavior of people, natural calamities, and political unrest, has saved the lives of about 2,000,000 children through a successful nation-wide immunization programme since 1990.

As public health workers in developing countries, we are excited and inspired by the success of vaccines. However, we are also very distressed by the huge gap of time between the universal availability of the newer vaccines in industrialized countries and their successful introduction and expansion in coverage in developing countries. For example, it is the 18th and 7th years since introduction of Hib and pneumococcal vaccines (popularly known as pneumonia and meningitis vaccines) respectively, in the USA and other developed countries. However, they are not yet available in most of the developing countries including those in South Asia and the Sub-Saharan Africa, where most of the children are actually dying.

Inequity between childhood pneumonia mortality and the availability of pneumococcal vaccine



Childhood pneumonia mortality



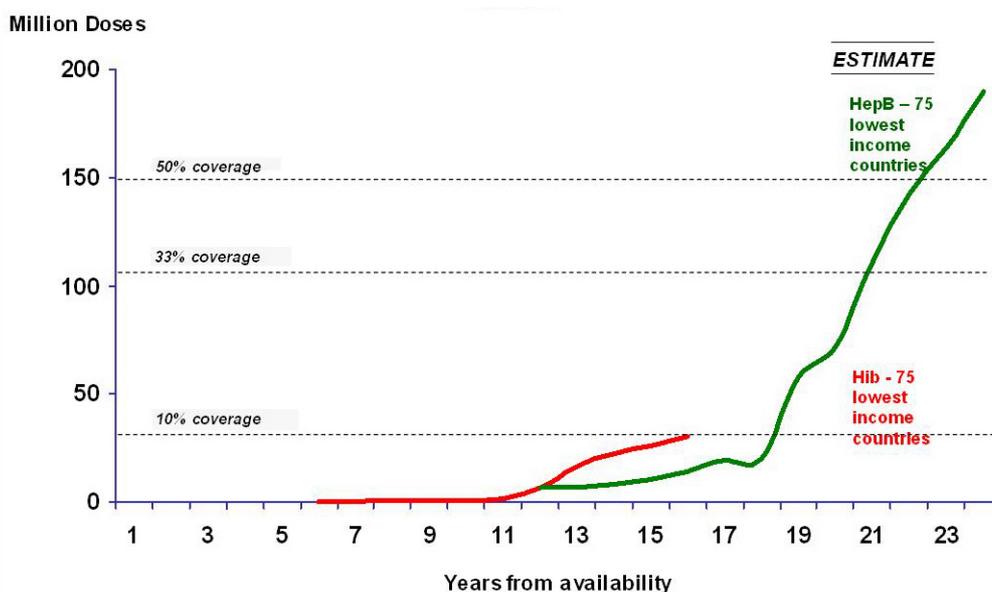
Pneumococcal vaccine available for routine Immunization

Another essential vaccine, Hepatitis B, has been licensed and in use in the developed part of the world for last two decades but is yet to be available in many of the developing countries. It is worth mentioning that where these vaccines are available in developing countries, it is often only the private sector which provides them to the affluent few who can afford them, while most of the children affected are from below the poverty line.

There are several reasons for this slow uptake of vaccine in national immunization programmes of developing countries. First, these countries have numerous problems — priorities are many but resources are few. Even when focusing on health issues alone, there is a staggering number of issues that must be addressed. So the countries need strong and convincing data on these diseases (which are mostly unavailable) in order to weigh various options for utilizing limited resources. In addition to lack of data on disease burden, the developing countries are also missing the strong and organized key opinion leaders of child health who are needed to convince the policy makers to allocate more funding towards this area and also to lobby for international funding for appropriate vaccines.

Moreover, the manufacturers have largely ignored developing country markets because there has been little or no scope for them to recover the costs of adapting to the need of developing countries. This is particularly true for the 7-valent pneumococcal vaccine which was developed purely targeting the population of North America and other developed countries, but has relatively limited applicability in many country settings where the strains of the organism that cause death and disability differ.

To overcome these limitations, the Global Alliance for Vaccine and Immunization (GAVI) has been formed, consisting of public health practitioners, philanthropists, and UN organizations. GAVI has created disease-specific initiatives for the accelerated introduction of vaccine, particularly for pneumococcus and Hib. These initiatives were created to expedite the uptake of essential vaccines in the resource-poor countries by helping them to take evidence-based decisions and apply for GAVI funding. One of the main aims of the GAVI initiatives is to make sure that the countries are showing interest to contribute and introduce the vaccine, and manufacturers are building the capacity to consistently supply adequate vaccine for the countries with large birth cohorts.



Historically 15-30 years passed before new vaccines reached the poorest children

However, the uptake rate, despite these initiatives, has not been as fast as was expected, and the success is mostly limited to the vaccines that were licensed more than a decade ago. This is mainly due to the high price of newly licensed vaccine, as the countries consider this as a barrier to sustainability at the end of GAVI funding. Further, GAVI is a short-term solution and limited in scope as it only considers currently available vaccines and cannot plan far ahead for the upcoming vaccines.

These limitations have specific implications on the pneumococcal vaccine - the existing 7-valent vaccine has limited use for developing countries, and next generation vaccines with higher valents will not be available before 2010.

Furthermore, without assurance of demand for its products, it will be extremely difficult to convince the vaccine manufacturing companies to customize a product as per the needs of developing countries and invest for increased capacity to supply the huge populations in countries like Bangladesh, India, Pakistan and others in Asia and Africa.

Finally, even if the countries do manage to collect convincing data on disease burden, they will neither be able to guarantee the purchase due to limited resources, nor will they have the capacity to bargain for the best price commensurate with the huge demand that their large populations could potentially generate.

The AMC and its potential impact on the developing world

Advance Market Commitment (AMC), an innovative financing scheme, has been initiated with a market-based solution to assure that life-saving vaccines reach the poorest children in the shortest possible time between introduction in developed vs. developing countries. AMC has selected pneumococcal vaccine for piloting this study, given the massive number of deaths caused by pneumococcus and the huge success of vaccines. It is expected that the impact of vaccines in respect of child mortality, and the response from the developing countries and manufacturers will be evident within a couple of years. An amount of \$1.5 billion has already been donated by the participating countries for this AMC scheme.

AMC aims to work with the companies not only to bargain a reasonable price based on advanced commitments about the large market for the product, but also to ensure that the vaccine formulation matches the needs of the developing countries. Specifically for pneumococcus, inclusion of common pneumococcal serotypes of developing countries will be a pre-condition. AMC will also work with the developing countries and let them know about the predictable financing from donors, steady supply from the companies with a modest co-payment by the countries. This will make the newly licensed pneumococcal vaccine available in the developing countries soon after licensing instead of after more than a decade.

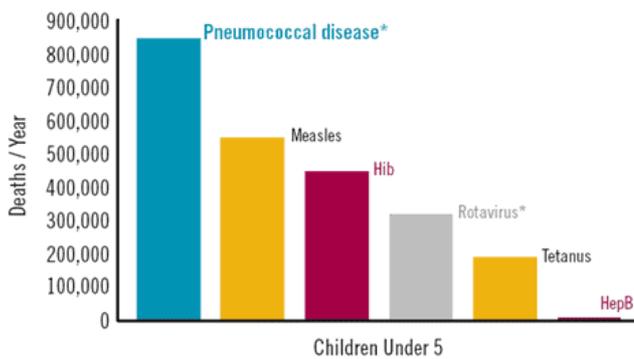
"The pneumococcal vaccine that prevented 9,100 pneumonia cases in a year in the USA, will be saving more than 10,000 pneumonia deaths in Bangladesh."

Excitement about the AMC scheme has already been observed in the developing countries; in contrast to the delay in introduction of Hib and HepB vaccines by more than a decade due to licensing issues, these countries are showing interest to introduce 10- or 13-valent pneumococcal vaccines as soon as they are licensed. AMC has indeed been able to create a win-win situation for all the parties concerned.

First, for the industries, by reducing the market risk of their investment, second, for the countries, by giving the signal that they can get specifically customized vaccine by making only a modest co-payment, and third, for the donors, who will be able to see how efficiently their money is being utilized to save millions of lives within the shortest possible time.

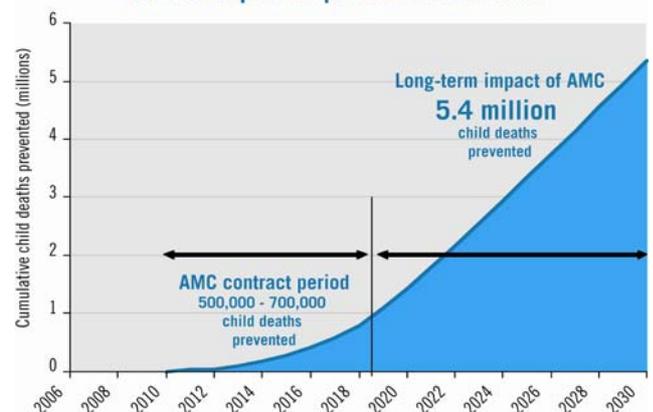
The AMC scheme has been planned for co-funding for 15 years, and during this time, 500,000 to 700,000 lives are expected to be saved. However, the next challenge will be to ensure the sustainability of immunization with pneumococcal vaccine in the post AMC period. This will depend on several factors, such as substantial reduction of vaccine price, so that the country can afford to pay for it; availability of evidence about the benefits of pneumococcal vaccine in respect of preventing child deaths, reducing hospitalization and saving national revenue in the health sector.

Leading Causes of Vaccine-Preventable Death in Children <5 Years Old



Source: WHO official mortality rates — June 2003
* Provisional estimates

Health impact of pneumococcal AMC



The future challenges

To make the expectations really come true and ensure that the impacts of vaccination are evident in the respective countries, academia and international organizations will need to ensure that the respective countries make evidence-based decisions in real-time. Evidence-based decisions for pneumococcal vaccine are very critical as the serotype varies from place to place and so does the coverage of pneumococcal disease by any vaccine formulation.

However, in order to achieve maximum benefit from availability of vaccine, it is important that the countries also strengthen their health systems so the vaccines can be delivered efficiently with high coverage.

Academia and international organizations need to facilitate the establishment of quality surveillance systems to monitor the disease burden and hence reveal the value of pneumococcal vaccine. Surveillance needs to be continued even after introduction of vaccine to appreciate the impact of vaccine and convince the policy makers of the value of co-payments that can make the vaccination programme sustainable. Post-vaccine introduction surveillance is critical for pneumococcal vaccine, as there is a possibility of emergence of pneumococcal disease with new serotypes, called replacement disease.

Quality surveillance, during pre- and post-vaccine introduction periods, is important to weigh the replacement disease carefully along with the benefits achieved, including disease prevented and death averted.

Poor surveillance systems may lead to misinterpretation of isolation of non-vaccine types and relay inaccurate signals to the policy makers. Therefore, continued support from international organizations such as WHO and other UN organizations, the World Bank Group, the Bill & Melinda Gates Foundation, the Wellcome Trust will be imperative to maintain a high quality surveillance team comprising of government policy makers, public health workers and academia of the respective countries.

As pneumococcus has more than 90 different serotypes, the fight against pneumococcal diseases will continue since the organism will not be eradicated by serotype-based vaccine(s), as often was the case for other vaccine-preventable diseases. Thus, it is very important to continue ongoing research to identify a species-wide, protein-based vaccine, which may lead ultimately to the elimination of this organism.

Vaccines to provide protection against the two leading causes of pneumonia deaths — Hib and pneumococcus — are widely available to the wealthy through the private sector but not yet routinely used in India and other major countries in the region.

**The Hindu : Opinion / News Analysis : Vaccines for South Asia and the world
Mathuram Santosham and Orin Levine**

Pneumococcus is killing at least 800,000 children the world over year after year. Meanwhile, the WHO position paper depicts clearly and suggests the worldwide introduction of a vaccine. Current evidence points to an effective pneumococcal vaccine that could begin to save lives now. We should not delay in making necessary decision and taking the proper actions to implement vaccine introduction. Time lost means lives lost. We cannot afford to wait until another million children die next year. We must act now.

Clinicians, investigators, scientists and all other people concerned have done a great deal to make the evidence clear. Now it's time to showcase and translate those works to the policy makers to make them understand the dire need of prompt action.

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