International Journal of Biological Research, 2 (2) (2014) 61-66

International Journal of Biological Research

Journal home page: www.sciencepubco.com/index.php/IJBR
doi: 10.14419/ijbr.v2i2.2923
Review Paper

Immunity in the first year of life and call for vaccination

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Abstract

Children present special needs because of their vulnerability and developmental peculiarities. Early stage protection is critical in children and the immunization in the first year is especially important. Hence to protect them against some of the most dangerous diseases during and beyond the first year of life, it is essential that infants should get all recommended vaccines at the right time. The vaccines work by building up the child's defense mechanism against diseases. Some vaccines require multiple doses for full protection and every child thus, must complete particular immunization schedule. A child who is not immunized is more likely to become sick, permanently disabled or undernourished, and could possibly die. This article explores the current knowledge about the importance of immunity before and after the beginning of human life and reviews the essential vaccines for infancy. It will ultimately help to explore science of immunology and vaccinology.

Keywords: *Infants, Infectious Diseases, Immunity, Immunization, Vaccine.*

1. Introduction

Even though about 2 million lives are saved every year due to vaccination, one-fifth of the world's children (about 19.3 million) still remain without basic immunization and millions of them die from vaccine-preventable diseases (Unicef immunization 2014). Figure 1 indicates the number of deaths due to vaccine-preventable diseases.

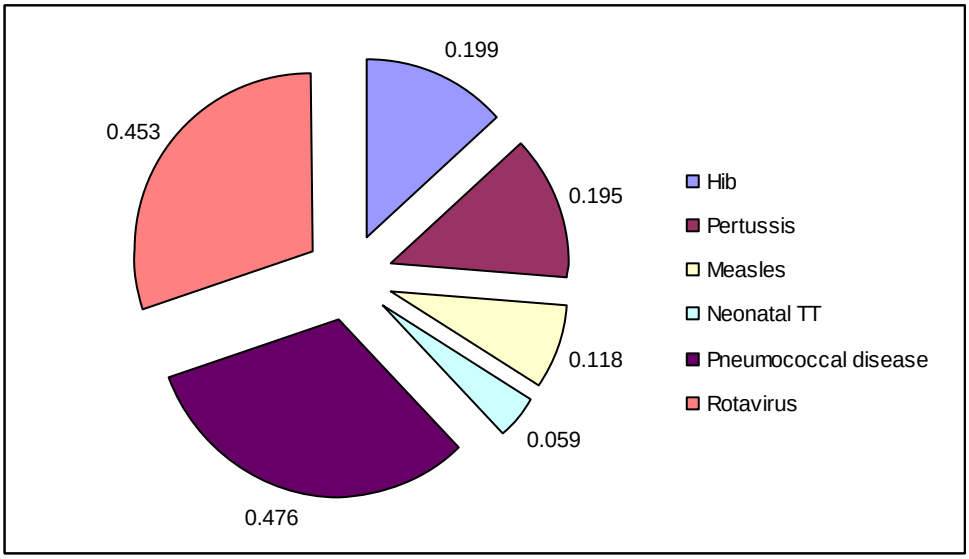

Fig. 1: Deaths Due to Vaccine-Preventable Diseases (in Million), Source: Global Immunization Data, October 2012

Vaccination is an important foundation in saving lives, increasing efficiency, improving poor life style and poverty. Thus, a child is scheduled to receive more vaccines during the first twelve months than any other time in his/her life. This busy vaccination schedule is necessary because the first twelve months is a very special time. During this period a child is not capable to fight against deadly diseases like measles, meningitis etc. since his immune system is not well developed. Therefore immunization is important to safe guard children from potential communicable diseases. Accordingly, more than 30 years ago six diseases viz; measles, diphtheria, neonatal tetanus, whooping cough, poliomyelitis and tuberculosis were specially selected by WHO and their member states and targeted through a plan called Expanded Programme on Immunization (EPI). At present along with the above mentioned vaccines,

many new vaccines are also introduced in different countries in the EPI schedule. The effective vaccination is not only based on technical knowledge of individual vaccine characteristics but also biology of immunization, epidemiology of specific diseases, and host characteristics. Some people worry that vaccines are not safe and may be harmful, especially for children. They may ask their health care provider to wait or even choose not to have the vaccine. But based on scientific studies, the American Academy of Pediatrics, the Centers for Disease Control and Prevention, the Institute of Medicine as well as many other organizations has conclude that the benefits of vaccines outweigh their risks. Hence, every parent should make an informed choice to vaccinate their child for protection against various infectious diseases and for better healthier tomorrow.

2. Immunological development

2.1. Transferable maternal immune protection and immune memory

The immune system matures at very early stage of fetal life. At times, there are certain antigens that may get transferred to foetus during pregnancy. Due to the antigen exposure, consequences for the newborn and infant are a possibility. The period shortly before and after birth may be the key to understanding immunologic memory (Zinkernagel et al. 1996). Since at this stage, the immune system is comparatively incompetent, the transfer of maternal immunity and memory is important for the survival of the fetus, newborn, and infant. The immune system of a pregnant woman stimulates cells that selectively prevent attack and refusal of fetal tissues (Rowe et al. 2012). Similarly for survival of birds and fish this function of transferred maternal antibodies is vital (Zinkernagel 2000, Zinkernagel 2001).

A memory response needs to be generated by the immune system once it is exposed to any antigen. This exposure to the pathogenic antigens can take place in two ways; from immunization, or by infection. These exposures train the system to identify and recognized various antigens and thus the immune memory is generated. When infant is exposed to same antigen further, the immune system will have a swift response and rapidly neutralize the antigens before they do any harm or ameliorate the severity of the infection.

2.2. Development of immunity after birth

Infant immunity is very naïve. Therefore response for few vaccines such as BCG, Oral Polio and Hepatitis B is better when they are planned at birth whereas other vaccines may not be as effective (Committee on Infectious Diseases 2012). The infant's immunity is intact but immature at birth. Every pathogen may cause a disease and possess its own peculiarities. Table 1 includes the highlights about important diseases with risk to young children.

The neonate and infant needs to generate immunity against every pathogen they come across. Mucosal immunity is developed very quickly in the early weeks of life. Its maturation and protection varies among the individuals but irrespective of gestational age at birth it is generally totally developed in the first year (Gleeson et al. 2004). Placental transfers of specific IgG antibody helps the new born to remain protected during the first few months of life (Palmeira et al. 2012). Additionally breast milk provides short-lived defense mechanism through IgA against many common diseases and it has also been shown to assist in the development of the infant's own immune system (Weiner et al. 1999).

Meanwhile, the maternal antibodies decrease over the period of time, and young children, may have underdeveloped immune systems, with much slower rate of antibodies production than adults. Thus, infants need to be vaccinated with several vaccines to help protect them against illnesses in early years of life. Some evidence, although weak, shows that breastfed infants respond better to some vaccines (Hanson 1998). However, the increase of lymphocytes is more important which happens due to the exposure to microbes which colonies the gut during birth.

Table 1: Diseases & Risk to Young Infants & Children

Disease	Risk to young infants & children
Diphtheria	Diphtheria is readily preventable by means of vaccination. In children younger than 5 who are not vaccinated, the mortality rate can be very high.
Polio	Polio mainly affects children under five years of age. One in 200 infections leads to irreversible paralysis. Among those paralyzed, 5% to 10% die when their breathing muscles become immobilized.
Tetanus	Any unimmunised person is at risk from tetanus including infants. The risk is greatest for the very young or aged over 60. Worldwide, about 50% of people who have tetanus die.
Pertussis	Young infants are at highest risk from complications of this disease. Most deaths occur in infants under 1 year of age. Breastfeeding offers no protection from pertussis regardless of the mothers' immune status.
Measles	Measles is one of the leading causes of death among young children even though a safe and cost-effective vaccine is available. In 2011, there were about 430 deaths every day or 18 deaths every hour from measles globally.
Hepatitis B	Consequences of hepatitis are inversely associated with age and 90% of infants during the first year of life may develop chronic infections associated morbidity and mortality.
BCG	In young children, haematogenous spread may result in severe primary disease, including miliary TB and TB meningitis. Neonates aged <6 weeks are regularly skin-test negative.
Rotavirus	Rotavirus is one of the most common causes of diarrhea in children and spreads quickly and easily. Rotavirus infects nearly every child before their 5th birthday.
Pneumococcal	Children two years of age and under have the highest rates of pneumococcal disease. The pneumococcus is also the most common bacterial cause of acute middle ear infections in children.
Hib	Hib can spread to cause mainly meningitis, pneumonia, epiglottitis, orbital cellulitis, osteomyelitis, pericarditis and otitis media. Invasive Hib disease burden is generally highest in children aged between 4 and 18 months.

Source: Information on various vaccines, by Aspen, GSK & Department of Health, Republic of South Africa

2.3. Herd immunity

Herd immunity proposes the theory that if the proportion of the individuals who are resistance to a particular disease is greater, then there is a lower probability that a susceptible individual will come into contact with an infectious individual. Thus it is a form of immunity that occurs when the vaccination of a significant portion of a population provides a measure of protection for individuals who have not developed immunity therefore it plays a very crucial role in protecting people who cannot be vaccinated. These mainly include children who are too young to be vaccinated, people with immune system problems, and those who are too ill to receive vaccines. For example after the introduction of conjugate vaccines against pneumococcal and Haemophilus infections indirect effect have been observed (Paul et al. 2011). However, it is seen that when immunization rates decreases, herd immunity can break down which leads to an increase in the number of new cases. It has been evident in, measles outbreaks in UK. Monitoring and measuring the impact of herd immunity is becoming increasingly important to understand effectiveness of vaccine and for decisions about vaccine introduction and use.

3. Essential vaccines

The concept of essential drugs was developed in 1977 to guide WHO member states to introduce the pharmaceutical products that satisfy the health care needs of the majority of the population (WHO TRS 615:1977, WHO TRS 895:2000). Now days, series of vaccinations starting from birth will protect an infant against deadly infectious diseases. It is one of the most important, cost effective public health interventions to ever take place.
The nature of vaccine greatly influences the type of immunity generated and protective efficacy. (Table 2) Examples of such vaccines include those recommended for use in routine childhood

Table 2: Correlates of Vaccine Induced Immunity

Vaccine	Vaccine type	Serum IgG	Mucosal IgG	Mucosal IgA	T cells
Diphtheria toxoid	toxoid	+ +	+		
Tetanus toxoid	toxoid	+ +			
Measles	live attenuated	+ +			+ ($CD8^+$)
Pertussis (whole cell)	killed	+ +			
Pertussis (acellular)	protein	+ +			
Tuberculosis (BCG)	live mycob				+ + ($CD4^+$)
Polio Sabin	live attenuated	+ +	+ +	+ +	
Polio Salk	killed	+ +	+		
Pneumococcal	protein	+ +	+ +		
Rotavirus	live attenuated			+ +	
Hib (glycoconjugates)	protein	+ +	+ +		
Hepatitis B (HBsAg)	protein	+ +			
Yellow fever	live attenuated	+ +			

++high, + moderate
Source: Book Vaccines by Stanley A. Plotkin, Walter A. Orenstein & Paul Offit, Chapter 2: Vaccine Immunology by Claire-Anne Siegrist, 2008

immunization programme; Bacille Calmette-Guérin (BCG) against tuberculosis, diphtheria-tetanus-pertussis (DTP), oral polio vaccine (OPV), tetanus toxoid (TT), measles, hepatitis B, haemophilus influenzae type b (Hib) and, where disease epidemiology supports them, yellow fever etc. Essentials vaccines for Japanese encephalitis B (WHO WER Japanese encephalitis 2006), rabies (WHO WER Rabies 2010) or rubella (WHO WER Rubella 2011) are covered by WHO recommendations in accord with national priorities.

3.1. Diphtheria

Diphtheria vaccines are based on diphtheria toxoid, a modified bacterial toxin that induces protective antitoxin. The WHO recommends 3 doses as a primary immunization series to the infants. The diphtheria containing vaccine has to be given at minimum 4 weeks apart starting as early as 6 weeks of age. Immunity against diphtheria is primarily depends on antibody against the diphtheria toxin. Following the immunization or during the disease or carrier stage, corynebacterium diphtheriae produces the diphtheria antitoxin. It is distributed throughout the body. Antitoxin levels below 0.01 IU/mL are considered as non-protective, whereas levels of 0.1 IU/mL or more are considered completely protective. Long term immunity is assured when antibody levels are 1.0 IU/ mL or more (WHO WER Diphtheria 2006). Cell-mediated responses to toxoid also happen and it is possibly associated to supporting immunologic memory (WHO WER Diphtheria 2006).
There is an age-related host response to immunization with diphtheria toxoid. The important factor is the modifying effect of passively-acquired maternal antibodies in young infants. Some studies showed infants without maternal antibodies and older children had similar response to diphtheria toxoid (Scheifele et al. 2009). Normally after second dose of diphtheria toxoid, the antibody level starts to increase. After three doses i.e. the primary immunization series, 94%–100% of children attain protective antibody levels i.e.> 0.01 IU/mL. Booster doses at the age of 12–24 months and at school entry have been recommended by world health organization.

3.2. Measles

A measles vaccine is a freeze-dried. It contains live attenuated measles virus propagated on human diploid cells. It induces humoral and cellular immune responses which is similar to natural measles disease. Antibodies start to appear around 12 to15 days after immunization and normally peak at 21 to 28 days. Antibodies especially IgM appear transiently, whereas IgG antibodies persist for many years in blood. IgA antibodies are mainly present in mucosal secretions. Virus-specific CD4+ and CD8+ T-lymphocytes are also induced by measles immunization (Ovsyannikova et al. 2003, Wong-C et al. 2004). Following vaccination development of protective antibodies depend on the presence of inhibitory maternal antibodies. Vaccine dose, strain and the immunologic maturity of the recipient, also plays vital role in inducing the protective immunity. One dose of measles vaccine gives approximately 82%-95% protective immunity level at 9 months of age (WHO WER Measles 2006). If given at the age of 11-12 months when immunity of all children has almost vanished, vaccine sero-conversion and effectiveness may be achieved up to 93%-100% (WHO WER Measles 2006).
Those children who poorly responded to first dose and those who never received a single dose should be given another opportunity for measles immunization. Poorly responded children generally have a distinctive primary immune response, wherein initial production of IgM antibodies is followed by high levels of IgG antibodies (Watson et al. 1996).

3.3. Tetanus

Tetanus vaccines are based on tetanus toxoid. Strains of Clostridium tetani grows in liquid medium which supports toxin production. If Toxoid is adsorbed on aluminium or calcium salts it increases the immune response. Immune response is antibody-mediated and mainly depends upon the capability of antitoxins to neutralize tetanospasmin. The immunity to tetanus can be achieved only by either active or passive immunization and clinical disease does not offer any protection in the future. If during the pregnancy the mother receives doses of tetanus toxoid, it offers protection to both child and mother against birth associated tetanus. This is because maternal tetanus antitoxin passes through the placenta to the fetus. 80% of tetanus antitoxin remains present in the circulation of new born during the initial months. Only IgG immunoglobulin is transfer in a selective manner to the fetus by human placenta which gradually increases IgG antibody levels from the second trimester of pregnancy until term.
The minimum amount of circulating antitoxin that in most cases ensures immunity to tetanus is assay-specific. As measured by an in vivo neutralization assay 0.01 IU/mL is the minimum level of antibody required for protection (Borrow et al. 2007). At birth, the newborn generally has equivalent or higher antibody concentration than the mother. Antitoxin levels for tetanus in cord and maternal serum were usually similar as per the previously available data. However around 20% to 30% of cases the maternal serum had a higher titer than the cord serum (Borrow et al. 2007). Efficacy has been in a range from 80% to 100% in most of the clinical trials. Also mortality due to neonatal tetanus has been substantially reduced in many countries after large-scale introduction of tetanus vaccination (WHO WER Tetanus 2006). The antibody titres, avidity and also the duration of sero-protection depend on a number of factors, like the age, number of doses and their intervals. For ini-

tial protection in infancy to 5 yrs three doses are enough. Further booster is needed for protection in adolescence, and another 1 or 2 more booster(s) dose will stimulate immune system well enough to protect the adulthood nearly for 20-30 years.

3.4. Pertussis

Whole cell pertussis (wP) vaccine is suspension of bacteria bordetella pertussis that has been inactivated usually by formalin. The immune response to whole cell pertussis (wP) vaccines is intended for an array of antigens of whole bacterial cells. Total collective effectiveness of whole cell pertussis vaccine in children receiving three doses of primary series was raged from 61 to 89% (Jefferson et al. 2003). Typically antibodies are passively transferred to newborns from their mothers. Although antibodies are acquired from mother, the vulnerability of newborns and infants has been well observed. Thus during first few months of life newborns might not be protected against the pertussis, reporting higher number of cases in the first six months of life.

Acellular pertussis vaccine (aP) is a new type of vaccine released around 1996. It takes helps of advances in protein chemistry and purification. The immunogenicity and effectiveness of the acellular and whole cell pertussis differ depending upon the case definition of pertussis used. In general the whole cell vaccine is more efficacious, however, the finest aP vaccines have higher efficacy when compared to wP (WHO WER Pertussis 2010). Recent study shows that, protection against whooping cough starts to weaken a few years after preschool children get their final diphtheria, tetanus and acellular pertussis (DTaP) shot because it might provide less-complete or shorter-lasting protection (Tartof et al. 2013). In order to maintain protection against pertussis throughout life, infant immunization schedules are being extended in many countries to include pre-school boosters, and also vaccination of adolescents and adults.

3.5. Poliomyelitis

Two polio vaccines are used throughout the world to combat poliomyelitis (polio). The first is as Polio Salk, it consists of an injected dose of inactivated (killed) poliovirus. Second is Oral Polio Vaccine (OPV); Polio Sabin has 3 vaccine strains (Sabin 1: type 1, Sabin 2: type 2 and Sabin 3: type 3). It is live, attenuated vaccine wherein polioviruses are derived by passage of their parent wild polio virus strains in nonhuman cell (WHO WER Polio 2010). When immunity is passively acquired by fetus from the mother, the concentration of type 1 and type 2 IgG antibodies is similar in newborn and the mother. However type 3 antibodies are higher in mother, suggesting differential transplacental transfer of this serotype. The half-life of maternal antibodies is about 30 days (range 21 to 50 days) and rate of its decay is constant (Robertson 1993).

A birth dose of OPV is not count towards the primary series and thus commonly recognized as zero dose, and it has been recommended in polio endemic regions and countries at high risk. . The primary series of three OPV or IPV (Injectable Polio Vaccine) immunization should be given as per national immunization programme, for example at 6-10-14 weeks, or at 2-4-6 months. In global polio eradication initiative OPV has been extensively used which eradicated WPV type- 2 and eliminated WPV type-1 and type-3 in few WHO regions. In remaining WHO regions, number of cases were drastically decreased (>99%) (WHO WER Polio 2010).

3.6. Bacille calmette–guérin (BCG)

BCG is a vaccine against tuberculosis that is prepared from a strain of the live attenuated tuberculosis bacillus. Protection against disease is associated with a Th1 T-cell response involving interferon (IFN)-gamma-producing CD4+ T-cells. IFN-gamma has a key role in protective immunity through activation of macrophages. Various other effectors molecules and immune cells like TNF-α, IL-12, IL-17, IL-23, γ/δT cells, NK T cells and regulatory T cells also takes part in tuberculosis protection (Nicole et al. 2008). Mycobacterium tuberculosis is an aerobic, intracellular pathogen that stimulates both cellular and humoral immune responses. It has been established that infectivity with mycobacterium other than M. tuberculosis, as well as the BCG vaccine, may bring a little safety against tuberculosis. The infection initiates from the inoculation site and travels through lymphatic system to lymphatic nodes. Thus it brings immunity similar to natural infection. Cell mediated immunity and activated macrophages plays major role in naturally acquired tuberculosis infection (Barker et al. 2011). BCG vaccine is recommended immediately after the birth, in high-disease burden countries. After 20 years the protection generally decline to non-significant level (WHO WER BCG 2004).

3.7. Hepatitis B

HBsAg is the active substance in recombinant hepatitis B vaccine. It has been produced in yeast or mammalian cells into which the HBsAg gene (or HBsAg/pre-HBsAg genes) has been inserted using plasmids. Healthy infants, children and young adults achieves protective antibody concentrations >95% after the primary 3-dose immunization series (WHO WER Hepatitis B 2009).

Hepatitis B vaccine should be administered along with combination vaccines or separately as part of existing routine immunization schedules. All newborns should be given 3 to 4 doses of vaccine for prevention. In cases where risk of mother-to-infant spread is high, the birth dose should be given within 12-24 hrs after the birth or as soon as possible. Vaccinees are considered to be protective for minimum 20 years and can be life long. In case of HBsAg positive mother, Hepatitis B Immune Globulin (HBIG) along with Hepatitis B vaccine should be administered within 12 hours of birth, using two separate syringes and separate sites for injection.

3.8. Haemophilus influenza type B

Conjugate Hib vaccines are liquid or freeze-dried preparations of polyribosylribitol phosphate (PRP) covalently bound to a carrier protein. Invasive hib disease is predominantly a disease of early childhood. The incidence of Hib disease is relatively low in the first few months of life due to the transfer of maternal IgG specific for PRP across the placenta. In some indigenous populations incidence of early invasive disease is high in spite of maternal antibodies. Generally, once maternal antibodies wane, the incidence of disease increases, but by the age of five years the incidence of disease is universally low and remains low throughout adulthood with only a small increase in the incidence in the very elderly (Farley et al. 1992). Like other bacterial-derived polysaccharides, PRP is classified as a T-independent antigen stimulating B cells directly without the help of T cells, and antigens of this type are known to be poorly immunogenic in childhood. Thus one of the reasons that young children are so susceptible to invasive hib disease is that they are unable to mount robust responses to pure polysaccharide antigens before approximately 18 months of age.

In protection against hib disease, humoral and cellular immunity plays a vital role. IgG, IgM and IgA antibodies to PRP may all be induced by infection as well as vaccination. After one month of primary immunization PRP antibody concentration of >0.15 μg/ml and ≥1.0 μg/ml are considered as serological marker for short term and long term protection respectively.

3.9. Pneumococcal

Pneumococcal vaccines based on chemical coupling of S. pneumoniae polysaccharides to an immunogenic protein carrier. This enhances the antibody response and induces immune memory (McCool et al. 1999).

The occurrence of pneumococcal infection is more during early childhood, and in elderly and those with lower immunity. Nasopharynx is the reservoir for bacteria and it is transmitted by droplet spread between individuals. During first year of life,

pneumococci carriage is most frequent, but varies across different environmental and socio-economic background. Recent studies show that large proportion of pneumonia in young children is caused by the pneumococcus. It kills around 700 000 to one million children having less than five years of age every year (Käyhty et al. 2009). Many clinical studies have reported high antibody concentrations in infants till the age of 4 months, mainly because of maternal immunization (Lehmann et al. 2002, Stevenk et al. 1996). Additionally antibody transfer from breast milk and placenta can be significant for protection. The serological criteria defined by WHO include (i) the percentage of subjects with serotype-specific IgG ≥0.35 µg/ml using a WHO reference assay (or an alternative and well-justified threshold value based on a specific in-house assay) and (ii) the serotype-specific IgG geometric concentration ratios.

3.10. Rotavirus

Presently available rotavirus vaccines are live, oral, attenuated strains of human and/or animal origin that replicate in the human intestine. Serum immunoglobulin IgM, IgA, and IgG levels as well as stool and intestinal antibodies are routinely used to measure immune responses following vaccination as a determinant of vaccine "take". For each serotype specific neutralizing antibody titres can also be measured. Rotavirus vaccine has shown around 70% seroprotection against rotavirus gastroenteritis (of any severity). For sever rota infection, the efficacy is higher and ranged from 85% to 100% as seen during various clinical trials across globe (Ruiz-Palacios et al 2006, Vesikari et al. 2006).

Severe rotavirus disease in humans is most common between 6 to 24 months of age. Till the age of 6 months maternal antibodies provides resistance to rotavirus after which alarming incidence of increase in rotavirus disease is seen (Ward et al. 2011). Due to immune response stimulated by earlier infections the severity of disease is generally less in adults and older children after further occurrence of disease. Both humoral and cellular immune response is necessary for protection against Rota infection. Though rotavirus infection provides short term immunity and protects from severe subsequent infections, it does not provide immunity for life long. Moreover, several cases of sequential illness have been reported.

4. Clinical trial issues and challenges

Immunity of newborns represents one of the largest challenges for vaccine clinical trials. Effective immunization is complicated by various factors, including the immaturity of the immune system, a general Th2 bias of the immune response, deficiency in antigen presentation, as well as interference with immunity by passively transferred maternal antibodies (Gudmundsdotter et al. 2008). Moreover, in case of pre-term and low birth weight infants, it becomes increasingly more difficult to assess the efficacy. These infants are also at increased risk of experiencing complications from vaccine-preventable diseases mainly due to associated factors like malnutrition, overcrowding and the presence of intestinal viruses and bacteria. In order to develop protective responses through immunization, it is important to clarify these first.

Technical limitations include a lack of immunological correlates (i.e. a measure of the effectiveness of vaccines by laboratory assays on a blood sample from the vaccine) and a lack of immunological tools that can be used to find correlates of protection and understand the phenomenon of sterilizing immunity. For example, it is difficult to determine the correlates of protection for the TB vaccine. Also, for pertussis antibodies, serological correlate of protection is not yet established (WHO WER Pertussis 2010, WHO TRS 941:2007). Immunization schedule differs as per current practices in the region, also as per manufacturer recommendations. E.g. few countries continue to give an additional BCG booster, while other recommends three BCG doses, with the third given between the ages of 12 and 15 (Zwerling et al. 2011). These issues pertaining to clinical development pose a challenge and require trial design, resources and timelines to be set accordingly.

5. Conclusion

The protection against infection afforded by vaccination is one of the great successes of medicine. Vaccines have prevented millions of deaths, more than any other remedial measure for last 20 years (Table 3). Experience and judgment of public health officials and specialists in clinical and preventive medicine are important in developing recommendations for immunization. It will maximize benefits and minimize risks and costs associated with immunization. Consequently, general guidelines for immunization practices must be based on evidence and expert opinion about vaccinations and current epidemiology of disease. Today, increasing number of the children is being administered with newer life-saving vaccines, like pneumococcal, rotavirus and varicella. At the same time several vaccines like dengue, clostridium difficile, pseudomonas aeruginosa, malaria and cholera are under development. New technologies would help in a big way to ensure vaccine tolerability, storage and logistics. It would enable immunization programs to save human lives.

There may be minor variations in vaccination schedule between various medical offices. Since there is a window of time when the baby is recommended to receive many of the vaccines, each medical practice may tailor the immunization schedule to fit into the flow of the practice. It will eventually make immunization a valuable tool for protecting public health.

Table 3: Levels and Trends in the Under-Five Mortality Rate, By Millennium Development Goal Region (MDG), 1990–2011 (Deaths /1,000 Live Births)

Region	Year						MDG target	Decline %
	1990	1995	2000	2005	2010	2011	2015	(1990-2011)
Developed region	15	11	10	8	7	7	5	55
Developing region	97	91	80	69	59	57	32	41
Northern Africa	77	59	45	34	26	25	26	68
Sub-Saharan Africa	178	170	154	133	112	109	59	39
Latin America	53	43	34	26	22	19	18	64
Caucasus & Central Asia	76	70	61	52	44	42	25	44
Eastern Asia	48	45	35	24	16	15	16	70
Excluding China	28	36	30	19	17	17	9	38
Southern Asia	116	102	88	74	63	61	39	47
Excluding India	119	103	87	72	62	60	40	50
South-eastern Asia	69	57	47	37	30	29	23	58
Western Asia	63	52	42	37	31	30	21	52
Oceania	74	67	61	56	51	50	25	33
World total	87	82	73	63	53	51	29	41

Source: Levels & Trends in Child Mortality Report 2012, by UN Inter-Agency Group.

6. Disclaimer

All opinions expressed herewith are those of the authors and do not reflect the views of their organization.

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