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Vaccination in Developing Countries: A Review of Probable Factors for Lower Responses to Vaccine

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ABSTRACT

Prevention of infectious diseases by immunization in children has markedly diminished the morbidity and mortality of once common contagious diseases in many countries worldwide. Immunization programs have led to the global eradication of smallpox, elimination of measles and poliomyelitis in regions of the world, and substantial reduction in the morbidity and mortality attributed to diphtheria, tetanus, pertussis, and measles. Childhood vaccination was estimated to prevent more than 2.5 million deaths for vaccine preventable- diseases each year. However, at current levels of coverage, it still causes 1.7 million deaths annually, most of them in developing countries.

The main objectives of this review are as following:

To overview the expanded programme of immunization and WHO global vision and strategies for vaccination.

To review underlying mechanisms that influence host immune response to vaccine, and differentiate primary from secondary vaccine failure.

To determine the environmental factors that may reduce the potency of the vaccines or vaccinees.

To explain the probable factors that lead to lower responses in vaccine recipients in developing countries.

Introduction

Expanded programme of immunization and Global immunization vision and strategies

Before 1974, in most developing countries vaccination programs were restricted to the urban School-aged children despite the fact that diseases mostly affect young children. Since 1974, the Expanded Programme of Immunization (EPI) was established to make immunization available to every child in the world by 1990. In this period, efforts were made to establish physical and human resources to deliver vaccination and monitor vaccine

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coverage. In the next years, the aims were expanded to control specific diseases. Current goals of the global EPI were laid out in the Global Immunization Vision and Strategy (GIVS) developed by WHO and UNICEF. The newly established GIVS outlined four major strategies: to increase vaccine coverage, introduce new vaccines and technologies, implementing surveillance within health systems and global independence.[1] The WHO encourages countries to select vaccination schedules that are epidemiologically relevant, immunologically effective, operationally feasible, and socially acceptable. In developing countries, the first priority of immunization suggested by EPI was to ensure that infants are completely immunized against targeted diseases at the youngest age possible. Booster doses should be considered when coverage levels for fully immunized infants exceed 80%. With increasing success of immunization programs and availability of new vaccines, the GIVS encourages countries to expand protection to older age groups both through booster doses and adding new vaccines for old children, adolescents – adults, and to integrate immunization with other health programs where feasible.[2] Under the direction of GIVS, many countries achieve high levels of vaccination coverage, however, the number of children under one year of age who did not receive DTP_3 vaccine worldwide was 23.2 million in 2009, most of them in developing countries. [2], [3]

How do vaccines induce immune Responses?

Induction of immunity in an adequate proportion of the population is required to control or eliminate a given disease. This can be provided by vaccination programs. Vaccine-induced effectors are essentially antibodies, "produced by B-lymphocytes", and cytotoxic T-lymphocytes above a threshold level. In addition, long-term protection requires the persistence of vaccine induced antibodies and/or generation of immune memory cells with the ability of rapid and effective reactivation upon subsequent antigen exposure. The generation and maintenance of both B and CD8-T cell responses is provided by CD4-T helper lymphocytes (T- dependent responses). Numerous determinants modulate the intensity of primary vaccine–induced responses. The main determinants include: vaccine types and nature, vaccine schedules and interval between doses and boosting, age of immunization, host underlying conditions, and environmental factors.[2,4]

The types and nature of a vaccine directly influence the magnitude of responses to it. Similar to natural infection, live attenuated viral vaccines replicate in the body and elicit the strongest immune responses through both B and T cell activation (T-dependent response). This induces higher and more sustained antibodies along with induction of immunologic memory in the vaccinees. However, in the most appropriate age for vaccination a minority (<5%) does not respond to a single dose (primary vaccine failure [PVF]). The rate is higher among infants who are vaccinated earlier than appropriate age for vaccination. This would result in accumulation of susceptible individuals in the community over time, and causes disease outbreaks.[5,6,7] The above mentioned pattern was observed in measles vaccination in both developed and developing countries. Outbreaks of measles occurred in highly vaccinated individuals in USA during 1980s-90s following single dose of measles vaccination.[8,9] In developing countries, where measles vaccine is usually administrated at the age of 9 months "with 100% vaccine coverage" approximately 15% of children are not protected and PVF can be expectedly play an increasing role in outbreaks in the future.[6,7,10, 11, 12, 13] Reduce in vaccine potency due to inappropriate handling and storage (more common in developing countries), would

complicate the situation and large outbreaks may occur. [13] Schedule consisting a second dose of measles containing vaccine, led to control and elimination of measles.[5, 6, 7, 10] Also, the same virus strain of vaccines produced by different manufactures may induce dissimilar immune response.[5,14] This pattern was observed in a nationwide measles epidemic in Ukraine and other immunogenicity studies reported from other developing countries.[15] During years 2005-06 more than 50000 measles case were reported.[16] Many reportedly had received two doses of measles vaccine, produced in former Soviet Union States. In two separate immunogenicity studies measles-mumps-rubella (MMR) and vaccines produced by manufactures in developing countries were evaluated among ≥12 month old infants and MMR revaccination in children aged 18 months Vs 4-6 years, respectively. The immune response rate to components of vaccine were much lower than expected or reported in developed countries.[17, 18]

Similar to live attenuated vaccines, most inactivated but polysaccharide vaccines exert their effects via both B and T-cells (T-dependent immune response) and stimulate immune system at the site of vaccine administration, and activation remains more limited both in time and space. For high and sustained antibody responses induction by inactivated vaccine during primary immunization series, schedules consisting repeated doses with appropriate space are required. The magnitude of infant's antibody response to multiple doses schedules reflects both the time intervals between doses (longer intervals stronger response) and the age that the initial and the last dose are administrated. Accelerated infant vaccine schedule recommended by EPI for developing countries may result in lower response rate. This may lead to more rapid loss of vaccine-induced immunity later in life. In the absence of subsequent antigen exposure naturally or booster doses, antibodies elicited by primary series of inactivated vaccine immunization wane over time, and reach below protective thresholds. This time correlates directly with antibody titers, i.e. higher titers induced by primary series would results in slower decline. However, in the absence of protective level of antibodies, immune memory may not be sufficient to protect against diseases characterized by a short incubation period [secondary vaccine failure (SVF)].[1] The need for boosters to confer long-term vaccine protection is illustrated for pertussis, where boosters are required to extend protection beyond childhood.[19],[20] The same is true for diphtheria as shown by outbreaks in Eastern Europe and former Soviet Union.[21],[22] The number and frequency of booster doses depend on the epidemiologic patterns of disease in a particular country, health service infrastructures, resource availability, and relative priority of boosters.[1,2] The EPI first priority of immunization was to ensure that infants are completely immunized against targeted diseases at the youngest age possible.[23] Booster dose should be considered where coverage exceeds 80%. Globally, in year 2009, the number of countries reaching ≥90% immunization coverage with DTP_3 was 122 and one dose of measles vaccine coverage of children by their second birthday was 82% .[3]

"However, polysaccharide antigens fail to activate T-cells, instead they activate B-cells directly (T– independent response), hence, they elicit weaker and shorter antibody responses without immune memory."

Age at the time of immunization is another important determinant that influences the immune responses to vaccines. Early life immune responses to all vaccine types markedly differ from those elicited in mature

hosts. This would be reflected by lower antibody responses and low number of memory B-Cells. These immune responses take place in an environment that may be influenced by the presence of maternal antibodies.[4] The inhibitory effects of this passive immunity on infants' B Cells responses influence all vaccine types, although, they are more prominent for live attenuated viral vaccines. This effect is antibody titer dependent or is a reflection of antibody titer to antigen dose ratio. [24]

The optimal timing for administration of a given vaccine depends on both age-specific risk for diseases/complications, and/or ability of vaccinees to induce response by vaccine. Early infancy has the greatest risk of serious complications for naturally occurring infections, but very young infants do not immunologically respond as well as older children.[4] In the developing world EPI vaccine-preventable infectious diseases were responsible for the majority of deaths among children <5 years of age. Since 1981 in developing countries EPI has recommended that infants should receive EPI vaccines as early as possible in life in order to minimize the time of being at risk of contracting these vaccine-preventable diseases. According to EPI primary series of Oral Polio Vaccine (OPV), inactivated Diphtheria-Tetanus toxoids and whole cell pertussis DTP vaccine should be adminstrated at 4-6 weeks of age and two subsequent doses should be delivered at 4-6 weeks intervals.[23] Although, the mentioned program has led to immune response rates similar to response in children vaccinated at older age and more spaced interval. However, the mean antibody titers were lower in younger one. OPV administrated in infants during the first week of life is not influenced by passively-acquired maternal antibodies, which resulted in intestinal local and serum antibody response in 50-100% and 30-70% of vaccinated newborns, respectively. Vaccination at the age of 4-8 weeks elicits response similar as older infants.[24] Wilkins et al evaluated the effects of age at time of initial dose and the interval between subsequent doses. They showed that optimum immune response to pertussis was best achieved by commencing immunization at five months of age or more.[25]In another study the inhibitory effects of maternally-originated antibodies on two-month old infants' immune responses to pertussis vaccine was determined. This evaluation indicated that there were no significant differences on seroimmunity rates and mean antibody titers between two groups of infants with and without antibody before vaccination.[26], [27]

In contrast, the effectiveness of vaccination against measles, the leading cause of vaccine-preventable deaths in children globally is greatly influenced by the level of maternal antibodies to measles –virus during infancy.[17]The optimal timing for measles immunization depends on the rate of antibody disappearance and the risk of exposure to measles-virus in the community. In many developing countries, where measles is highly endemic, routine measles vaccination is recommended at the age of 9 months. In a high quality practice of vaccination, measles elimination cannot be achieved by a single dose of measles vaccine if the coverage is uniformly high, timely, and sustained.[28] Some studies indicated that children immunized at routine time had significantly higher antibody titers than children immunized at ≤10 months and reimmunized at ≥15 months of age.[29] Assuring adequate supply of safe and effective vaccines will continue to be a major challenge during the next decade. The global supply of EPI vaccine is fragile, and is threatened because of decreasing number of manufactures. Developing counties manufactures are now playing an increasing role in EPI vaccines production. Initial assessments of many vaccine producers in developing countries highlighted the need for improvements in production

processes. Less potent vaccines produced in developing countries may result in a lower immune response quantitatively and qualitatively in vaccines.[16, 17, 18]To assure the quality of EPI vaccines produced in developing countries, WHO has led efforts to examine the global status of vaccine production, supply, quality, and to strengthen national regulatory authorities in those countries.[1]

Accelerated vaccine schedules recommended by EPI, limited availability of booster doses. PVF and SVF along with lower vaccine coverage may have important role in lowering the rate of vaccine-induced immunity in developing countries which may have great impact on immunization programs.

Environmental factors also play a vital role in the effectiveness of vaccines. Vaccine must be properly shipped, stored and handled to avoid loss of their biologic activities and potency. Exposure to temperature higher or lower than recommended may result in loss of vaccine potency, leading to inadequate immune response in vaccinees. Frequent logistic problems, insufficient refrigeration equipments, and unreliable power or fuel supply may threaten the potency of vaccine, especially in tropical countries. Although success in the implementation of the cold chain has greatly reduced this problem but it resulted in higher vaccine wastage which in turn threatens secure vaccine supply. In addition, other factors that may influence the vaccine potency or host immune responses include: inappropriate maintenance of cold chain for specific vaccines, use of reconstituted vaccine, drawing of a vaccine into multiple syringes before their immediate need, inappropriate route of administration, inappropriate space between live vaccines and interference of IgG.[30], [31], [32]

Certain underlying conditions which are more common in developing countries may also negatively influence the immune responses to vaccines. These include acute and chronic diseases and stress, nutritional deficiency[33, 34, 35, 36], and also conditions that may limit the persistence of antibody in the host because of higher catabolism rates such as malaria or by increased Entero – Urinary tract losses.

Conclusion

In spite of brilliant past and promising future, still millions of people do not benefit from protection provided by vaccines. Based on this review, in developing countries many factors result in hyporesponsiveness or lower protection achieved by vaccination. The most important factors contributing to this decay are the nature of vaccines, accelerated vaccine schedules, administration of the final dose at earlier age, maternal antibodies inhibitory effects, ABC limited facilities for maintaining cold chain, acute or chronic infectious diseases or illnesses and nutritional deficiencies which are more common in developing than developed countries. Furthermore, low vaccine coverage or supply and limited resources are somewhat responsible for lower responses to vaccine in developing countries.

To reach the disease reduction and control, and immunization coverage goals, policy makers and global partners must be dynamized to sustain and even increase assistance to poor countries. Further reduction of mortality from vaccine preventable diseases must remain as one of the principal priorities for global public health action. To overcome the aforementioned problems, expanding services in countries that need them most, assuring a sufficient vaccine supply, increase the quality of vaccines produced by developing countries, increasing vaccine coverage, active surveillance for vaccine-preventable diseases along with socio-economic improvement are among the top priorities to achieve EPI goals in near future in the world.

Conflict of Interest

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