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Review

The role of vaccines in elimination and global eradication of measles: A review of literature

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This review summarizes the role of vaccines in elimination and global eradication of measles-a review of literature. Measles eradication is defined as the interruption of measles transmission worldwide as a result of deliberate efforts; intervention methods may no longer be needed. It represents the sum of successful elimination efforts in all countries. Indeed, measles transmission has been interrupted in several countries, reinforcing the view that measles eradication is technically feasible using existing vaccines, laboratory techniques and intervention strategies. However, measles still accounts for 10% of global mortality from all causes among children aged less than 5 years (That is, approximately 1 million deaths annually). Vaccination proper coverage is key indicator of campaign success and to predict control on measles. In Nigeria where there is perennial, low routine vaccination coverage and where the quality of the mass immunization campaign is not high enough, large and persistent measles outbreaks continue to occur with high morbidity and mortality. Immunization and vaccination remains one of the most cost effective strategies to prevent infectious diseases. However, the most effective and efficient way to protect the health of children is by immunization before the risk of disease arises. Vaccination has succeeded in eradicating small pox in the world, soon would be achieved with polio and measles will be next to reach the same degree of disease control (viz, worldwide eradication) as has occurred with smallpox. The efficacy of vaccination and immunization in reducing the incidences of several diseases is clearly shown by the success story of measles control in developed countries of the world. However, intensified efforts are necessary to implement appropriate control and elimination strategies, including supplementary vaccination campaigns, expansion of routine vaccination services, and surveillance.

Key words: Antibody, elimination, eradication, immunization, measles, measles virus, measles vaccine, vaccination.

BACKGROUND OF THE STUDY

Measles remains a leading cause of death among young children, despite the availability of a safe and effective vaccine for the past 40 years. An estimated number of 345 000 people with the majority of them being children, died from measles in 2005 (the latest year for which figures are available) (WHO, 2007). Measles is one of the most contagious diseases known. Almost all non-immune children contract measles if exposed to the virus.

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As a respiratory disease, measles virus normally grows in the cells that line the back of the throat and in the cells that line the lungs. Measles is a human disease with no known animal reservoir (WHO, 2007) . The name measles is derived from the latin, misellus, meaning miserable (WHO, 2007). It is one of the most contagious diseases known to man and often occurs in explosive epidemics characterized by high fever of 38°C or more; plus the appearance of maculopapular rash of about 3 days or more; with one or more of the following symptoms: coryza, cough, conjunctivitis and Koplik spots in the oral mucosa of measles' victims (White and Fenner, 1994). Measles and its complications are responsible for more children deaths world wide than all other childhood vaccine preventable diseases combined and more than any other single specific agent. This is best illustrated by Christensen's Greenland study in 1953. It produces significant illness, death, and lifelong disabilities including brain damage, blindness, deafness (Pan American Health Organization, 2005; WHO, 2007); and infects ap-proximately 40 million people resulting in nearly 1 million deaths annually in developing countries (Oldstone, 1998). Mortality rates can exceed 10% in certain areas and severe sequelae of measles infections include giant cell pneumonia, inclusion body encephalitis and subacute sclerosing pan encephalitis [SSPE] (Wen bo xu et al., 1998). It is spread through respiration (contact with fluids from an infected person's nose and mouth, either directly or through aerosol transmission), and is highly conta-gious, 90% of people without immunity sharing a house with an infected person will catch it. These serious com-plications are rare in developed countries where measles vaccine is widely available, the highest mortalityis however found in poor nations (WHO, 2004).Measles transmission has been interrupted in several countries, reinforcing the view that measles eradication is techni-cally feasible using existing vaccines and intervention strategies. However, measles still accounts for 10% of global mortality from all causes among children aged less than 5 years (That is, approximately 1 million deaths an-nually) (CDC, 1998). The disease has remained the fifth leading cause of deaths among children less than five years of age, worldwide (Strebel et al., 2003). It accounts for 44% of total deaths due to vaccine preventable diseases (VPD), among children less than 15 years, the highest mortality occurring in poor communities with malnutrition, overcrowding and low vaccination coverage (WHO, 2002).

Today, despite the availability of safe, effective and relatively inexpensive vaccine for more than 40 years, measles still kills more than any other vaccine preventable disease among children as shown in Table 1(Rima et al., 1997; WHO/AFRO, 2004; WHO, 2006).

However, uptake of vaccination services is dependent not only on provision of these services but also on other factors including knowledge and attitude of mothers (Matsumura et al., 2005; Torun and Bakirci, 2006), density of health workers (Anand and Bärnighausen, 2007),

Table 1. Measles cases and deaths 1989-2007.

Year	Number of cases	Number of deaths
1989	33678	831
1990	115682	1399
1991	44026	388
1992	85965	1032
1993	54734	373
1994	106084	695
1995	49880	671
1996	102166	2031
1997	73677	147
1998	104069	1804
1999	217159	749
2000	110242	269
2001	169001	2294
2002	87941	811
2003	141633	2929
2004	82227	204
2005	149561	648
2006	18669	225
2007	12925	230

Source: Adu (2008).

accessibility to vaccination clinics and availability of safe needles and syringes (Odusanya et al., 2008).

Immunization and vaccination remains one of the most important public health interventions and a cost effective strategy to reduce both the morbidity and mortality associated with infectious diseases. Over two million deaths are delayed through immunization each year worldwide (Odusanya et al., 2008; WHO, 2009). Despite this, vaccine preventable diseases remain the most common cause of childhood mortality with an estimated three million deaths each year (Centre for Global Development, 2005). In recent times, vaccination has had a major impact on measles deaths. From 2000 to 2005, more than 360 million children globally received measles vaccine through supplementary immunization activities. Moreover, improvements have been made in routine immunization over this period. These accelerated activities have resulted in a significant reduction in estimated global measles deaths. Overall, global measles mortality decreased by 60% between 1999 and 2005. The largest gains occurred in Africa where measles cases and deaths decreased by nearly 75% (WHO, 2007).Thus, there is a lot of pressure on health in different countries in controlling the disease through vaccination. Indeed, measles is targeted by the World Health Organization (WHO) in its expanded programme of immunization (EPI).

Therefore, this review summarizes the roles of vaccines in elimination and the global eradication of measles. It also summarizes the current state of the disease and the knowledge regarding its elimination and the global

Table 2. Different vaccines available for measles disease.

Disease immunized	Component vaccine	Virus strain	Propagation medium	Growth medium
Measles	Attenuvax	Enders' attenuated Edmonston strain (Merck Co., 2006).	chick embryo cell culture	Medium 199
Mumps	Mumpsvax (Merck Co., 1990, 1999).	Jeryl Lynn (B level) strain (Young, 1967)	chick embryo cell culture	Medium 199
Rubella	Meruvax II	Wistar RA 27/3 strain of live attenuated rubella virus	WI-38 human diploid lung fibroblasts	MEM (solution containing buffered salts, fetal bovine serum, human serum albumin and neomycin, etc.)

Source: Wikipedia, the free encyclopedia (2009).

eradication and describes examples of how vaccines have contributed to measles control as well as the current trends in eradication of measles in Nigeria. The authors have previously reported on the role of vaccine derived poliovirus (VDPV) in the global eradication of polio (Okonko et al., 2008) and global eradication of measles: a highly contagious and vaccine preventable disease-what went wrong in its eradication in Africa (Okonko et al., 2009)?

MEASLES VACCINES

Historical development

In 1963, the first vaccine for measles appeared (Kerksiek, 2009). In the United States, the vaccine was licensed in 1971 and the second dose was introduced in 1989 (Banatvala and Brown, 2004). It is widely used around the world; since introduction of its earliest versions in the 1970s, over 500 million doses have been used in over 60 countries. The vaccine is sold by Merck as M-M-R II, GlaxoSmithKline Biologicals as Priorix, Serum Institute of India as Tresivac, and sanofi pasteur as Trimovax (Wikipedia, 2009). In the early 1990s, a second dose of the MMR vaccine was recommended. This recommendation was made because outbreaks of measles swept across the United States in the late 1980s and early 1990s. Most of the people who were infected with measles during these epidemics were adolescents and young adults. An investigation of what went wrong found that many people who caught measles had never been immunized. So the primary reason for recommending a second dose of MMR was to give children two chances to get one vaccine. The other reason that a second dose of MMR vaccine was recommended was to allow for more children to develop a protective immune response. About 95% of children will develop immunity after one shot, but about 99% of children will develop immunity to measles after two shots. Immunizing that additional 4% of children is important when trying to protect against a disease as highly contagious as measles. The addition of mumps and rubella vaccines in this recommendation increases the percentage of children who develop immune responses to those viruses as well (Offit, 2008).

Types, formulation and the safety profile of measles vaccine

The following vaccines and treatment are available for measles disease (Table 2). The component viral strains of MMR (measles, mumps and rubella, also known as German measles) vaccine were developed by propagation in animal and human cells. The live viruses require animal or human cells as a host for production of more viruses. For example, in the case of mumps and measles viruses, the virus strains were grown in embryonated hens' eggs and chick embryo cell cultures (Table 2). This produced strains of virus which were adapted for the hens' egg and less well-suited for human cells. These strains are therefore called attenuated strains. They are sometimes referred to as neuroattenuated because these strains are less virulent to human neurons than the wild strains. The Rubella component, Meruvax, is propagated using a human cell line (WI-38, named for the Wistar Institute) derived in 1961 from embryonic lung tissue (ViroMed Laboratories, 2004) (Table 2). This cell line was originally prepared from tissues of aborted fetuses, raising religious objections (Pontifical Academy for Life, 2005).

Inactivated vaccine

This vaccine was intended for use in young children less than 1 year of age who are most prone to severe complications. It was thought to be advisable to avoid the use of a live vaccine. It was found that at least 3 doses were needed to elicit a protective antibody response but the antibody levels soon waned. This leave the vaccines open to attack by the natural virus. In some cases, the nature of the partial immunity led to serious hypersensitivity reactions to infection (Atypical measles). The exact

mechanism is still uncertain but it was thought that the vaccine lacked an important antigen of the virus and thus immunity was not complete. In view of the above and the fact that antibody levels decline rapidly after administration of the killed vaccine, live vaccination is now generally recommended and individuals previously immunized with the killed vaccine should be re-immunized with the live vaccine. The killed vaccine has now been withdrawn.

Live vaccine

Live vaccines are now usually used. The seroconversion rate is 95% and the immunity lasts for at least 10 years or more, possibly lifelong. The virulence of the attenuated strain now in use is so low that encephalitis has only been noted in 1 in 1 million recipients. SSPE has been reported in children given the live vaccine. However, the rate is lower than that following natural infection. Therefore the vaccine is safe for use in very young children. The live vaccine is now incorporated as part as the MMR vaccine.

Live-attenuated vaccine

The use of live-attenuated vaccine for postexposure prophylaxis is not indicated. The measles vaccine is concontained in a combination vaccine called MMR. MMR vaccine was recommended to be given after an interval of at least 3 months, at around the usual age. MMR is given as a series of two doses at 12 to 15 months of age and at 4 to 6 years of age. The Rubella component, Meruvax, is propagated using a human cell line (WI-38, named for the Wistar Institute) derived in 1961 from embryonic lung tissue (ViroMed Laboratories, 2004). This cell line was originally prepared from tissues of aborted fetuses, raising religious objections (Pontifical Academy for Life, 2005).

Vaccination with the current live attenuated measles vaccine is one of the most successful and cost-effective medical interventions. However, as a result of persisting maternal antibodies and immaturity of the infant immune system, this vaccine is poorly immunogenic in children less than 9 months old.

Immunity against the live vaccine is less robust than natural immunity and protection less durable (Pütz et al., 2003).

Intranasal measles vaccine spray

Earlier it was determined that inspiration of aerosolized measles vaccines may be as effective as its injection in induction of measles antibodies formation. Intranasal measles vaccine spray introduction may be a useful method of child re-vaccination in the process of measles eradication. This method is useful for investigation of “mucosal immunity" in children or adults (Liashenko et al., 1999).

MMRV vaccine

The MMRV vaccine, a combined measles, mumps, rubella and varicella vaccine, has been proposed as a replacement for the MMR vaccine to simplify administration of the vaccines (Vesikari et al., 2007). Preliminary data indicate a rate of fever-induced seizure of 9 per 10,000 vaccinations with MMRV, as opposed to 4 per 10,000 for separate MMR and varicella injections; U.S. health officials therefore do not express a preference for use of MMRV vaccine over separate injections (Klein et al., 2008; Times online, 2009).

Human normal immunoglobulin (HNIG)

HNIG is always given to all severely immunocompromised children irrespective of their immunization status since it has been reported that severe measles infection can occur in those who had been immunized and had a documented low-level antibody response.

Vitamin A supplements

All children in developing countries diagnosed with measles were recommended to receive two doses of vitamin A supplements which were usually given 24 h apart. Giving vitamin A at the time of diagnosis of measles has helped prevent eye damage and blindness. Moreover, vitamin A supplementation has been shown to reduce the number of deaths from measles by 50% (WHO, 2007).

Administration, effectiveness and efficacy of the measles vaccine

The MMR vaccine is a mixture of three live attenuated viruses, administered via injection for immunization against measles, mumps and rubella (also called German measles). All three diseases are highly contagious. MMR II is supplied freeze-dried (lyophilized) and contains live viruses. Before injection it is reconstituted with the solvent provided. The MMR vaccine is administered by a subcutaneous injection. It is generally administered to children around the age of one year, with a second dose before starting school (That is age 4/5). The second dose is not a booster; it is a dose to produce immunity in the small number of persons (2 - 5%) who fail to develop measles immunity after the first dose (CDC, 2004a). The second dose may be given as early as one month after the first dose (Vesikari et al., 2007). As vaccine-induced measles antibody develops more rapidly than following natural infection, MMR vaccine can be used to protect susceptible contacts during a measles outbreak. To be effective, the vaccine must be administered within three

days of exposure. If there is doubt about a child's immunity, vaccine should be given since there are no ill effects from immunizing individuals who are already immune. Immunoglobulin should be given to those for whom the vaccine is contraindicated.

As with all vaccinations, long- term effects and efficacy are subject to continuing study. MMR gives highly effective protection against all three diseases, and has the potential to eliminate these infections, including congenital rubella syndrome, saving many lives and preventing serious illness. At the population level, the high protective efficacy of MMR vaccine has been demonstrated by the marked fall in disease rates in countries where the vaccine has been introduced. This is particularly clear in countries that have long used a two-dose policy, such as Finland, where the diseases have been practically eliminated (Peltola et al., 1994). Since MMR vaccine was introduced in the UK, notifications of measles have fallen to the lowest recorded levels. Studies conducted during outbreaks of measles and mumps show that both single-antigen and MMR vaccines provide high levels of protection, especially in individuals who have received two doses (Vitek et al., 1999; Salmon et al., 1999). However, even with high levels of vaccine uptake, outbreaks can still arise in unimmunized groups, and can spread to people who are incompletely protected despite vaccination (e.g. who have had an inadequate response to a single dose) (Peltola et al., 1994; Vitek et al., 1999; Salmon et al., 1999).

The impact of the vaccinations has been monitored in several prospective studies (Heinonen et al., 1998). A prolonged immunoepidemiological follow-up of a large group of children immunized against measles revealed a high epidemiological efficacy of a single vaccination. The study by Bolotovskii et al. (1990) showed that groups of children seronegative with respect to measles appeared, as a rule, after unsatisfactory immunization and not due to loss of postvaccinal immunity with time. Properly immunized children in whom the formation of anti-measles antibodies had occurred in response to the injection of live measles vaccine retained postvaccinal immunity for more than 15 year (Bolotovskii et al., 1990).

In addition to a very favourable safety profile, good immunogenicity and excellent clinical effectiveness have also been demonstrated with the use of MMR II vaccine. Since 1996, not a single case of measles has been found in Finland, although cases have been searched actively and serological confirmation has been required (Heinonen et al., 1998). Though, there may also be some concern about (vaccine) virus spread during the final stage of an eventual measles eradication program. Opinions may differ with respect to the potential threat that some of these concerns may be to the WHO goal of measles elimination, but there is a consensus that the development of new measles vaccines cannot wait. Candidate vaccines are based on viral or bacterial vectors expressing recombinant viral proteins, naked DNA, immune stimulating complexes or synthetic peptides mimicking neutralizing epitopes. While some of these candidate vaccines have proven their efficacy in monkey studies, aerosol formulated live attenuated measles vaccine are evaluated in clinical trials (Pütz et al., 2003). However, the broad implementation of childhood vaccines was one of the greatest public health accomplishments of the twentieth century. These programs should be celebrated, and efforts should be continued to further improve the efficacy and safety of vaccines. Widespread implementation of vaccine programs in the U.S. has led to a greater than 99% decline in cases of measles and rubella (Ellison, 2007).

THE ROLE OF VACCINES IN GLOBAL ERADICATION OF MEASLES

Before the era of measles vaccination, measles was often treated with prophylactic antibiotics at the primary healthcare level, even when complications had not yet developed (Chalmers, 2002) . Trials of prophylactic antibiotics in measles infection were made several years ago, some of them randomised, but none of them complied with the current standards for design of a randomized controlled trial (Shann et al., 2006). On this background, the WHO proposed that a priority for measles research should be a randomised, double blind, placebo controlled trial of prophylactic antibiotics in measles (WHO, 1995) . Human beings have benefited from vaccines for more than two centuries. Yet the pathway to effective vaccines has been neither neat nor direct (Stern and Markel, 2005). WHO and the CDC organized worldwide Measles elimination project. The objective was to decrease morbidity and mortality cases in society or community and to prevent from remission of measles until global target is not achieved, by maintaining low level of susceptibility and to eliminate measles. Since, elimination is defined as interruption of transmission in a sizeable geographic area, and because of continued threat of reintroduction of virus, vaccination need to be continued. Measles fell sharply after immunization was introduced. Before the widespread use of a vaccine against measles, its incidence was so high that infection with measles was felt to be "as inevitable as death and taxes (Babbott Jr., and Gordon, 1954). Today, the inci-dence of measles has fallen to less than 1% of people under the age of 30 in countries with routine childhood vaccination (Wikipedia, 2009).

Sequence analyses have shown that all of the measles vaccine strains are representatives of genotype A (Rota et al., 1994a, b). This includes both vaccines derived from the original Edmonston isolate of 1954 (e.g., Moraten, Schwarz, Edmonston- Zagreb, AIK-C) as well as vaccines derived from other wild type viruses isolated during the 1950s and 1960s in China and Japan (e.g., Shanghai- 191, Chanchun-47, CAM-70). While this suggests that genotype A viruses had a wide distribution in

the pre-vaccine era, it is also possible that genotype A viruses were more frequently detected because they were easier to isolate in the cell culture systems available at the time. Genotype A viruses have been isolated from sporadic measles cases in the last 10 years, but there have been no reports that this genotype has been associated with any large outbreaks. Though it is possible that wild type genotype A viruses are still circulating, there is a strong likelihood that recently detected genotype A viruses are vaccine viruses or laboratory contaminants. Efforts are underway to attempt to identify a set of genetic markers to distinguish wild type, genotype A viruses from vaccine viruses. A small proportion of measles vaccine recipients experience rash and fever 10 - 14 days following vaccination (Rota and Bellini, 2003).

The role and benefit of vaccination against measles in preventing illness, disability, and death has been well-documented. The first 20 years of licensed measles vaccination in the U.S. prevented an estimated 52 million cases of the disease, 17,400 cases of mental retardation, and 5,200 deaths (Bloch et al., 1985). During 1999 - 2004, a strategy led by the World Health Organization and UNICEF led to improvements in measles vaccination coverage that averted an estimated 1.4 million measles deaths worldwide (CDC, 2006a) . The combined MMR vaccine was introduced to induce immunity less painfully than three separate injections at the same time and sooner and more efficiently than three injections given on different dates. In 2005, the Cochrane Library published a review of 31 scientific studies. One of its main results: "We could not identify studies assessing the effectiveness of MMR that fulfilled our inclusion criteria even though the impact of mass immunization on the elimination of the diseases has been largely demonstrated." Its authors concluded, "Existing evidence on the safety and effectiveness of MMR vaccine supports current policies of mass immunization aimed at global measles eradication in order to reduce morbidity and mortality associated with mumps and rubella" (Demicheli et al., 2005).

The role and effectiveness of the measles vaccine has been dramatic. In 1962 (one year before the first measles vaccine was made available in the United States), 4 million people were diagnosed with measles, 48,000 were admitted to hospitals and 3,000 people died. Be-tween 1990 and 1991 the city of Philadelphia was in the grip of a measles epidemic. At the center of the epidemic was a religious group that refused immunizations for themselves and their children. Children with measles developed high fever; a red, raised rash that started on the face and spread to the rest of the body; and "pink eye." For some, the disease got much worse. Seven children in the church developed a severe form of pneu-monia as the measles virus infected their lungs. The lungs filled with pus - breathing became fast, labored, and difficult. By the time these children were taken to the hospital, it was too late. They had died from measles (Offit, 2008).

Though, measles still rages throughout developing countries and is one of the leading causes of death worldwide. It has almost been eliminated from the United States compared with what it used to be in the past. For instance, in the late 1980s and early 1990s in the United States, low immunization rates against measles were associated with epidemics of measles. About 11,000 people were hospitalized and 120 killed by measles virus. But in 2005, only 66 cases of measles were reported to the CDC; however, an outbreak that occurred in 2007 is as a result of an international youth sporting event. Thus, showing another cases of imported measles virus.

Also, in Nigeria, the measles vaccination programme in recent year gives hope that elimination of measles underway through an intensified vaccination and immunization programme. In October 2006, Nigeria launched a massive immunization campaign to protect 29 million children against measles, a highly contagious virus that kills more Nigerian children than any other vaccine-preventable disease. Though, this measles immunization campaign targeted 29 million Nigerian children (Njoku, 2006), the disease continued to roam every nook and crannies of some states, Borno state for instance. The disease is still not through with the people of the state as it was reported to have made in-road into the other twenty local government areas (Olugbode, 2007).

High vaccine coverage was achieved in Gambia with EPI. With time the number of vaccinated children who are not protected against measles, poliovirus 3 and tetanus increases. Besides the maintenance of high vaccine coverage in infants and young children, booster doses of some of the EPI vaccines in adolescents should be considered (Viviani et al., 2004). While the United States are on the verge of eliminating measles, increased travel can lead to spread from other countries as evidenced by a measles outbreak associated with an international youth sporting event that occurred in three states in the U.S. during the fall of 2007. But with intensified vaccination and immunization priogramme, the elimination of measles will be achieved, and because the measles vaccine has no serious permanent side effects, its benefits still clearly outweigh its risks (Offit, 2008).

However, the MMR vaccination coverage in many countries improved rapidly and finally reached a high level during last years (Mrozek-Budzyn and Kiełtyka, 2008).

CHALLENGES IN THE ROLE OF VACCINES IN ERADICATION OF MEASLES

A key issue is the duration of vaccine efficacy in developing countries (WHO, 2000). Despite intense efforts to eradicate it, measles still infects 30 - 40 million people worldwide and causes half a million deaths a year (WHO, 2006). It is the leading killer among vaccine preventable diseases and causes an estimated 44% of the 1.7 million vaccine preventable deaths among children

each year (WHO, 2002). The case fatality rate of measles in developing countries is high, particularly among infants, and reaches 30% among patients admitted to hospital (Loening and Coovadia, 1983). Even in affluent countries, the complication rate is high and epidemics cause severe morbidity, permanent sequelae, and death (Van Den et al., 2002). The potential impediments to eradication of measles include the lack of appreciation of disease severity, the transmission among adults, waning immunity, possibility of transmission from subclinical cases, misinformation, quality, intensity and duration of vaccine-induced immunity, low vaccination rates and coverage, the burgeoning acquired immune deficiency syndrome epidemic, vaccine failures, global travel and international spread of measles, and the threat from bioterrorism (Orenstein et al., 2000; Meissner et al., 2004; Kerksiek, 2009). Global measles eradication will face a number of challenges to achieving and sustaining high levels of vaccine coverage and population immunity, including increasing urbanization and population density/ growth and demographic changes, conflict and political instability, and public perceptions of vaccine safety and risk of unsafe injections. To achieve the measles mortality reduction goal, continued progress needs to be made in delivering measles vaccines to the world's children (Moss, 2009). In view that a safe and effective vaccine has been available for 40 years, which obstacles account for the failure to make greater progress in worldwide measles control?

BIOLOGICAL FEASIBILITY OF ERADICATING MEASLES

Despite these challenges, a compelling case can be made in favor of measles eradication, and many experts as well as the authors believe that it is in our future that eradication of measles would be achieved. But, the question is when. The biological feasibility of eradicating measles include 4 criteria: (1) The role of humans in maintaining transmission, (2) The availability of accurate diagnostic tests, (3) The existence of effective vaccines, and (4) The need to demonstrate elimination of measles from a large geographic area. The efficacy of vaccination and immunization in reducing the incidences of several diseases were clearly shown by the success story of measles control in developed countries of the world (Cutts and Markowitz, 1994). Recent successes in interrupting measles transmission in the United States, most other countries in the Western Hemisphere, and selected countries in other regions provide evidence for the feasibility of global eradication (Orenstein et al., 2000).

ECONOMIC IMPLICATIONS OF GLOBAL MEASLES ERADICATION

There are few data on the cost of improving routine measles coverage, only one longitudinal study has been published. Measles eradication would avert the current annual 1 million deaths and save the $1.5 billion in treatment and prevention costs due to measles in perpetuity (Orenstein et al., 2000). Different approaches have been taken to assess the economic costs, benefits, and cost-effectiveness of measles control, elimination, and eradication. These analyses indicate that programs to control measles are highly cost-effective. Additional programmatic investments to interrupt measles transmission are also cost-effective and may be cost-saving in some countries. Greater agreement is needed concerning appropriate approaches to economic analysis of measles eradication, including consideration of marginal and opportunity costs, is needed so that these estimates can be used to formulate policy and estimate budgetary resources required to achieve eradication. Measles eradication presupposes a substantial investment in infrastructure (That is, physical capital and surveillance and management systems) and “human capital” (That is, training of primary health-care personnel, front-line supervisors, and development of management re-sources). Benefits of the investment will include a) Elimination of illness and death caused by measles virus, b) Elimination of the recurring costs and risks associated with measles immunization, and c) A permanent contribution to development of primary health services in developing countries. Proper management of the investment requires specific and intentional efforts to maximize the benefits that can accrue to the overall health system from eradication efforts. Specific benchmarks should be developed to monitor interaction of eradication efforts and primary health-care development (CDC, 1997a, b, 1998).

CURRENT TRENDS IN THE ROLE OF VACCINES IN ERADICATION OF MEASLES

Before the availability of measles virus vaccines, the WHO estimated that 8 million deaths due to measles and its associated complications occurred annually among children. By 1999, with the introduction of increasingly aggressive immunization approaches through the World Health Organization's Expanded Program of Immunization, this annual measles-associated mortality rate had been reduced to 873,000 deaths, but, nonetheless, measles has accounted for 48% of the 1.6 million deaths due to vaccine-preventable diseases occurring annually among children. Only malaria, in the absence of vaccine, was reported to be associated with a mortality rate greater than that associated with measles in children less than 5 years of age (Katz, 2005).

In 1963, the first vaccine for measles appeared. At that time, measles was a common childhood disease, infecting – alone in the United States - 3 to 4 million individuals each year, causing some 50,000 hospitalizations, 1000 permanent disabilities and 400 - 500 deaths. The measles vaccine had an immediate impact, steadily

reducing the incidence and mortality of the disease in Western countries (Kerksiek, 2009).

In 1977, the Expanded Programme on Immunization (EPI) was approved by the World Health Assembly (WHA, 1998).

In 1985 - 1986, an outbreak of measles in 1985 - 1986 in a community where measles vaccine trials had been carried out from 1974 - 1976 allowed the assessment of the role of secondary vaccine failures in previously immunized children (Mathias et al., 1989). Mathias et al. (1989) concluded that secondary vaccine failures occur and that while primary failures account for most cases, secondary vaccine failures contributed to the occurrence of measles cases in an epidemic. A booster dose of measles vaccine may be necessary to reduce susceptibility to a sufficiently low level to allow the goal of measles elimination to be achieved.

In 1988, it was reported that immunization and vaccination remains one of the most cost effective strategies to prevent infectious diseases. The most effective and efficient way to protect the health of children is by immunization before the risk of disease arises. Vaccination has succeeded in eradicating small pox in the world (Fenner et al., 1988).

In 1990, it was reported that the occurrence of secondary vaccine failure and vaccine-modified measles does not appear to be a major impediment to measles control in the developed countries like United States but may lead to underreporting of measles cases and result in overestimation of vaccine efficacy in highly vaccinated populations (Edmonson et al., 1990).

In 1991, a measles outbreak occurred in Fukuoka, Japan, in which Hidaka et al. (1994) observed 15 cases of measles vaccine failure (MVF). However, the introduction of enhanced diagnostic tests for IgM detection such as I gM-capture EIA, with results which may be positive for patients with measles reinfection due to secondary vaccine failure, has highlighted the difficulty in differentiating between primary infection or reinfection due to primary and secondary vaccine failure (Erdman et al., 1993; Hidaka et al., 1994; Helfand et al., 1997; Paunio et al., 2000; Pannuti et al., 2004). Measles reinfection due to secondary vaccine failure is probably more common than suggested by studies relying on specific I gM (Paunio et al., 2000), because measles- specific I gM is also inducible by reinfection (Erdman et al., 1993). The estimation of IgG antibody avidity is useful for identifying primary and secondary immune responses, but there have been few reports of its use during measles outbreaks (Pannuti et al., 2004). The results of the study by Hamkar et al. (2006), which showed that 18.4% of 365 measles cases confirmed by a positive I gM test mounted a secondary immune response, provide further evidence that the presence of I gM cannot be used as a reliable indicator of a primary immune response.

In 1993, after 27 years of no known exposure to measles, an outbreak occurred in Palau in 1993 which offered the opportunity to study this issue and the measles vaccine effectiveness (Guris et al., 1996). It was unknown whether vaccine-induced immunity is life-long in the absence of periodic exposure to measles virus. Guris et al. (1996), similar to the estimates previously obtained in the area, measles vaccine effectiveness in Palau was lower than the estimates obtained in the United States. A second dose of vaccine further reduced the risk for developing measles (Guris et al., 1996). Guris et al. (1996) found no evidence that waning immunity was an important problem in the limited population with no known previous exposure to measles virus and that the small number of vaccinated contacts precludes a definitive assessment.

In 1992 and 1993, Tesoro et al. (1992, 1993) also reported that despite outbreaks of measles in surrounding communities and in New Jersey, none of their patients developed measles and that waning immunity was not found to be a factor in their patients. According to Tesoro et al. (1992, 1993), identification of high- risk groups and selective measles revaccination should be considered as an alternative to universal revaccination in populations such as theirs, since it is more cost-effective and may prove equally successful.

In 1994, protection from live measles vaccine was found to have persisted for up to 27 years after vaccination in the United Kingdom (UK). Ramsay et al. (1994) reported that the protective efficacy of the live measles vaccine has remained as high as 87% and that between 1976 and 1990, the overall efficacy of the live vaccine was 92% and that there was no evidence of a decline in efficacy over a period of the 15 years. Their study suggested that protection from live measles vaccine persisted from up to 27 years after vaccination, and that no change in the current UK measles immunization policy should be made on the grounds of waning immunity.

In 1994, the Expanded Programme on Immunization (EPI) of the World Health Organization (WHO) has a global target of reducing measles incidence by 90% and mortality by 95% from pre-EPI levels by 1995. Both developed and developing countries that have given priority to measles control have substantially reduced measles morbidity and mortality, and some have come close to eliminating measles. A variety of vaccination schedules and strategies have been used, which reflect the differing program goals, health services infrastructure, and availability of resources in different countries. Failure to control measles has usually been due to a failure to implement planned strategies adequately. The highest priority in measles control is to assist countries, especially the lowest-income countries, to implement vaccination programs more effectively (Cutts and Markowitz, 1994).

In 1997, the absence of a follow-up vaccination campaign, in addition to low routine vaccination coverage, may have contributed to the outbreak of measles in the state of São Paulo, Brazil in 1997 (CDC, 1997a, b). However, factors not directly related to implementation of

the measles control strategy (e.g., in-migration of susceptible young adults from rural areas, high population density, and independent adult transmission) may also have influenced the course of the outbreak. Analysis of the São Paulo experience supports the idea that elimination strategies are unlikely to succeed if they are not implemented completely throughout a country or region (CDC, 1997a, b, 1998).

In 1998, efforts to control measles in many Western countries suffered a setback following a 1998 false report by Wakefield et al. (1998) that the MMR vaccine is linked to autism; in England the MMR vaccination rates dropped from 95 to 80% (and only approximately 60% in some parts of London). Though, public confidence in the vaccine is slowly returning after numerous subsequent studies have failed to confirm the link, but an estimated three million children (approximately 25%) in the UK are missing at least one of the two MMR doses recommended for full immunity (15% don't respond to the first shot) (Kerksiek, 2009).

In 1999, Hennessay et al. (1999) reported an occur-rence of measles epidemic in Romania; with 32,915 cases and 21 deaths reported between November, 1996 and June, 1998, despite high vaccination coverage since the early 1980s. Most cases were unvaccinated children aged less than 2 years and vaccinated school-aged children. This epidemic gave room for a case-control stu-dy among preschool children and a cohort study among primary-school children in order to estimate the effective-ness of Romanian-produced measles vaccine, and to evaluate age at vaccination and waning immunity as risk factors for vaccine failure. Both studies indicated that measles vaccine was highly effective. Waning was not identified as a risk factor since vaccine effectiveness was similar for children vaccinated 6 - 8, 9 - 11, and 12 - 14 years in the past (Hennessay et al., 1999). Hennessay et al. (1999) concluded that because specific groups were not at risk for vaccine failure, an immunization campaign that targets all school-aged children who lack two doses may be an effective strategy for preventing outbreaks. A mass campaign followed by increased first- dose cove-rage should provide the population immunity required to interrupt indigenous measles virus transmission.

In 2000, the United States was declared free of endemic measles, and Europe has set the goal to be measles-free by 2010. Another vaccination success story! So it seemed. But now, measles is making a comeback, causing an increasing number of outbreaks over the last few years. And with less than 80% immunization coverage in some countries, an epidemic may not be far away (Kerksiek, 2009).

In 2001, it was reported by CDC that indigenous transmission of measles virus has been eliminated in the United States, the most populous country in the region of the Americas, and only 3 of 41 countries in the region reported indigenous measles transmission during 2001 (CDC, 2000a, b, 2001). The vaccination programme has been most effective in the USA, where measles immunization is compulsory. The incidence rate has also declined dramatically in the UK but without the rigorously pursued vaccination as practiced in the US, it is not likely to be as effective as that in North America.

In 2003, the success of mass vaccination campaigns in southern Africa has suggested that measles elimination is possible even in developing countries with a high incidence of human immunodeficiency virus infection (Biellik et al., 2002). On September 22, 2003, the Pan American Health Organization announced that the western hemisphere had been free of endemic measles for 10 consecutive months (PAHO, 2003). In 2007, the WHO estimated that measles caused 197,000 deaths. This is a huge number but a dramatic decrease from previous years: between 2000 and 2007, massive vaccination efforts decreased global measles deaths by 74%, and mortality was reduced by 90% in the eastern Mediterranean and Africa. The WHO and UNICEF have the goal to reduce global measles deaths by 90% by 2010 (Kerksiek, 2009). In countries where they have been fully implemented, the strategies adopted to eliminate measles (That is, catch-up, keep-up, and follow-up) in the Western Hemisphere have substantially reduced or eliminated measles.

In 2008, CDC reported that in some countries (particularly in the Americas and the United Kingdom), most measles cases were now caused by international importations. Consequently, eliminating measles from these countries requires improvements in measles control in other parts of the world. In the United States, most virus importations originate from Europe and Japan, indicating that developed countries, as well as developing nations, need to improve measles control. Countries can help improve international communication about areas where measles virus is circulating by notifying their respective WHO regional offices about measles importations. Such communication can help national health authorities strengthen surveillance and undertake appropriate remedial actions (CDC, 2008a, b).

In 2008, the result of the false report of 1998 (Wakefield et al., 1998) is that, the highest number of measles cases (1,348) was reported in 2008, the highest ever reported for 13 years, and measles was declared to be again endemic in the United Kingdom. The British Health Protection Agency (HPA) has warned that unless vaccination rates increase significantly, there is a real threat of an epidemic of between 30,000 to 100,000 measles cases (Kerksiek, 2009).

In 2009, measles also hit other European countries hard. In February of this year, the WHO European office reported that 8145 measles cases were reported over the previous of 12 months, with 86% of the cases coming from Austria, Germany, Italy, Spain, Switzerland, the UK and Israel. Switzerland has been particularly hard; an ongoing outbreak that started in 2006 peaked in March 2008, with 2195 cases reported that year (approximately

14 measles cases per 100,000 inhabitants; in contrast, the UK registered 1.6 cases per 100,000 people) . The virus strain from Switzerland, which is thought to have originated in Japan, caused further outbreaks in Germany, Austria and Norway (Kerksiek, 2009). Recent international efforts to control measles infections through aggressive vaccination programs have had a great deal of success. In particular, the Pan American Health Organization (PAHO) reported record low numbers of measles cases in the Americas during 2000 - 2001, reflecting the overall success of measles control programs in the Western Hemisphere (CDC, 2001). However, despite these successes, measles remains an endemic disease in many areas of the world, and among children, it is still the most common cause of death from a vaccine-preventable disease (Rota and Bellini, 2003). In comparison to many other vaccine-preventable diseases, for example polio or smallpox, measles is highly contagious; among unimmunized individuals exposed to the virus, 90% will catch it. An extremely high vaccination rate – approximately 95% according to a World Health Organization (WHO) estimate - is therefore required to effectively contain the disease. Unfortunately many countries, even those with ample resources, are far away from this goal (Kerksiek, 2009).

In 2009, it was reported that, in the third world, malnutrition aggravates measles infection and there are 900,000 measles related deaths per year. Vaccination in these areas has failed to yield dramatic results. The problem is that the vaccine is usually given at 12 months of age (it should not be given in younger individuals because the presence of maternal antibodies may lead to a poor response) but infection in these areas often occurs earlier in life. Vaccination should therefore be performed on younger children than in the developed world.

However, this must be balanced with the fact that the success rate is lower in younger children (50 - 75% in 6 month-old-children as opposed to 95% for 12-month-old children.). Measles is highly infectious and has a very high attack rate and thus it might be extremely difficult to eradicate the virus altogether through vaccination, but it would be achieved (Kerksiek, 2009).

Maintenance of high routine vaccination coverage and community-based surveillance (That is case identification, reporting, and investigation) require adequately trained and equipped primary health-care personnel. Strengthening the primary health-care system and EPI in developing countries, although perhaps not essential for interruption of measles virus transmission, greatly facilitates achieving and maintaining measles elimination in a country or region.

NEXT STEPS IN GLOBAL ERADICATION OF MEASLES THROUGH VACCINATION

Global efforts have reduced measles deaths by 90% since 2000 (Kerksiek, 2009). Assessing immunization coverage helps to evaluate progress in achieving programme objectives and in improving service delivery (Bonu et al., 2003). In addition, evaluation of immunization coverage provides evidence whether substantial progress towards achieving vaccination targets is being made. Such positive evidence is required for continuing support from donor-supported initiatives like the Global Alliance for Vaccines and Immunizations (GAVI) (Brugha et al., 2002). According to Meissner et al. (2004), is it possible that measles can reach the same degree of disease control (viz, worldwide eradication) as has occurred with smallpox and soon may be achieved with polio? Then, several conditions must be satisfied before any vaccine-based eradication program can be successful (Orenstein et al., 2000).

Firstly, no reservoir for the virus

There must be no reservoir for the virus apart from humans. This is the case for measles virus, and chronic shedding of measles virus (That is greater than 2 months after rash onset) has not been documented (Permar et al., 2001). Subacute sclerosing panencephalitis is caused by a persistent infection with a defective measles virus; however, this condition is not infectious. Measles virus cannot survive in the environment for more than a few hours apart from human infection or growth in tissue culture.

Secondly, adequate test for rapid diagnosis

There must be an adequate test for rapid diagnosis. A sensitive and specific enzyme-linked immunosorbent assay for measles immunoglobulin M is often positive on the first day of rash and is widely available for surveillance, rapid diagnosis, and identification of measles cases (Meissner et al., 2004).

Thirdly, availability of safe and effective form of intervention

A safe and effective form of intervention must be available. Although the nucleotide sequences of certain measles genes show evolutionary drift, there is only a single strain of antigenically stable measles virus, and the measles virus vaccine elicits an immune response that is active against all known isolates (Meissner et al., 2004).

Finally, evidence of a prolonged period of interruption and elimination

Evidence of a prolonged period of interruption and elimination of endogenous transmission has been demonstrated in a number of countries. Thus, it seems that measles satisfies these conditions needed for eradication (Meissner et al., 2004).

The next steps

The next steps for measles control and elimination activities should include design of a global strategy, preparing an operational plan and budget, obtaining political support, developing a partner/donor coalition, and implementing the strategy. Each step requires action at national, regional, and global levels. In addition, a consensus must be developed concerning the timing of measles elimination in relation to polio eradication. Specifically, should measles elimination be undertaken simultaneously with efforts to eradicate polio? Or should the efforts be undertaken sequentially? It is therefore suggested that measles elimination should not be undertaken at the national level before poliovirus transmission is interrupted. At the global level, in contrast, activities aimed at achieving measles eradication should begin before polio eradication is achieved. Polio eradication must remain the first priority (CDC, 1997a, b, 1998, 2008a, b).

Funding of measles eradication should also be considered. Projects that attract donor support have been successful (or have a high probability of success) in the past, and are both politically and socially popular, it provide visibility and recognition for donors, and have a specific goal and target date for completion. To attract support from potential partners and donors among governments, non-governmental organizations, and the private sector, advocates of measles eradication should develop consensus concerning their objectives and strategies and communicate these objectives simply and directly. To succeed, advocates of eradication must reach consensus concerning the global disease burden of measles, likely cost savings from eradicating the disease, and resources required from external sources to accomplish the goal. The advocacy strategy should include identifying the key messages concerning measles eradication, forming coalitions of partners (including those in the private sector), and identifying advocates for fund-raising. Consistency in messages about each aspect of measles eradication is essential to the success of the advocacy strategy (CDC, 1997a, b, 1998, 2008a, b).Immunization strategies designed specifically to improve measles control and reduce measles deaths in densely populated urban areas of low-income countries should be developed and supported by national governments, WHO, and UNICEF. These strategies should be directed to vaccinating populations not covered by routine vaccination services or previous catch-up vaccination campaigns. When supplementary vaccination campaigns are conducted in such high-risk urban areas, all children in the target age range should be vaccinated regardless of measles vaccination status or history of previous measles disease. Disease surveillance is essential to monitor the impact of supplementary vaccination activities and should be developed as part of these strategies (CDC, 1997a, b, 1998, 2008a, b).

Combining measles vaccination campaigns with other public health interventions (That is administration of oral poliovirus vaccine or non-vaccine interventions such as vitamin A supplementation) should be encouraged. However, no single combination of interventions is appropriate in all circumstances; the combination of interventions must be specific to the needs and capacities of countries where they are implemented. For example, countries that can afford combination vaccines should consider using MR vaccine or MMR vaccine. Simultaneous administration of yellow fever vaccine could also be considered in countries at risk for yellow fever (CDC, 1997a, b, 1998, 2008a, b).

SUMMARY

The principal objectives of the WHO measles elimination initiative are (Commonwealth of Australia, 2000): to cease measles-related morbidity and mortality, by interrupting indigenous transmission of measles; and to prevent re-introduction of measles until global eradication is achieved, by maintaining uniformly low levels of population susceptibility. To facilitate progression from the 'outbreak prevention' phase to the 'elimination' phase, and in order to achieve elimination objectives, very high vaccination coverage levels are needed, especially in closed settings such as schools where contact rates are high. Uniformity of coverage is also important, because pockets of susceptible persons are capable of perpetuating endemic transmission (Commonwealth of Australia, 2000). To eradicate one of humankind's great scourges is a challenge that is not easily met. Before global eradication of measles can be achieved, additional work is needed to address operational barriers (e.g., injection safety), to build political and financial commitments, and to develop effective partnerships. As has been learned from the Polio Eradication Initiative, the availability of effective vaccination strategies alone is not sufficient to ensure that eradication can be achieved (Meissner et al., 2004). Immunization and vaccination programs world wide now prevent greater than 1.5 million deaths from measles in developing countries. Yet approximately 1 million children continue to die each year from measles - a preventable and potentially eradicable disease (Tamin et al., 1994). The success of any immunization programme is dependent, to a large extent, on the quality and level of vaccination coverage (Adu, 2008). Therefore to prevent future outbreak of measles, the measles immunization and vaccination programme should be intensified. These will bring about the successful eradication of measles. If measles is to be eradicated, there must be a sustained political, financial, and societal commitment to this challenge. Though, the goals for measles reduction set for 2010 are out of reach, eradication of measles is most likely to be possible, if eradication of polio becomes successful and the challenges to measles reduction are well prepared.

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