A review of Measles Vaccine Failure in Developing Countries

T. M. Akande

Nigerian Medical Practitioner Vol. 52 No 5-6, 2007 (112-116)

Summary

Measles is one of the major preventable childhood killer diseases in developing countries. Annually about 70 million cases occur worldwide. Measles vaccine has been developed over decades to prevent and control measles. Although national immunization programs prevent over 80 million cases of measles and 4.5 million deaths annually, it is estimated that over 30 million cases and 875,000 deaths still occur every year. High transmission of measles despite high coverage with 1-dose measles vaccine has been reported in some developing countries. Some of the reasons for vaccine failure in developing countries include; poor seroconversion, questionable potency of vaccines due to problem with cold chain that ultimately affect the quality of vaccine and waning immunity. To prevent outbreaks of measles in developing countries, there is need for second dose of measles vaccine to take care of vaccine failures. This measure is necessary even in countries where there is high coverage with one dose of measles vaccine. The relevant International Agencies need to develop second dose measles vaccination policies for developing countries as obtains in some developed countries.

Key words: Measles vaccine, failure, developing countries

Introduction

Measles is a contagious disease caused by measles virus. Measles virus is paramyxovirus of a single serological type. The disease is highly communicable with an incubation period of about 10 days (with a range of 7 to 18 days). The disease is characterized by prodromal fever, conjunctivitis, coryza, cough and presence of Koplik spots. A characteristic maculopapular rash appears on the third to seventh day beginning on the face and become more generalized. Man is the only source of the measles virus.

WHO Expanded Program on Immunization in 1989 estimates that 1.6 million die from measles each year in developing countries (excluding China) making it the biggest killer among the six EPI target diseases.(1,2) Globally about 70 million cases occur annually. Immunization of children against measles therefore prevents mortality and morbidity not only during the acute phase but also during subsequent months.(1) Standard measles vaccine is associated with a mortality reduction greater than that caused only by prevention of measles.(3)

In 1989, the World Health Assembly resolved to reduce measles morbidity by 90% and measles mortality by 95% compared with the pre-vaccine era. In 1990 the World Summit on Children set a target of 90% for measles vaccine coverage by 2000.(4)

Despite achieving and sustaining global measles vaccination of about 80% over the past decade, measles remains the fifth leading cause of death among children less than 5 years old worldwide. In 2000 an estimated 31 million cases of measles occurred and resulted in 777,000 deaths. Measles accounted for 44% of total deaths due to vaccine preventable diseases among children less than 15 years old.(5)

Although national immunization programs globally prevent over 80 million cases of measles and 4.5 million deaths annually, it is estimated that over 30 million cases and 875,000 deaths still occur every year. This represents 50 – 60% of the estimated 1.6 million deaths caused annually by childhood vaccine-preventable diseases.(6) Measles is one of the most contagious human diseases and large outbreaks continue to occur in countries despite high vaccination coverage using a single dose vaccination.(5)

Studies suggest that measles infection occurring in vaccinated children may be related to the intensity of exposure and the fact that many children that have some degree of immunity secure a milder infection raises questions on vaccination programs. Measles immunity is usually life long, and it has been assumed that vaccination-induced immunity would provide permanent protection. It is often concluded that those vaccinated children who later develop measles have not reacted to the vaccine.(7)

The Global measles mortality reduction and regional elimination strategic plan 2001 -2005 endorsed a new recommendation on measles vaccination, that in addition to the first dose of measles vaccine at nine months of age, there should be a second opportunity for measles vaccination for all children so that a dose can be given to children who have not been vaccinated previously or have not responded to the first dose.(4,8-11)

Children vaccinated with measles vaccine seem less susceptible than do other unvaccinated children because there are significantly fewer index cases among them, vaccinated secondary cases have lower mortality rate and

Dept of Epid & Community Health,
College of Health Sciences,
University of Ilorin, Ilorin, Nigeria.

Correspondence

vaccinated index cases may be less infectious because they give rise to fewer secondary cases than do unvaccinated index cases. Reduced susceptibility, milder infection, and lower infectivity suggest that some of the vaccinated children who develop measles have a degree of immunity.(7)

High transmission of measles despite high coverage with 1-dose measles vaccine have been reported in Harare, Zimbabwe, the failure rate from the standard Schwartz measles vaccine also appear to be high.(12) Marufu et al reported changes in transmission pattern of measles following an outbreak in Gweru city in Zimbabwe. High measles transmission was found among school age children, 49% of cases were in children aged 60 – 119 months and 68% of them had been vaccinated. The high transmission in school age children could spill into the community generating secondary cases among the younger sibling and this could result in high morbidity and mortality.(13)

In many countries in developing countries one dose routine immunization is provided to children about 9 months of age. In addition catch-up campaigns, periodic (every 3 -5 years) follow up campaigns of children 9 months to 5 years are provided to assure maintenance of high measles population immunity.(5) Between 1990 and 2000, reported global routine immunization coverage with one dose of measles vaccine among infants remained 80%. However, coverage varied widely between countries within regions. African Region reported the lowest coverage both in 1995 and 2000. Sixteen countries (almost all in Africa) reported coverage below 50%.(4)

Despite high single-dose measles immunization coverage since 1980s and high 2-dose coverage since 5 years, Romania experienced a measles epidemic between November 1996 and June 1998, apart from unvaccinated children younger than 2 years, largest cases occurred among persons aged 8 through 18 years, 73% of the measles cases had been previously vaccinated. The measles vaccine efficacy studies conducted during the epidemics found the measles vaccine to be highly effective, indicating that measles among vaccinated school children was primarily due to vaccine failure, failure to respond to a single dose of measles vaccine.(14) Although a single properly administered dose of vaccine should be adequate, even a few errors and low failure rates leave enough susceptible individuals to permit continued outbreak.

Seroconversion

As a result of a study on serological response to measles vaccination in India, John et al. concluded that it is difficult to protect the majority of measles susceptible population with a single dose regardless of the immunization schedule, a second dose of measles vaccine may be necessary to increase herd immunity.(15) Vaccination of susceptible children using live attenuated vaccine demonstrated failure of seroconversion in most children below 15 months and indicated maximum serological protection when vaccinated at about 15 months of age when immediate threat of infection is removed by effective control of the disease in susceptibles.(16)

Vaccine efficacy in a study in rural Senegal was found to be 76% (95% CI: 36 – 91) in children ≥ 10 years of age as compared with 81% (95% CI: 66 – 90) in children aged < 5 years.(17) In another study in Zaire where most children were vaccinated before the age of 9 months the reported vaccine efficacy was 69%.(18) In the same study in Zaire, death rate was significantly higher for the non-seroconverters and between age of measles vaccination and 3 years of age, seroconverters had a cumulative mortality risk of 4.5% vs 15.1% for non converters, indicating a 3-fold difference.(18) Seroconversion following studies done 30 – 70 days after first measles vaccination in rural Kenya was found to be 71%. The mean age of the children at vaccination was 11.6 ± 4.8 months and the range was 2 – 38 months.(19) Mahomva et al. found vaccine efficacy following vaccination to control an outbreak of measles in Zimbabwe to be 68% which is low,(20) while in Chad vaccine efficacy was found to be 71% (95% CI:, 59 – 80%). (21)

Isik et al in a study in Istanbul where children received first dose measles vaccine at 9 months and second dose at 15 months found that passive antibody positivity rate was 5.2% at 9 months. Seroconversion rate was 77.6% after the first dose and 81.9% after the second dose. The study also found that 86.7% of those that were seronegative after first dose became seropositive after the second dose at age of 15 months. (22)

Factors associated with vaccine failure

Factors related to seroconversion in the child

An important factor in the waning of passively acquired antibody is the variation in antibody durability in the infant. In poor families children acquire many infections and passively acquired antibody is swept out.(23) Conditions of overcrowding and intensive exposure that cause high measles mortality are the same conditions that lead to a high rate of vaccine failure.(7) Hasley et al and Lyamuya et al in their studies found that malnutrition and acute infections did not affect seroconversion rates.(24,25) However, Migasena et al in their own study among Thai infants reported that infections concurrent or subsequent to measles vaccination adversely affected antibody responses in their study subjects.(26)

Children with high pre-existing antibody titers fail to seroconvert. Children with lower pre-existing antibody titer seroconverted, but the resulting antibody titer was significantly lower than in children without pre-existing antibody titer.(27) Metintas et al also reported that the presence of maternal antibody reduces success of vaccination against measles.(28) Hasley et al studied servoconversion among Haitian children and found that seroconversion rate increased from 45% at 6 months to 100% at 12 months and suggested that lowest rate of vaccine failure compatible with acceptably low rates of

infection could be achieved by vaccination after 8 months of age.(24)

Black et al in their study in Brazil found that children because of their young age failed to develop protective levels immunity after vaccination, approximately after 18 months of initial vaccination 46% of the children maintained low levels of neutralizing antibody but did not have a measurable haemaglutination-inhibition titer. Revaccination did not elicit an IgM response in most children but stimulated IgG production and the IgG titers fell again within 3 months. This result suggests that early administration of measles vaccine may produce a cohort of children with inadequate immunity that can not be fully immunized by revaccination.(29)

Quality of vaccine

Adu et al. in a study conducted in Ibadan, Nigeria among children at least 9 months old, found immune response was directly related to the titer of vaccines used. For the vaccine that met the minimum WHO required standard it stimulated responses in 87.5% - 100% of children vaccinated. Some of the vaccines in use did not meet the WHO standard.(30) When vaccinated children develop measles it is usually assumed that seroconversion did not occur because maternal antibodies neutralized the vaccine, because immunoglobulins were administered simultaneously, or because improper handling of the vaccine inactivated it. A lot of vaccine failures have been reported in developing countries.(7)

The quality of vaccine used for vaccination in which some had below WHO standard of log 10^{-3} $TCID_{50}$ at the point vaccination has been found to be responsible for low seroconversion in vaccinated children. This usually has to do with the cold chain management particularly at the lower levels.(30-32) A study on vaccine potency and efficacy in Nigeria found only 1 (7.14%) of 14 vials used for measles vaccination had virus titer of 3.5 Log while the rest had less than 3.0 Log – the recommended human dose by WHO and this was reported as a factor in vaccine failure and adequate serocoversion.(33) This is similar to findings by Onoja et al in a study conducted in Ibadan, Nigeria.(34)

Waning immunity

In a study of antibody prevalence in Gambia among children who had received one dose of measles vaccine, measles antibody concentration were $\leq$ 1:8 in 8.2% of 8 – 9 year-old vaccinated children while in a previous survey of 3 – 4 year-old children this was 11.3%. The study found that immunity acquired after measles vaccination had waned over - 8 years as indicated in the fall in the Geometric Mean Concentration between the surveys.(35)

Data from field studies (36) in Guinea-Bissau, southern India, and Senegal suggest declining measles vaccine efficacy and increasing measles infection rates with age and time since vaccination. The effect may be more pronounced for children vaccinated with a single dose at the age of 9 months. Other factors leading to lower population immunity in these settings are: reduced transfer of maternal antibodies to infants, causing increased susceptibility at young ages, and lower antibody levels in immune individuals because of reduced boosting from re-exposure to natural measles. Improved measles control or eradication will require higher immunity levels and better vaccine efficacy. This can be achieved through a two-dose strategy.

In a study in Peru children were found to have excellent antibody responses after measles vaccination but only 23% generated detectable lymphoproliferative responses to measles antigens less than what obtains among children in developed countries. This may contribute to the less than uniform success of measles vaccination programs in developing countries.(37)

Way out for vaccine failure

A study in Ethiopia (27) showed that a primary vaccine failure rate estimated to be 21% (95% CI: 12 -34). Primary vaccine failures have been attributed to the presence of residual maternal antibody, at the time of vaccination, damaged vaccine, receipt of immune globulin, genetic factors and other incompletely understood factors. After a second dose, > 99% of vacinees experience seroconversion and develop immunity.(38) In Niger, Kaninda et al reported vaccine effectiveness increased with age at vaccination from 78% with single dose administered at 6 months of age to 95% at 9 months and vaccine effectiveness with two-dose strategy was 93%. (39)

Planning of measles immunization programs should consider their impact on survival and not only on the problem of vaccine failure. In areas in which the incidence of measles among young children is high, high frequency of vaccinated children with measles should not necessarily lead to raising the age at which vaccinations are given.(7) Issues to consider in given second dose of measles vaccine include sociological and biological drawbacks. If vaccines are given too early the mothers are falsely secured and the vaccine discredited when measles follows. When children are vaccinated while they have passive antibody, they can be made refractory to re-immunization. In the later circumstance, revaccination may produce only a transient secondary response and even twice or thrice vaccinated children may remain unprotected.(40)

Conclusion

Measles remain a disease of public health importance in developing countries. Measles vaccine has significant efficacy for the control of this preventable disease. Even in countries with high single-dose immunization coverage measles epidemics have been reported. Measles vaccine failures resulting from various factors remain a problem that need to be tacked for measles control and eventually measles eradication. Second-dose measles vaccination program have been shown to reduce the problem of vaccine failures. The second dose will help to take care of vaccine failure resulting from presence of residual maternal antibody and damage to vaccine during the first dose as

well as too early vaccination with the first dose. Relevant International Agencies need to develop second dose measles vaccination policies for developing countries as obtains in some developed countries.

References

1. Aaby P, Clemens CJ. Measles immunization research: a review. Bulletin of the World Health Organization. 1989; 57(4): 443 – 448.
2. Akramuzzaman SM, Cutts FT, Hossain MJ, Wahedi OK, et al. Measles vaccine effectiveness and risk factors for measles in Dhaka, Bangladesh. Bulletin of the World Health Organization 2002; 80: 776 – 782.
3. Aaby P, Jensen H. Do measles vaccines have non-specific effects on mortality? Bulletin of World Health Organization 2005; 83(3):238
4. Henao-Restrepo A, Strebel P, Hoekstra EJ, Birmingham M, Bilous J. Experience in Global Measles Control, 1990 – 2001. Journal of Infectious Diseases 2003; 187 (Suppl 1): 15 – 21.
5. Stebel P, Cochi S, Grabowsky M, Bilos J. et al. The unfinished measles Immunization Agenda. Journal of Infectious Diseases 2003; 187 (Suppl 1): 1 -7.
6. Miller M, Redd S, Hadler S, Hinman A. A model to estimate the potential economic benefits of measles eradication for the United States. Vaccine 1998; 16 (20): 1917 – 1922.
7. Aaby P, Bukh J, Leerhoy J, Lisse IM, Mordhorst CH, Pederson IR. Vaccinated children get milder measles infection: A community study from Guinea- Bissau. The Journal of Infectious Diseases. 1986; 154 (5): 858 – 863.
8. WHO / UNICEF. Global measles mortality reduction and regional elimination. Strategic Plan 2001 – 2005. Department of Vaccines and Biologicals, World Health Organization, Geneva.2001.
9. Measles Technical Working Group: Strategies for measles control and elimination: Report of a meeting, Geneva, 11 -12 May, 2000. Department of Vaccines and Biologicals, World Health Organization, Geneva 2001: 3.
10. World Health Organization. State of the world's vaccines and immunization. World Health organization Publication 2003: 53.
11. Garly M, Aaby P. The challenge of improving the efficacy of measles vaccine. Acta Tropical 2003; 85: 1 – 17.
12. Kambarami RA, Nathoo KJ, Nkrumah FK, Pirie DJ. Measles epidemic in Harare, Zimbabwe, despite high measles immunization coverage rates. Bulletin of the World Health Organization 1991; 69(2): 213 – 219.
13. Marufu T, Siziya S. Impact of multiple-dose measles vaccination on measles transmission patterns in Gweru, Zimbabwe. Journal of Tropical Paediatrics 2001; 47: 335 – 338.
14. Ion-Nedlcu N, Pitigo D, Popa M, Hennessey K. Measles elimination: A mass immunization campaign in Romania. American Journal of Public Health 2001; 91 (7): 1042 – 5.
15. John S, Lalitha G, George K, Joseph A. Serological response to early measles vaccination. Journal of Tropical Pediatrics 2004; 50 (3); 175 – 177.
16. Bhaskaram P, Radhakrishna KV, Madhusudan J. Seroepidemiological study to determine age for measles vaccination. Indian J Med Res1986; 83:480 – 486.
17. Cisse B, Aaby P, Simondon F. et al. Role of schools in the transmission of measles in rural Senegal: implications for measles control in developing countries. Am J Epidemiol 1999; 149: 295 – 301.
18. The Kasongo Project Team. The influence of measles vaccination on survival pattern of 7 – 35 month-old children in Kasongo, Zaire. Lancet 1981; 1:764 – 7.
19. Kaan JA, van Vlokhoven PCA, Schneeberger PM. immunogenecity of measles vaccine from a hospital based and outreach program in rural Kenya. Tropical Doctor 1992; 22(1): 30 – 32.
20. Mahomva AI, Moyo IM, Mbengeranwa LO. Evaluation of a measles vaccine efficacy during a measles outbreak in Mbare, City of Harare Zimbabwe. Central African Journal of Medicine 1997; 43 (9): 254 – 256.
21. Ndikuyeze A, Cook A, Cutts FT, Bennett S. Priorities in global measles control: report of an outbreak in N'Djamena, Chad. Epidemiol Infect. 1995; 115: 309 – 314.
22. Isik N, Uzel N, Gokcay G, Kilic A, et al. Seroconversion after measles vaccination at nine and fifteen months of age. Pediatr Infect Dis J, 2003; 22: 691 – 5.
23. Black FL. Measles active and passive immunity in a worldwide perspective. Prog Med Virol. Basel, Karger 1989; 36: 1 – 33.
24. Hasley NA, Boulos R, Mode F, Andre J, et al. Response to measles vaccine in Haitian infants 6 – 12 months: Influence of maternal antibodies, malnutrition and concurrent illnesses. New England Journal of Medicine 1985; 313 544 – 549.
25. Lyamuya EF, Matee MIN, Aaby P, Scheutz F. Serum levels of measles IgG antibody in children under 5 years in Dar-es-Salam, Tanzania. Annals of Tropical Paediatrics 1999; 19: 175 – 183.
26. Migasena S, Simasathien S, Samakoses R, Pitisuttitham P, et al. Adverse impact of infections on antibody responses to measles vaccination. Vaccine 1998; 16(6): 647 – 652.
27. Enquselassie F, Ayele W, Dejene A, Messele T, et al. Seroepidemiology of measles in Addis Ababa, Ethiopia: implications for control through vaccination. Epidemiol Infect 2003; 130: 507 – 519.
28. Metintas S, Etiz S, Akgun Y, Kalyoncu C, Sarboyaci MA, Isikli B. A serological survey of measles vaccine

in a rural region of Eskisehir in Turkey. Public Health 1997; 111: 373 – 376.

29. Black FL, Berman LL, Libel M, Reichelt CA, et al. Inadequate immunity to measles in children vaccinated at an early age: effect of revaccination. Bulletin of World Health Organization 1984; 62 (2): 315 – 319.
30. Adu FD, Akinwolere OAO, Tomori O, Uche LN. Low seroconversion rates to measles vaccine among children in Nigeria. WHO Bulletin 1992; 70 (4): 457 – 460.
31. Adu FD, Adedeji AA, Esan JS, Odusanya OG. Live viral vaccine potency: an index for assessing cold chain system. Public Health 1996; 110:325 – 330.
32. Arya SC, Agarwal N. Efficacy of measles vaccine interlinked with potency and storage. Acta Tropica 2004; 90: 223 – 225
33. Omilabu SA, Oyefolu AO, Ojo OO, Audu RA. Potency status and efficacy of measles vaccine administered in Nigeria: a case study of three EPI centers in Lagos, Nigeria. Afr. J. Med. med. Sci 1999; 28: 209 – 212.
34. Onoja AL, Adu FD, Tomori O. Evaluation of measles vaccination program conducted in two separate Health centres. Vaccine 1992; 10 (1): 49 – 52.
35. Viviani S, Mendy M, Jack AD, Hall J, et al. EPI vaccines-induced antibody prevalence in 8-9 year-olds in the Gambia. Tropical Medicine and International Health 2004; 9 (10): 1044 – 1049.
36. World Health Organization. Report of a meeting on research related to measles control and elimination. Geneva, 27 – 29 March 2000. Department of Vaccines and Biologicals, World Health Organization 2000:8, 18.
37. Bautista- Lopez N.L., Vaisberg A, Kanashiro R, Hernandez H, Ward BJ. Immune response to measles vaccine in Peruvian children. Bulletin of World Health Organization 2001; 79(11): 1038 – 1046.
38. Meissner HC, Strebel PM, Orenstein WA, Measles vaccines and the potential for worldwide eradication of measles. Special article Paediatric 2004; 114(4): 1065 – 1069.
39. Kaninda A, Legros D, Jataou AM, Malfait P. Measles vaccine effectiveness in standard and early immunization strategies, Niger, 1995. Pediatr Infect Dis J 1998; 17: 1034 – 9.
40. Black F. Measles. In Chapter 17, Viral infections of humans: Epidemiology and Control, 4th Edition, New York: Plenum Medical Book Company. 1997: 507 – 529.