

Two Doses of Measles Vaccine Reduce Measles Deaths

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Two doses of measles vaccine to children reduce measles related deaths. The first dose is delivered through the routine immunization system to infants and the 2nd dose through campaigns or routine immunization system, whichever strategy reaches the highest coverage in the country. Experience in 46 out of 47 measles priority countries has shown that measles vaccination using mass vaccination campaigns can reduce measles related deaths, even in countries where routine immunization system fails to reach an important proportion of children. The gradual adoption of this strategy by countries has resulted in 74% reduction in measles related deaths between 2000 and 2007. The 2010 goal to reduce measles mortality by 90% compared with 2000 levels is achievable if India fully implements its plans to provide a second dose measles vaccine to all children either through campaigns in low coverage areas or through routine services in high coverage areas. Full implementation of measles mortality reduction strategies in all high burden countries will make an important contribution to achieving Millennium Development Goal 4 to reduce child mortality by two thirds in 2015 as compared to 1990.

Key words: Measles, Mortality, Supplemental immunization activities, Two dose strategy.

The introduction of a second dose for measles vaccination using mass vaccination campaigns[†], along with improved routine immunization, has averted an estimated 3.4 million measles deaths between 2000 and 2007 in countries with previously high measles burden. In the last nine years, 46 out of 47 countries with more than 95% of the global measles deaths in 2000, introduced a 2nd chance for measles vaccination, resulting in 74% reduction of measles deaths between 2000 and 2007. Impressive progress was made in the African region by 2006 and sustained in 2007, where measles deaths were

reduced by 89% from 395,000 in 2000 to 45,000 in 2007(1,2) (*Fig. 1&2*).

In November 2008, the Strategic Advisory Group of Experts (SAGE) on immunization has recommended that all children should receive two doses of measles containing vaccine: the first dose during routine vaccination program and the second dose either through routine services or through mass campaigns (SIAs)[†], depending on which strategy achieves the higher coverage(3-5). This is an important change to the previous recommendation that one dose of measles containing vaccine would be sufficient to control measles.

As of 2009, all but one country has adopted a two dose strategy for measles control. India is currently in the process of introducing the 2nd dose of measles vaccination in their childhood vaccination program. This is important, as one out of six people live in India and an estimated 123,000 child deaths annually could be averted by offering timely two doses of measles vaccine to Indian children(1,2).

[†]Campaigns or supplementary immunization activities (SIAs) are generally carried out using 2 approaches. An initial, nationwide catch-up SIA targets all children aged 9 months to 14 years; it has the goal of eliminating susceptibility to measles in the general population. Periodic follow-up SIAs then target all children born since the last SIA. Follow-up SIAs are generally conducted nationwide every 2–4 years and target children aged 9–59 months; their goal is to eliminate any measles susceptibility that has developed in recent birth cohorts and to protect children who did not respond to the first measles vaccination.

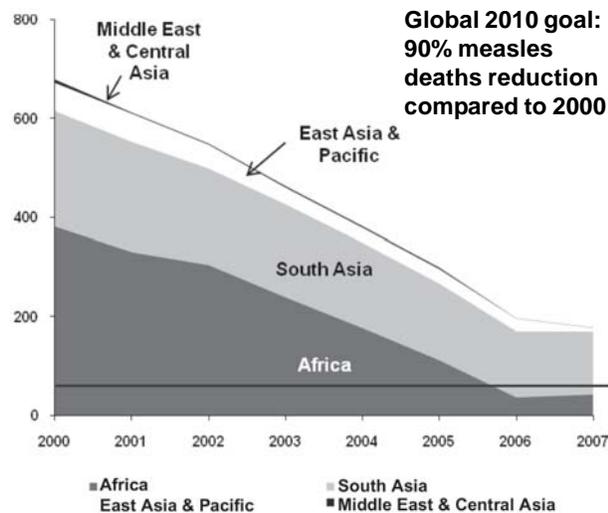


FIG. 1 Estimated measles death, 2000-2007 per region(1,2).

MEASLES KILLS

Measles is one of the most contagious viral diseases and affected almost every child before widespread use of the measles vaccine. About 6 million measles related deaths were estimated to occur globally each year before the use of the live attenuated measles vaccine, licensed in 1963(6). Although measles deaths in industrialized countries are rare, measles is often fatal in developing countries with increased risk of deaths for children under 5 years of age, those living in overcrowded conditions, who are malnourished (especially with vitamin A deficiency), and those with immunological disorders, such as advanced HIV infection(7,8). Measles infection leads to immune suppression in the host, lasting for up to one month, that reduces patients' defenses against complications such as pneumonia, diarrhea, and acute encephalitis. Pneumonia, either a primary viral pneumonia or a bacterial super-infection, is a contributing factor in about 60% of measles-related deaths(7,8).

Globally, measles case fatality rates (CFR) vary widely among countries, regions, age and within the same community in different years. Higher CFRs occur in outbreaks, among children under 5 years of age, in secondary cases, in cases with complications, and in unimmunized individuals. Vaccination is associated with milder disease(7,8). Sudfield and Halsey reviewed the CFRs of 25 studies in Indian

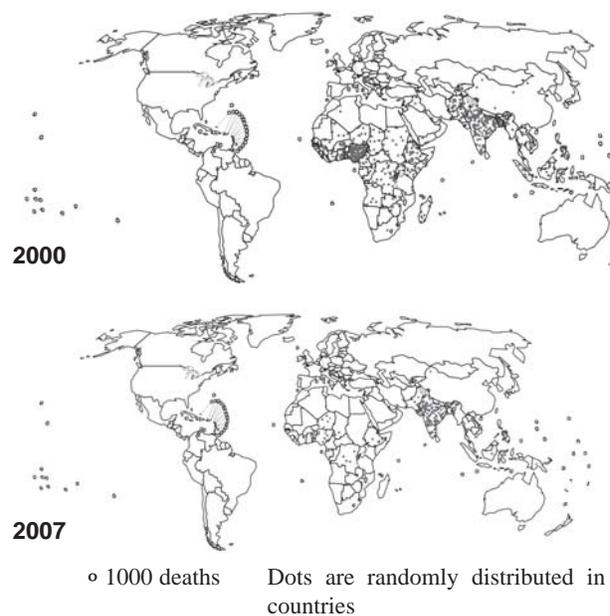


FIG. 2 Distribution of 750,000 estimated measles deaths, 2000 and 2007(1,2).
 ◦ 1000 deaths Dots are randomly distributed in countries
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FIG. 2 Distribution of 750,000 estimated measles deaths, 2000 and 2007(1,2).

communities, presented elsewhere in this issue (mean CFR = 4.27%, range 0.00% - 31.25%, median = 1.63%, range 0.00% - 31.25%). This review reveals that CFR decreased over time, probably due to higher vaccination coverage. In addition, children living in rural areas are more at risk of dying from measles than those living in urban settings(9).

CONTROL STRATEGIES

After the introduction of measles vaccine in the routine immunization program, along with improved nutrition, living conditions and case management, measles related annual deaths reduced to an estimated 2.5 million by 1980(10). As a result of the increase in coverage with the 1st dose of measles to 72% in 2000, as compared to 16% in 1980(11), a further substantial reduction in measles mortality was achieved. Starting in the 1990s, an increasing number of countries introduced a second dose of measles vaccine in their routine program, as reported to WHO and UNICEF joint reporting system. The

Pan American region provided a second dose for measles in supplementary immunization activities that resulted in the elimination of measles by 2002 in that region (*i.e.* the region had no indigenous cases, as distinct from imported cases, for more than 12 months)(12).

Despite these results, in 2000, measles was still the leading cause of vaccine preventable deaths in children and the fifth leading cause of death from any cause in children under five years old(13). Responding to this situation, in 2001, the American Red Cross, UNICEF, the United Nations Foundation, the CDC, and WHO launched the Measles Initiative aimed at reducing the death rate from measles in Africa, where nearly 60% of measles deaths were occurring(14). In 2004, the Initiative extended its mandate to other regions (notably, Asia) where measles was a significant burden. WHO and UNICEF identified 47 high-burden countries for priority action.^{††} All these countries had low coverage of the measles first routine dose (with an average coverage of 58%) and offered only one dose of measles vaccine to their children in 2000.

The Initiative adopted the WHO-UNICEF strategy to reduce measles mortality (3-5,15) that is based on the experience in the Americas:

- achieving high coverage of the first measles containing vaccine (MCV1) in infants
- offer a second dose through campaigns (SIAs[†]) or offer in the routine program reaching very high coverage;
- laboratory backed surveillance of new measles cases to detect outbreaks and monitor progress; and
- enhanced case management, including vitamin A supplementation.

^{††} The 47 measles priority countries are: Afghanistan, Angola, Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Cameroon, Central African Republic, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, India, Indonesia, Kenya, Laos, Liberia, Madagascar, Mali, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Papua New Guinea, Republic of the Congo, Rwanda, Senegal, Sierra Leone, Somalia, Sudan, Timor-Leste, Togo, Uganda, Tanzania, Vietnam, Yemen, and Zambia.

FAILURE OF ROUTINE SYSTEM TO REACH CHILDREN

In the 47 high burden countries for measles^{††}, the routine vaccination program reached on average only 58% of the infants in 2000. Although the coverage increased to 72% in those countries by 2007, adding a 2nd dose to this weak program would not have resulted in a significant increase of population immunity, as an important part of the children are missed by the routine health delivery system. Therefore, a different strategy was adopted to reach previously missed children and increase population immunity.

In countries where the system fails to reach a large part of the children, the only effective delivery system to reach over 95% of the children nationwide is mass vaccination campaigns. Therefore, offering the second dose through a campaign is the preferred strategy to ensure sufficient children are protected from measles to significantly reduce outbreaks. In the measles priority countries, an average of 28% of children have not received their first dose of measles vaccination before their first birthday in 2007, and in Niger, Chad, Somalia and Laos, more than half of the children are missed through the routine system.

In 2007, 23 million infants did not receive the 1st dose of measles vaccination. Two thirds of them live in eight countries: India (8.5 million), Nigeria (2.0 million), China (1.0 million), Ethiopia (1.0 million), Indonesia (0.9 million), Pakistan (0.8 million), DRC (0.6 million) and Bangladesh (0.5 million)(11).

CATCH-UP CAMPAIGNS IN AREAS WITH POOR ROUTINE IMMUNIZATION COVERAGE

Measles catch-up campaigns have been conducted in 46 of the 47 priority countries that adopted the strategy and vaccinated all children aged 9 months through 10-14 years, depending on the epidemiology of the country[†]. The impact of the campaigns has been overwhelming with over 90% reduction in measles cases, and across Africa, many hospitals have closed their measles wards.

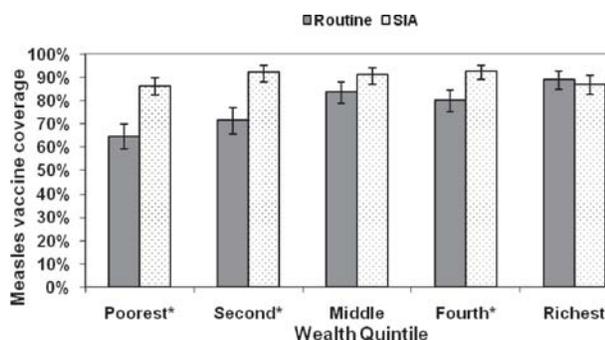
Subsequently, every 2-4 years follow-up campaigns have been conducted to administer the second measles dose to children born after the previous campaign. The frequency of the follow-up

campaigns depends on the coverage of the routine immunization. Generally, major outbreaks can be avoided by conducting follow-up campaigns before one birth cohort of susceptible is reached.

Well organized campaigns reach children across all wealth quintiles evenly, whereas routine immunization program tends to reach fewer children in the poorest quintiles. In Kenya, routine vaccination reached 65% [95% CI: 59%-70%] of the children of the poorest quintile, whereas 89% of the richest children were reached [95% CI: 85%-93%]. During the campaign the coverage was evenly distributed among all wealth quintiles(16)(**Fig.3**). This indicates that campaigns reach the unvaccinated children, including those from poorest families.

Realizing that measles is a more dangerous disease in malnourished children and those living in overcrowded conditions, the campaign approach seems an appropriate strategy to ensure that the poorest children are reached and protected against measles.

Recently, countries have been organizing periodic intensified routine immunization services or Child Health Days, where routine immunization services, including measles vaccination, are offered in underserved areas, often together with other life



Lines above and below the point estimates of coverage represent 95% confidence intervals and (*) indicates a statistically significant ($\alpha=0.05$) difference between routine and SIA measles vaccination coverage

FIG. 3 Nationwide measles vaccination coverage among children aged 9-23 months through routine vaccination immunization programme and SIA[†], Kenya 2002(16).

saving interventions. This strategy has been adopted, as the number of un-immunized children stagnated in recent years at more than 20 million. While health systems take many years to develop and expand, extra outreach sessions can ensure that the poorest children are also protected against vaccine preventable diseases.

INTEGRATION

Measles vaccination has offered an excellent platform to deliver other life saving interventions to the children, such as long lasting insecticide treated nets, vitamin A, de-worming tablets, and polio vaccines. Since 2001, the Measles Initiative with other partners has supported the distribution of more than 37 million long lasting insecticide treated nets for malaria prevention, 81 million doses of de-worming medicine, more than 186 million doses of vitamin A, and more than 95 million polio vaccines. Of the 33 countries conducting measles SIAs in 2008, 29 (88%) integrated at least one other child survival intervention with measles vaccination.

TWO DOSE VACCINATION SCHEDULES FOR MEASLES

To date, countries have adopted a delivery approach for measles vaccine according to the capacity of their health system to reach high population immunity. To stop transmission of measles virus, 93-95% population immunity is needed, that requires a two dose schedule, as vaccine efficacy after a single dose varies between 85 and 95%, depending on the age at vaccination(5).

Countries with strong health systems deliver 2 doses in the routine system only (41 of the 198 countries) or provide 2 doses during the routine, in addition to having conducted a one-time catch-up campaign (37 countries). Fifty-four countries provide two doses of measles vaccines in the routine, and regularly conduct campaigns. Sixty countries provide one dose of measles vaccination in the routine and conduct regular campaigns. Finally, India has plans to begin introduction of a second dose of measles vaccines in the near future (**Fig.4**).

Importantly, there are countries in each of the categories that have successfully stopped measles

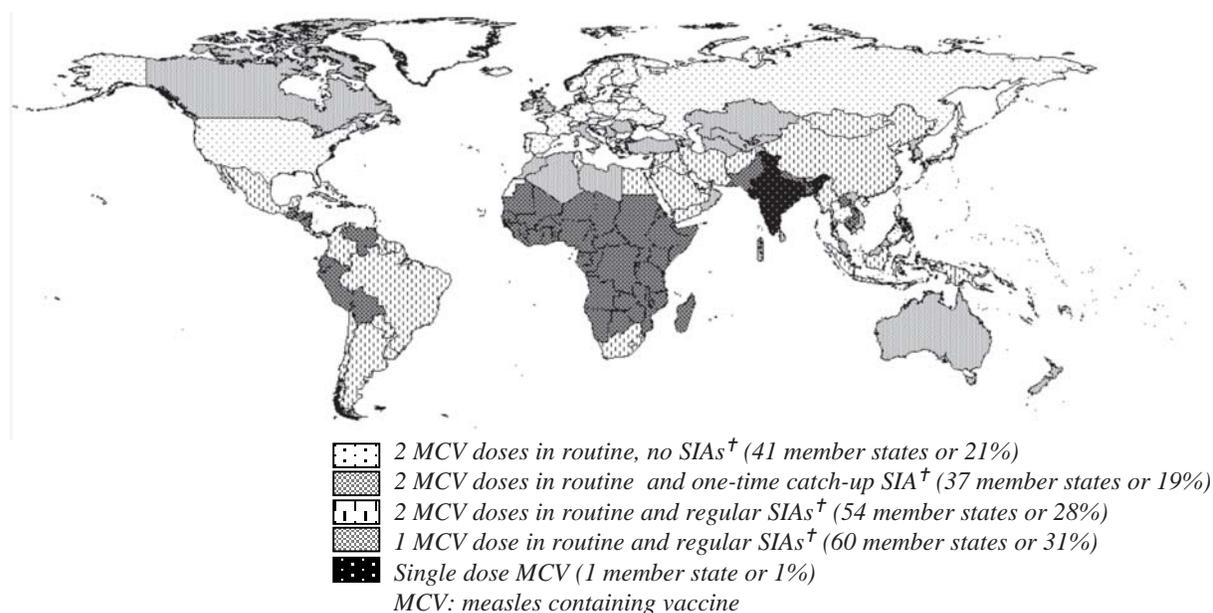


FIG. 4 Measles vaccination delivery strategies, 2008.

transmission through achieving and maintaining very high coverage with their delivery strategy, with the exception of settings which use a single measles dose delivery only.

According to the latest SAGE recommendations, it is beneficial for countries to introduce a 2nd measles dose as part of the routine vaccination programme, if the health system is sufficiently strong and has reached at least 80% of the infants with the first measles dose during 3 consecutive years. To ensure sufficient population immunity, campaigns should be continued until the 1st and 2nd routine measles dose reached 95% of the eligible children(4).

CONCLUSIONS

Significant reduction of mortality due to measles is achieved by offering two doses of measles vaccines to all children. So far, 46 of the 47 priority countries have adopted this strategy, further reducing the measles related deaths by 74% between 2000 and 2007. In these countries, all children are now offered two doses of measles vaccine, one in the routine program and a second through campaigns by renewed delivery strategies to reach previously unreached communities, besides closely monitoring disease burden. Two of the 46 countries (Vietnam

and Indonesia) with stronger health systems have recently also started introducing 2nd dose of measles in the routine immunization system.

Based on the experience in 46 out of 47 priority countries, the 2010 goal to reduce measles mortality by 90% compared with 2000 levels(17) is achievable, if India fully implements its plans to provide a second dose measles vaccine to all children either through campaigns or through routine services. Full implementation of measles mortality reduction strategies in all high burden countries will make an important contribution to achieving Millennium Development Goal 4 to reduce child mortality by two third in 2015, as compared to 1990.

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REFERENCES

1. World Health Organization. Progress in global measles control and mortality reduction, 2000-2007. *Wkly Epidemiol Rec* 2008; 49: 441-448.
2. Centers for Disease Control and Prevention. Progress in Global Measles Control and Mortality Reduction, 2000-2007. *MMWR* 2008; 57: 1303-1306.
3. World Health Organization. Meeting of the immunization Strategic Advisory Group of Experts, November 2008- conclusions and recommendations. *Weekly Epidemiol Rec* 2009; 84: 1-16.
4. World Health Organization. Meeting of the immunization Strategic Advisory Group of Experts, April 2009- conclusions and recommendations. *Wkly Epidemiol Rec* 2009; 84: 213-236.
5. World Health Organization. Measles vaccines: WHO position paper. *Wkly Epidemiol Rec* 2009; 84: 349-360.
6. Clements CL, Hussey GD. Measles. *In*: Murray CJL, Lopez AD, Mathers CD, eds. *Global Epidemiology of Infectious Diseases*. Geneva: World Health Organization; 2004.
7. Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis* 2004; 189 (Suppl 1): S4-S16.
8. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009; 38: 192-205.
9. Sudfield CR, Halsey NA. Measles case fatality ratio in India; a review of community based studies: *Indian Pediatr* 2009; 46: 983-989.
10. Plotkin S, Orenstein W, Offit P. *Vaccines*, 5th ed. Philadelphia: Saunders; 2008.
11. World Health Organization. United Nations Children's Fund. WHO/UNICEF review of national immunization coverage, 1980-2007. Geneva, Switzerland: World Health Organization; 2008. Available at http://www.who.int/immunization_monitoring/routine/immunization_coverage/en/index4.html. Accessed 20 September, 2009.
12. de Quadros CA, Andrus JK, Danovaro-Holliday MC, Castillo-Solórzano C. Feasibility of global measles eradication after interruption of transmission in the Americas. *Expert Rev Vaccines*, 2008; 7: 355-362.
13. Stein CE, Birmingham M, Kurian M, Duclos P, Strebel P. The global burden of measles in the year 2000—a model that uses country-specific indicators. *J Infect Dis* 2003; 187 Suppl 1: S8-S14.
14. Wolfson L, Strebel P, Gacic-Dobo M, Hoekstra EJ, McFarland JW, Hersh BS. Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study. *Lancet* 2007; 369: 191-200.
15. World Health Organization. United Nations Children's Fund. Measles mortality reduction and regional elimination strategic plan 2001-2005. Geneva, Switzerland: World Health Organization; 2001. Available at <http://www.who.int/vaccines-documents/docspdf01/www573.pdf>. Accessed 20 September, 2009.
16. Vijayaraghavan M, Martin RM, Sangrujee N, Kimani GN, Oyombe S, Kalu A, *et al.* Measles supplemental immunization activities improve measles coverage and equity: Evidence from Kenya. *Health Policy* 2007; 83: 27-36.
17. World Health Organization. Global immunization vision and strategy 2006-2015. Geneva, Switzerland: World Health Organization; 2005. Available at http://www.who.int/vaccines-documents/docspdf05/givs_final_en.pdf. Accessed 20 September, 2009.