The Unfinished Measles Immunization Agenda

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Despite achieving and sustaining global measles vaccination coverage of about 80% over the past decade, worldwide measles remains the fifth leading cause of mortality among children aged <5 years. In May 2002, the United Nations Special Session on Children endorsed the goal of reducing measles deaths by half by 2005. Countries and World Health Organization (WHO) regions that adopted aggressive measles control or elimination strategies have shown excellent results. In 2001, countries in the Americas reported an all time low of 537 confirmed measles cases. Substantial progress in measles control has also been achieved in the WHO Western Pacific Region, in seven southern African countries, and in selected countries in WHO European, Eastern Mediterranean, and Southeast Asian regions. The ongoing measles disease burden and availability of safe and effective measles mortality reduction strategies make a compelling case to complete the unfinished agenda of measles immunization.

This supplement captures recent experiences and lessons learned with measles control and elimination at the global, regional, and country levels. The 46 papers are organized under three topic headings. The first of these, Public Health Importance of Measles, provides the latest global estimates of the morbidity and mortality burden of measles [1], describes recent trends in measles incidence and vaccination coverage [2], and estimates the future savings for seven industrialized countries that would result from global measles eradication [3].

The next section (the largest) describes regional and country experiences with different measles control strategies. This section is subdivided by each of the six World Health Organization (WHO) regions with particular focus on progress in reducing measles mortality in the African Region [4] and the highly successful efforts of the Pan American Health Organization (PAHO) to eliminate measles from the Western Hemisphere [5]. In Africa, a new partnership coordinated by the American Red Cross has been formed with the goal of reducing measles deaths to near zero by 2005. The Eastern Mediterranean Region has made remarkable progress in measles control [6]. Some countries (e.g., Oman and Tunisia [7]) have interrupted measles transmission, while others are still battling endemic poliovirus transmission. Successful implementation of a mass measles vaccination campaign in central Afghanistan provides valuable lessons for accelerating measles control in complex emergency situations [8].

The diversity of the European Region [9] is illustrated by the experience with measles control in Germany [10] and the ongoing measles disease burden in Turkey [11] compared with highly successful elimination efforts in England and Wales [12], Romania [13], and Albania [14]. Supplementary immunization activities (SIAs) in the latter two countries provided a unique opportunity to introduce combined measles and rubella vaccine as part of a comprehensive program to prevent congenital rubella syndrome. The Southeast Asian Region is represented by the experience in Sri Lanka,
where despite high single-dose coverage, a large outbreak (>15,000 cases) occurred among infants, adolescents, and young adults [15]. In the Western Pacific Region, substantial progress in measles control has been made in China [16], and South Korea has successfully implemented strategies to eliminate measles by 2005 [17]. In contrast, Japan continues to experience periodic large outbreaks due to delays in vaccinating preschool-aged children [17].

The final section is on epidemiologic and laboratory aspects of program monitoring. It highlights the latest information about the safety of measles vaccine when used in mass campaigns [18], the methods available to ensure injection safety, and the appropriate disposal of used injection equipment [19], state-of-the-art approaches to measles diagnosis [20], development of a global measles laboratory network [21], and an up-to-date description of measles virus genotypes found worldwide [22]. This supplement notes key lessons learned and implications for improved measles control in the twenty-first century drawn from experience across the countries and regions described.

**LESSONS LEARNED**

**Measles is a highly contagious killer disease.** Despite achieving and sustaining global measles vaccination coverage of about 80% over the past decade, measles remains the fifth leading cause of death among children <5 years old worldwide (figure 1) [23]. In 2000, an estimated 31 million cases of measles occurred and resulted in 777,000 deaths. WHO regions with the most measles deaths were Africa (452,000), Southeast Asia (202,000), and the Eastern Mediterranean (81,000) [23]. Measles accounted for 44% of total deaths due to vaccine-preventable diseases among children <15 years old [24]. The highest measles mortality occurs in poor communities with malnutrition, overcrowding, and low vaccination coverage and in emergency situations. Routine vaccination coverage in Kano, Nigeria, is 20% and during a large measles outbreak in 2001, >36,000 cases were reported that resulted in about 14,500 deaths (Foster SO, personal communication). A household survey of the Kohistan District, Afghanistan, in April 2001 found that measles accounted for 17 (16%) of 108 deaths [25].

Measles is one of the most contagious human diseases and large outbreaks continue to occur in countries that have achieved high vaccination coverage with a single-dose strategy (e.g., Sri Lanka [15], South Korea [17]). High population density facilitates transmission as illustrated by an outbreak in a Tanzanian refugee camp [26] and persistent transmission in the eastern provinces of China despite a strong immunization program [27]. In African countries with low-to-moderate routine measles vaccination coverage, mass vaccination campaigns of limited scale (e.g., urban, “rolling,” or nationwide targeting a limited age range, e.g., children aged 9 months to 4 years) were insufficient to prevent large measles outbreaks [4].

**Measles vaccine is safe and effective.** In all countries and regions that have attained high coverage with measles vaccine, regardless of the vaccine virus strain or manufacturer, measles incidence has been substantially reduced [2]. Countries and regions that have implemented aggressive measles control or elimination strategies (e.g., the Americas and southern Africa) have seen measles cases and deaths reduced to all time record low levels and, in many cases, measles virus transmission has been interrupted [5, 28–30]. The remaining global measles disease burden occurs in countries and regions (sub-Saharan Africa, Southeast Asia, and select countries in Europe, the Middle East, and the western Pacific) that have low uptake of measles vaccine (i.e., low coverage with the first dose and/or do not provide a second opportunity for measles immunization) [24].

The safety record of measles vaccine when administered through routine health services to infants and young children is well documented [31]. Experience with measles vaccine or combined measles-rubella vaccine during mass vaccination campaigns reported in this supplement confirms that serious adverse events are rare [18]. No deaths were associated with measles or measles-rubella vaccine during mass vaccination of over 20 million children and adolescents in the United Kingdom (UK), Canada, Australia, South Korea, Costa Rica, Romania, and New Zealand [18]. The risk of encephalitis after measles vaccination in recent campaigns was about 1 per 1 million doses administered, although the case definition and confirmation of such cases has been difficult. Acute anaphylaxis was reported in <1 vaccinee per 1 million doses administered [18].

Allegations that the combined measles-mumps-rubella vaccine may cause autism and/or inflammatory bowel disease among recipients has led to some erosion of measles coverage in the UK, Sweden, and a few other industrialized countries.
Because most of the control programs described in this supplement use monovalent measles or bivalent measles-rubella vaccines, it seems unlikely that these alleged problems will impinge on the progress of global measles control.

**Importance of strong routine immunization.** The critical importance of vaccinating each new cohort of infants soon after they lose the protection of transplacentally acquired measles antibody is evident in every country report. Unvaccinated preschool-aged children comprise the group most susceptible to measles and provide the "fuel" for epidemics. This was evident both in countries that had interrupted transmission and then experienced outbreaks (e.g., Haiti [32]) and countries that have improved routine immunization coverage, but continue to have periodic outbreaks (e.g., Ghana [33] and Mozambique [34]). In Ghana, health sector reform and decentralization have led to more resources and accountability at the district level and have contributed to increased immunization levels [33].

**A single-dose vaccination strategy is not sufficient for good control.** Because of the contagiousness of measles, even sustained high coverage with a single-dose strategy does not prevent periodic large outbreaks with significant morbidity and mortality, disruption of school or work programs, and substantial costs for hospitalization and patient treatment and for outbreak control activities. These findings were seen in Sri Lanka [15], many countries in Latin America [5], Romania [13], and South Korea [17] before catch-up vaccination campaigns were conducted.

In these outbreaks, the age distribution of cases was usually bimodal, indicating transmission occurred among preschool-aged children (infants too young for vaccination, toddlers who missed vaccination, and children who failed to develop immunity after vaccination) and older school-aged children, many who had been vaccinated as young children but failed to respond. In some outbreaks, the second peak in incidence was among young adults who were born when measles vaccine was being introduced and escaped both measles vaccination and circulating measles virus. The absence of large numbers of measles cases and outbreaks among vaccinated young adults (e.g., in former East Germany [10]) suggests that waning of vaccine-induced immunity is not a major factor contributing to population susceptibility to measles.

**A second opportunity for measles immunization is essential for effective measles control.** High coverage with a second opportunity for measles immunization can provide the additional population immunity needed for effective measles control. In countries with good access to health services (e.g., England and Wales [12], Romania [13], Albania [14], Oman [6], Shandong and Henan provinces in China [27]) the second opportunity for measles immunization is provided through a routine two-dose vaccination schedule. In many of these countries, a one-time catch-up campaign was needed to provide immunity to older school-aged children who either were not vaccinated as children or failed to mount an immune response to measles vaccine.

In countries where access to preventive health services may be limited (e.g., parts of Latin America [5], Turkey [11], and Zimbabwe [30]), in addition to a one-time catch-up campaign, periodic (every 3–5 years) follow-up vaccination campaigns of children aged 9 months to 5 years are needed to assure the maintenance of high measles population immunity. The contribution of campaigns to population immunity is greater if they can achieve high coverage and access previously unvaccinated children to the same extent as those who already received a dose of measles vaccine (e.g., Burkina Faso) [35].

The 2001–2005 WHO/UNICEF Strategic Plan for Measles Mortality Reduction and Regional Elimination recommends that all children receive a second opportunity for measles immunization [36]. This recommendation reflects the evolution in measles immunization policy that occurred in many countries during the late 1980s and 1990s. In the 1990s, countries were classified as being either in the control or elimination phase, and there was much debate about the wisdom of a second opportunity for measles immunization in less developed countries. The debate centered on the relative merits of delivering vaccine through routine health services versus mass vaccination campaigns. The recommendation of a second opportunity for measles immunization for all children has resulted in a convergence in the vaccination strategies used in both developed and less developed countries. With the strategy debate largely resolved, the critical issue now is how to achieve and maintain very high coverage at each immunization opportunity.

**SIAs can be highly effective.** In the African Region, SIAs of limited scale (e.g., targeting only urban areas or only children aged 9 month to 4 years), although they protected previously unvaccinated children, were not an effective strategy to prevent epidemics [4]. In contrast, nationwide SIAs in Latin America, Europe, and Africa targeting children of all age cohorts with high levels of measles susceptibility (most often ages 9 months through 14 years) were successful in preventing outbreaks and in reducing measles mortality to zero (e.g., Zimbabwe [30]). In countries with strong epidemiologic and virologic surveillance (e.g., England and Wales [12]), the interruption of measles transmission was documented with a high degree of certainty.

To be successful, SIAs must target and achieve uniformly high coverage in all geographic areas and across all age groups with relatively high susceptibility to measles (i.e., >5%) [37]. Moreover, in countries with low-to-moderate vaccination coverage, mass campaigns offer the opportunity to mobilize additional resources to reach previously unvaccinated children. Because most children vaccinated in catch-up and follow-up vaccination activities are >1 year old, interference by maternal
antibodies is minimal, and measles vaccine administered during SIAs results in very high seroconversion rates. The recent experiences in Latin America and Africa indicate that, given appropriate training and supervision, SIAs are safe, have relatively low vaccine wastage rates, and can be conducted well in areas with incomplete cold chains [4, 5].

** Interruption of measles virus circulation can be achieved and sustained. ** In 2001, WHO and UNICEF established the goals of reducing measles deaths by 50% by 2005 (compared with 1999 estimates) and of achieving interruption of indigenous measles transmission in large geographic areas with established elimination goals [36]. The mortality reduction goal was endorsed in May 2002 by the United Nations (UN) Special Session for Children [38]. To achieve these goals, WHO and UNICEF recommend a comprehensive strategy that includes routine childhood immunization, periodic measles SIAs, and careful measles surveillance.

Reports elsewhere in this supplement from the Americas [5], England and Wales [12], Romania [13], Brazil [39], and Zimbabwe [30] indicate that measles virus circulation can be stopped in large geographic areas and maintained over time through aggressive vaccination and surveillance efforts. Interruption of measles virus circulation has been sustained for many years in Cuba (since 1988) [5], the United States (USA; since 1997) [40], England and Wales (since 1995) [12], and Brazil (since 2000) [39].

The precise immunity level at which measles transmission is interrupted is not known; however, seroprevalence studies in the USA and other developed countries suggest it is in the range of 90%–95% [41]. This experience is consistent with mathematical models that estimate the herd immunity threshold for measles in industrialized countries is 91%–93% [42]. This level of immunity must be maintained uniformly across all age cohorts and geographic areas of a country to sustain interruption of measles transmission.

Interruption of measles virus circulation has important benefits and, resources permitting, should not be postponed. It affords protection to susceptible vulnerable members of the community (e.g., infants and immunocompromised persons) and prevents large epidemics and their associated morbidity, mortality, and financial costs. Response to large measles outbreaks can be expensive, time consuming, and divert staff involved in both clinical and preventive services.

** Infants and children have the right not to die of measles. ** Given the availability of a safe, effective, and inexpensive vaccine and proven vaccination strategies, infants and children have the right not to die of measles. The International Covenant on Economic, Social and Cultural Rights, which has been ratified by 145 countries, outlines the right of all persons to enjoy the benefits of scientific progress [43]. Moreover, the covenant requires governments to assure the availability and accessibility of public health services to all, especially the most vulnerable members of the population. It is morally unacceptable to allow nearly 800,000 infants and children to die of measles each year when an effective public health intervention is readily available.

** Postelimination epidemiology is driven by importation of measles from endemic areas. ** After interruption of endemic measles transmission, measles continues to be imported from countries with poor measles control. These importations test the population immunity and provide a useful means for monitoring elimination [44]. If immunity to measles is high, as in England and Wales during 1995–2001, importations result in isolated sporadic cases or in small clusters of measles cases without widespread transmission [12]. In such situations, no outbreak response vaccination is required. In contrast, if population immunity to measles is low and endemic transmission is reestablished following an importation, as in Haiti [32], a large-scale vaccination campaign and extensive outbreak investigation may be required to control the outbreak.

** Integrated epidemiologic and laboratory surveillance is critical. ** Ongoing assessment of vaccination coverage (to monitor accumulation of susceptible persons) and disease surveillance (to monitor disease burden and virus transmission) is critical for directing program activities and advocacy. In Burkina Faso, a coverage survey after the 1999 campaign found that campaign coverage was similar in children who had previously received a dose of measles vaccine through routine services and those who had escaped vaccination [35]. Although monitoring vaccination coverage is essential for monitoring population susceptibility to measles, case-based measles surveillance with laboratory confirmation of measles infection is the reference standard for evaluating program impact [28, 29].

When measles incidence is very low (e.g., after a successful catch-up campaign), the clinical diagnosis of measles becomes unreliable. In such settings, each suspected measles case requires laboratory confirmation. The most widely used diagnostic assay for measles is an IgM ELISA performed on a serum specimen [20]. In England and Wales, oral fluid specimens are widely used [12]. ELISA testing of serum eluted from filter paper blood spots is being evaluated and may provide advantages of easier specimen collection and transportation [20]. A network of provincial, national, regional, and two global laboratories (Public Health Laboratory Services, London, and Centers for Disease Control and Prevention [CDC], Atlanta) is being established to ensure quality control of diagnostic assays and support for virus isolation and genetic sequencing [21]. Molecular epidemiology has proved valuable in documenting elimination of indigenous virus strains (e.g., D6 in the Americas) and for tracing the geographic origin of importations [22].

The surveillance indicators initially developed in the WHO Region of the Americas [45] have been adopted elsewhere. The experience in the Americas of using rapid coverage assessments
during campaigns [46] is being expanded as a supervisory tool in other regions and countries.

**Implications for Measles Control**

**Political commitment.** The resolution by Western Hemisphere ministers of health, after the certification of polio eradication in September 1994, to eliminate measles by 2000, was clear evidence of the strong political commitment to measles control in the Region of the Americas [45]. Political will to control measles is high in sub-Saharan Africa and south Asia where measles remains a major killer of children. In contrast, in some industrialized countries measles is not a high public health priority as reflected by low vaccination coverage rates (e.g., Japan, Italy, France, Germany). Further progress in measles control will require that industrialized countries devote the resources necessary to reduce measles virus circulation in their own populations and help finance vaccination and surveillance activities in developing countries.

The benefits of aggressive measles control are well illustrated in the comparison between the former East and West Germanys [10]. On the basis of this experience and the occurrence of recent outbreaks, Germany recently adopted the European regional goal of measles elimination by 2010. Similarly, Japan must improve measles control at home before assuming a leadership role in any future elimination effort in the WHO Western Pacific Region [17].

**Partnerships and advocacy.** The polio eradication initiative demonstrated the importance of partnerships for successful disease control that involve ministries of health, the WHO, UNICEF, and private organizations (e.g., Rotary International, UN Foundation) [47]. The Global Alliance for Vaccines and Immunization (GAVI) is attracting new financial (e.g., Bill and Melinda Gates Foundation, UN Foundation, and national governments) and political support for immunization infrastructure, with a goal to achieve ≥80% vaccination coverage with the third dose of diphtheria-tetanus toxoids–pertussis vaccine in all districts, should lead to greater measles vaccination coverage and, in turn, improve measles control.

The Measles Initiative was formed in January 2001 to greatly reduce measles deaths in Africa over the ensuing 5 years. This initiative is coordinated by the American Red Cross and includes the following major partners: the UN Foundation, UNICEF, WHO, and the CDC. During 2001–2002, the Measles Initiative supported mass vaccination campaigns in 14 African countries that vaccinated >60 million children and prevented thousands of measles deaths [48]. This partnership must expand to address the measles mortality burden in the remaining African countries and other regions, especially south Asia.

**Full implementation of measles mortality reduction strategies is needed.** Measles outbreaks in São Paulo State, Brazil [5], Haiti [32], and Venezuela and Colombia [49] occurred because of underlying weakness in routine immunization services or a poor quality or delayed follow-up vaccination campaign. In contrast, countries in the Americas and southern Africa that have fully implemented the elimination strategies recommended by PAHO have not had large measles outbreaks [4, 5]. The delivery of quality immunization services through routine or supplemental activities requires thorough planning, budgeting, financing, supervision, and management at each program level. Coordination and cooperation among partners will be critical for success. Funding for immunization waste disposal and introduction of case-based surveillance should be included in the overall plan of action for measles control or these activities will remain neglected [19].

**Integration and coordination of accelerated measles control activities.** The pace of global immunization activities (e.g., polio eradication, introduction of hepatitis B and *Haemophilus influenzae* type b vaccines, maternal and neonatal tetanus elimination, the initiative for safe injections, and renewed efforts to improve routine immunization services) has increased rapidly over the past 5 years and offers new opportunities to integrate and coordinate accelerated measles control activities. Efforts to strengthen routine immunization services directly benefit measles control by increasing on-time coverage and helping to assure high population immunity among infants and young children who are at the highest risk of dying of measles. Because of the high visibility of measles as a childhood killer, measles coverage and disease incidence can be used as markers of availability and utilization of primary health services.

The WHO and UNICEF recommendation of offering a second opportunity for measles immunization to all children should become part of the routine schedule for childhood vaccination. For countries providing the second opportunity for measles immunization through SIAs, these activities must be regularly scheduled (e.g., every 3–5 years depending on routine measles vaccination coverage) and become part of the programs.

With adequate funding and logistical support, administration of vitamin A and oral poliovirus vaccine have been successfully combined with measles SIAs [35]. In addition, in countries with programs to prevent congenital rubella syndrome, measles SIAs provide an opportunity to deliver rubella vaccine, usually in the form of bivalent measles-rubella vaccine. Surveillance for measles and rubella can be integrated into one system for surveillance of febrile rash illnesses.

**Assurance of adequate supplies of measles vaccine.** The excess capacity in global measles vaccine production available in the late 1990s has been reduced such that current supply closely approximates the anticipated demand [50]. This leaves little margin for unexpected production problems or increases
in demand. The WHO/UNICEF recommendation of providing a second opportunity for measles immunization for all children will effectively double the demand for measles vaccine over time. In addition, the decision of a large country to conduct a catch-up campaign can induce a sudden drain on vaccine supplies. For these reasons, multiyear forecasting of measles vaccine requirements is needed to avoid cancellation of program activities due to lack of vaccine on the global market [51].

**Research and development.** The March 2000 meeting of the Steering Committee for Measles Research highlighted the unanswered questions regarding effective measles control and the feasibility of global eradication [52]. These include the interaction between the human immunodeficiency virus (HIV) pandemic and measles, the ability of PAHO strategies to stop measles transmission in Asian and African megacities, the potential for an easier and cheaper delivery method (e.g., aerosol administration or needle-free jet injection) of existing measles vaccines, and the development of new vaccines that could induce immunity in the presence of maternal antibodies. In July 2000, the Bill and Melinda Gates Foundation donated $41 million to support the development of subunit and vectored measles vaccines (so-called “stealth vaccines”) that may be immunogenic in very young infants (i.e., overcome maternal antibodies and immunologic immaturity) [53]. In March 2002, WHO formed a product development group to bring an aerosol delivery system that uses existing measles vaccines to licensure by 2009.

Ongoing program evaluation and operational research is needed to improve the efficiency of vaccination and surveillance strategies and to minimize the risks of unsafe injections and immunization waste disposal. In addition, the safety of measles vaccine in HIV-infected persons needs further evaluation. Economic analyses of the benefits and costs of full (i.e., interruption of transmission) versus partial implementation of measles control strategies in different settings are needed to guide future investments in the health sector.

**CONCLUSION**

This supplement shows how excellent measles control can be achieved through full implementation of recommended strategies that use existing measles vaccines. The ongoing measles morbidity and mortality, despite the availability of safe and effective vaccines and proven strategies, make a compelling case that all countries should aggressively implement the strategies outlined in the WHO/UNICEF Strategic Plan for Measles Mortality Reduction. The challenge is to build the political commitment, financial support, and program capacity to complete the unfinished agenda of measles immunization.

**References**

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