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Recommendations and Reports

Advances in Global Measles Control and Elimination:

Summary of the 1997 International Meeting

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Advances in Global Measles Control and Elimination: Summary of the 1997 International Meeting

SUMMARY

A meeting concerning advances in measles control and elimination, the third in a series, was held in Atlanta during August 1997. The meeting was cosponsored by CDC, the Pan American Health Organization, the World Health Organization, and the United Nations Children's Fund. Meeting participants concluded that substantial progress has been made toward controlling measles. Measles transmission has been interrupted in several countries, reinforcing the view that measles eradication is technically feasible using existing vaccines and intervention strategies. However, measles still accounts for 10% of global mortality from all causes among children aged <5 years (i.e., approximately 1 million deaths annually). Progress toward measles control varies substantially among countries and regions. Intensified efforts are necessary to implement appropriate control and elimination strategies, including supplementary vaccination campaigns, expansion of routine vaccination services, and surveillance. These strategies and estimates of the resources required to implement them will require adjustment based on accumulating experience. Programmatic and financial obstacles must be overcome if the final goal of measles eradication is to be achieved.

INTRODUCTION

The Third Meeting on Advances in Measles Control and Elimination was held in Atlanta from August 27 through 29, 1997. The meeting was cosponsored by CDC, the Pan American Health Organization (PAHO), the World Health Organization (WHO), and the United Nations Children's Fund (UNICEF). The objectives of the meeting were to

- review experience in measles control and elimination at global, regional, and national levels;
- discuss present and future priorities for technical, programmatic, and laboratory support of measles control and elimination;
- review technical and programmatic issues in measles control, particularly measles surveillance, laboratory methods for confirmation of suspected cases, isolation and typing of measles viruses, vaccine and injection safety, and the phasing of measles control and elimination activities with polio eradication and other activities of WHO's Expanded Programme on Immunization (EPI);
- present findings of cost-benefit analyses of global measles control strategies (including eradication) and discuss the use of these findings to develop political and financial support; and
- improve coordination and cooperation among partners in measles control and elimination.

This report, which summarizes the discussions and conclusions of the meeting, should be read in conjunction with the report of the Second Meeting on Advances in Measles Control and Elimination (*1*), which concluded,"Participants agreed that measles eradication is technically feasible with available vaccines and recommended adoption of the goal of global eradication with a target date during 2005–2010, with the proviso that measles eradication efforts should not interfere with polio eradication but should build on the successes of the global Poliomyelitis Eradication Initiative."

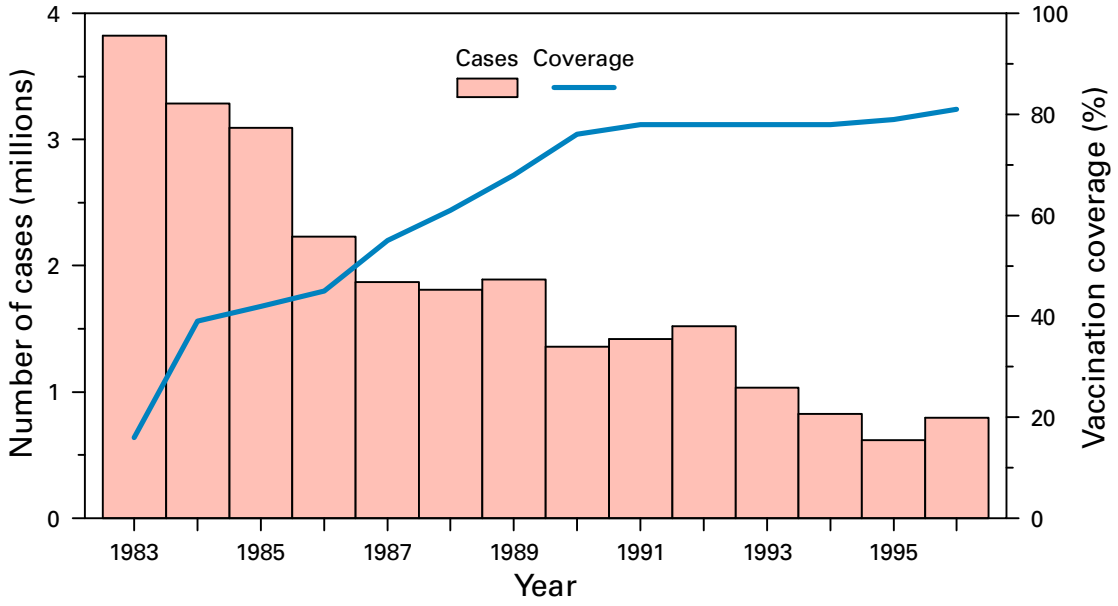
GLOBAL EXPERIENCE WITH MEASLES CONTROL

The efforts of individual countries and global efforts through the EPI have substantially reduced measles morbidity and mortality throughout the world. Worldwide, for 1996, global coverage of the population of children aged 1 year with one dose of measles vaccine is estimated at 81% (*2*) (Figure 1). However, progress in controlling measles varies substantially among WHO regions (Figure 2). An estimated 36.5 million cases and 1 million deaths caused by measles still occur each year. About half of these deaths occur in Africa. Sixteen of 19 countries in which fewer than 50% of children aged 1 year have received at least one dose of measles vaccine are in Africa. Despite poor measles surveillance, Africa also has the highest reported incidence of measles.

Measles Elimination in the Western Hemisphere

In September 1994, the member nations of PAHO established the goal of eliminating measles from the Western Hemisphere by 2000. The strategy adopted included three complementary approaches to immunization:

FIGURE 1. Reported number of measles cases and vaccination coverage* — worldwide, 1983–1996



*Coverage reported as of August 29, 1997.

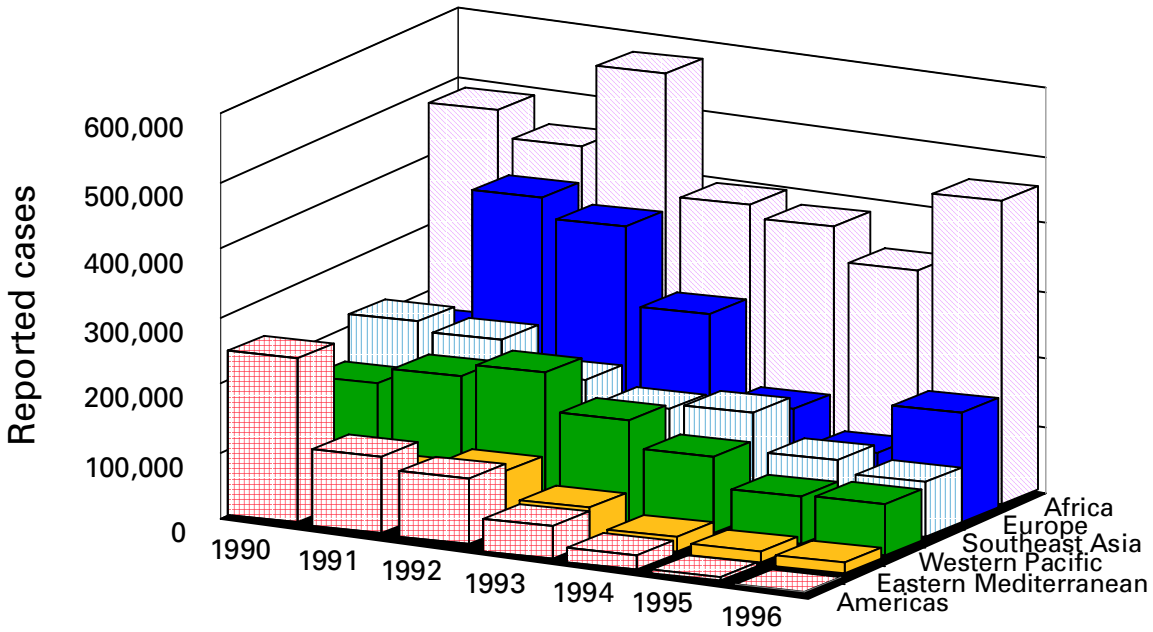
- "Catch-up": a one-time-only mass campaign to vaccinate all children aged 9 months to 14 years, without regard to disease or vaccination history;
- "Keep-up": routine vaccination with measles, measles-rubella (MR), or measles-mumps-rubella (MMR) vaccine at age 12 months; and
- "Follow-up": periodic campaigns conducted approximately every 4 years to vaccinate all children aged 1–4 years, without regard to disease or vaccination history.

Application of this strategy has substantially reduced measles transmission in the Americas (Figure 3).

Several countries including Chile, Cuba, and the nations of the English-speaking Caribbean have reported no cases of measles for ≥3 years. In other countries of the region, measles transmission is now occurring only sporadically. During 1996, 2,109 confirmed cases of measles were reported in the Western Hemisphere—the fewest ever reported. Of these cases, 44% were confirmed by laboratory tests or epidemiologically linked to laboratory-confirmed cases, and 56% were classified as "clinically confirmed" (i.e., neither confirmed by serologic test nor epidemiologically linked to a serologically confirmed case). Of the laboratory-confirmed cases, 816 (88%) occurred in the United States and Canada. Most countries in the region reported sporadic cases or no cases of measles.

Obstacles to measles elimination in the Americas include increasing numbers of infants and children who are susceptible to measles, the circulation of measles virus in other parts of the world, and importation of cases of measles and subsequent spread of measles virus. The number of infants and children susceptible to measles in a population tends to increase over time even when high routine vaccination coverage

FIGURE 2. Reported measles incidence by WHO* regions, 1990–1996

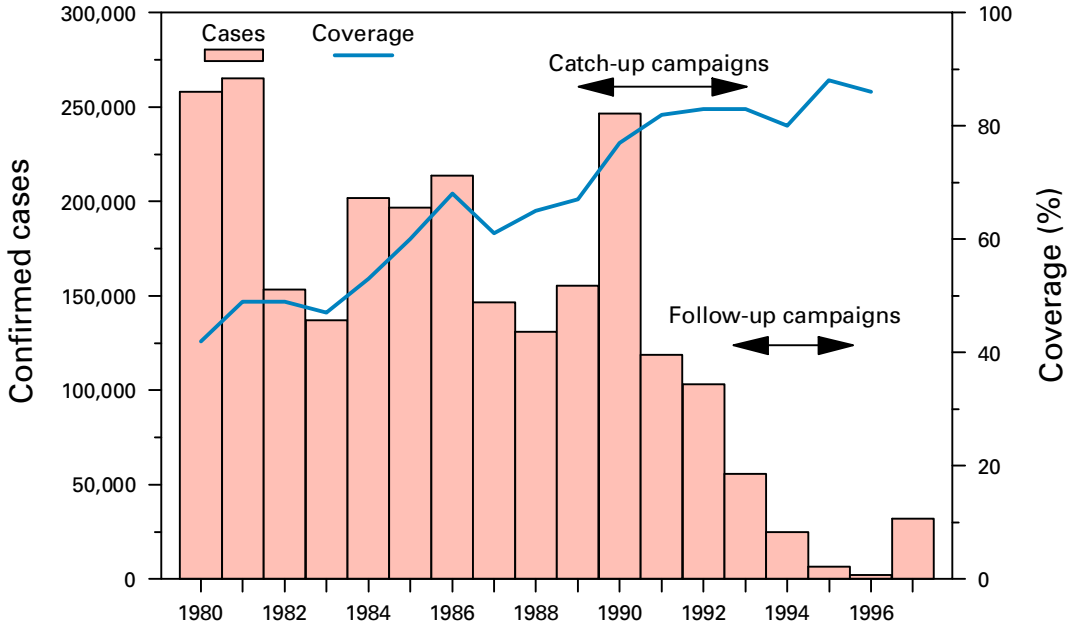


*World Health Organization

with a highly effective vaccine is maintained. For example, in a population with an annual birth cohort of 100,000 children, 90% routine vaccination coverage, and 90% vaccine efficacy, approximately 19,000 children are added each year to the population that is susceptible to measles.

The state of São Paulo, Brazil experienced an outbreak of measles during 1997. By the end of December, >31,000 cases had been reported. This outbreak occurred after several years during which few measles cases occurred because of a catch-up measles vaccination campaign in 1987 and a campaign conducted during 1992 to vaccinate children aged 1–10 years with MMR vaccine. After the 1992 campaign, health authorities in São Paulo state implemented a two-dose measles vaccination strategy. The first dose is routinely administered to infants aged 9 months and the second dose to children aged 15 months. During the 1997 outbreak, most cases occurred among residents of metropolitan São Paulo. During the 1997 outbreak, most cases occurred among residents of metropolitan Sao Paulo. Provisonal data concerning the age and vaccination status of cases indicate that 64% occurred among persons aged ≥15 years, most of whom were unvaccinated; 16% occurred among infants and 6% among children aged 1–4 years, many of whom also were unvaccinated. The highest age-specific incidence rates were observed among infants (849 cases per 100,000 population), followed by persons aged 20–29 years (307 cases per 100,000 population) and children aged 1–4 years (91 cases per 100,000 population). The outbreak spread to other states in Brazil and other countries in the Western Hemisphere.

FIGURE 3. Reported measles cases — region of the Americas, 1980–1997*†



*Coverage for children at age 1 year.
†Cases reported through January 30, 1998.

Source: Pan American Health Organization, World Health Organization.

Factors contributing to the outbreak in São Paulo have not been completely clarified but may include

- the aggregation of susceptible young adults, many of whom had migrated to metropolitan São Paulo from impoverished rural areas;
- the high population density of metropolitan São Paulo; and
- the presence of many preschool-aged children who were susceptible to measles because of the low first-dose coverage achieved by routine vaccination services and the absence of follow-up campaigns.

Genomic sequencing of virus strains isolated from persons with measles in São Paulo during 1997 revealed that these strains were identical or nearly identical to viruses circulating in parts of Europe, indicating that the outbreak may have been triggered by importation of measles virus from Europe.

In Canada, introduction of measles vaccine in 1963 substantially reduced the occurrence of measles. The country relied on a one-dose measles vaccination strategy until 1995, when a major outbreak (i.e., >2,000 cases) prompted adoption of a two-dose vaccination schedule. The second dose is administered to children aged 18 months or 4–5 years. The two-dose strategy was implemented in all 12 Canadian provinces during 1996 and early 1997. Canada's National Advisory Committee on Immunization further recommended that all children and adolescents who had previously received a single dose of measles-containing vaccine receive a second dose. Six provinces completed catch-up vaccination of school children in 1996, achieving 90% coverage. However, during January through April 1997, a measles outbreak occurred in British Columbia and spread to Alberta. British Columbia had carried out catch-up vaccination in 1996, achieving 75% coverage of preschool-aged children and approximately 90% coverage of school-aged children. The outbreak in British Columbia primarily involved young adults (i.e., college students) who were not vaccinated during the 1996 catch-up effort. Alberta had not carried out catch-up vaccination and its outbreak, which occurred from February through July 1997, primarily involved school-aged children.

In the United States, measles incidence is at the lowest level ever measured. In 1996, a total of 488 cases was reported and, in 1997, a total of 135 cases. International importations and cases directly linked to international importations accounted for more than half of all cases reported in 1996 and 1997. During 1996, the reported incidence of measles in the United States was <1 per 1 million population in all age groups. Measles vaccination coverage among children aged 2 years reached 91% in 1996, and 98% of children entering school had received at least one dose of measles-containing vaccine. Approximately 64% of all school-aged children had received two doses of measles vaccine. Evidence from case investigations and molecular epidemiologic studies indicates that measles transmission has been interrupted in the United States at least three times—in late 1993, in 1995, and in 1996. During 1992–1996, Japan, Germany, the Philippines, the United Kingdom, France, India, and Italy were the leading sources of measles cases imported to the United States. In 1997, leading exporters of measles cases to the United States were Germany, Italy, Brazil, China, France, Pakistan, and the Philippines (Figure 4). The increasing proportion of all measles cases caused by imported virus strains indicates that further reduction of

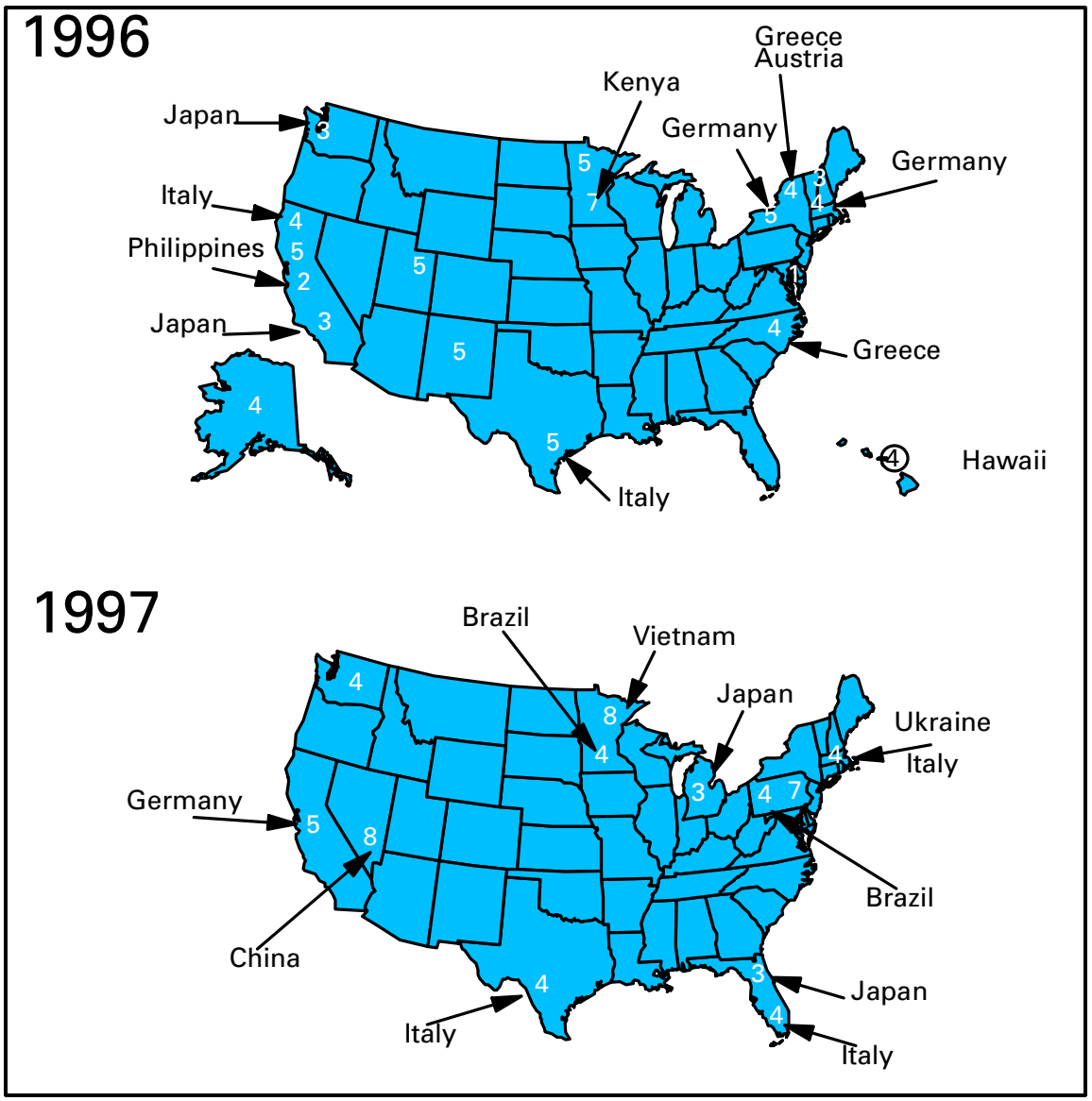
measles incidence in the United States requires international cooperation and improved global control of measles.

Other Global Experiences with Measles Control and Elimination

Africa

In South Africa, measles vaccine was added to the National Immunization Days (NIDs) for polio eradication in 1996. During 1997, efforts were made to ensure that all

FIGURE 4. Measles virus importations to the United States — Virus genotype* and source countries†, 1996 & 1997



*Numerals indicate viral genotype, determined by genomic sequencing.
†Source countries determined by epidemiologic investigation; numeral without arrow indicates source country unknown.

children aged 1–14 years had received measles vaccine during catch-up vaccination campaigns in 1996 or 1997. Analysis of South Africa's experience during the 1996 NIDs revealed several issues to be addressed in future NIDs in which multiple vaccines are administered (i.e., training personnel to administer injections, disposing appropriately of used needles and syringes, and dealing with different target age groups for the two vaccines). The combined 1996 and 1997 campaigns achieved 91% coverage of the eligible age cohort, although coverage varied substantially among provinces and within provinces. South Africa is moving to eliminate measles, but accomplishing the goal will require strengthening surveillance, improving routine vaccination services, and conducting follow-up campaigns.

Several other countries in southern Africa that have made substantial progress in polio eradication, and which have strong basic EPI programs (i.e., Namibia, Botswana, Zimbabwe, and Swaziland), also have launched or are planning catch-up measles vaccination campaigns. These countries have not yet established laboratory-based surveillance.

Western Pacific Region

The Western Pacific Region of WHO includes the most populous as well as some of the smallest countries of the world. Most countries in the region are now free of polio and are devoting more attention to measles. Approximately 100,000 cases of measles are reported in the region each year, despite measles vaccine coverage exceeding 90%. Many countries of the region are now implementing supplemental measles control activities. During 1996, Mongolia conducted a catch-up campaign to vaccinate children aged 9 months through 11 years, achieving 97% coverage. Few cases of measles were reported in Mongolia from July through December 1996, and no confirmed cases were reported from January through May 1997.

Many of the Pacific island nations have been free of measles for some time, although periodic outbreaks caused by measles importations continue to occur. The number and size of these outbreaks have decreased steadily since the introduction of measles vaccination in the mid-1970s. The 20 island nations of Melanesia, Polynesia, and Micronesia are planning intensified measles control efforts. Through coordinated action, these nations hope to emulate the successful measles elimination efforts of the English-speaking Caribbean islands. No measles cases were reported in these 20 nations during 1995, but four outbreaks—all in Polynesia—occurred in 1996.

Other countries in the Western Pacific Region (e.g., Australia, New Zealand, and the Philippines), have already begun measles elimination initiatives or are considering them. Nationally, New Zealand has achieved 87% coverage with one dose of measles-containing vaccine, but in some segments of the population, coverage is substantially lower. A mass vaccination campaign was planned in July 1997 to prevent an anticipated epidemic in these populations, but onset of the epidemic began in April. The mass campaign was started in May and probably limited spread of measles.

China, which implemented a two-dose measles vaccination schedule in 1985, experienced substantial reductions in measles morbidity and mortality beginning in 1987. Fewer than 75,000 cases were reported in 1996, and only 108 deaths were reported in 1995 compared with more than 1 million cases and 4,200 deaths in 1981. In 1997, China issued a national plan for accelerated measles control. The national plan called

for the development of provincial plans of action but did not establish a formal national target date for measles elimination.

Eastern Mediterranean Region

In October 1996, participants in a Consultation on Measles Control/Elimination in the Eastern Mediterranean Region recommended that enhanced control measures be undertaken with the aim of eliminating measles from the region. However, participants also recognized that substantial differences existed among the countries of the region in vaccination strategies, vaccination coverage, sensitivity of surveillance, and occurrence of disease. Eight of the 23 countries in the region use a one-dose measles vaccination strategy; in the 15 that use a two-dose strategy, the age at which the second dose is administered and the vaccine of choice (measles vaccine or combination vaccines [MR or MMR]) vary. In 1996, region-wide coverage of children aged 2 years with at least one dose of measles-containing vaccine was ≥80% but varied considerably. In two countries, vaccination coverage among children aged 2 years was <50%.

A proposed plan and target date for elimination of measles from the region by 2010 was approved by the WHO Regional Committee in October 1997. The Gulf Council countries (i.e., Kuwait, Oman, Bahrain, Qatar, Saudi Arabia, and United Arab Emirates) are aiming for measles elimination by 2000.

During NIDs conducted during a 1994 cease-fire in Sudan's ongoing civil conflict, measles vaccine was administered to 61% of children aged <5 years. During a similar 1995 "Tranquility Days" cease-fire, vaccination for polio, measles, and other diseases and other public health interventions (i.e., Vitamin A distribution and Guinea worm eradication activities) were also conducted in war-affected areas. Coverage with measles vaccine in Sudan is now approximately 75%, and ten of 26 states have measles vaccination coverage >80%. Coverage in war-affected areas is much lower (<30%). As a result of special efforts to immunize war-displaced children, substantially fewer outbreaks of measles have occurred in refugee camps.

European Region

A strategic plan for elimination of measles from the WHO European Region by 2007 has been developed by the WHO European Advisory Group and will be presented to the WHO European Regional Committee for consideration during 1998. A questionnaire regarding measles control practices and strategies was sent to all 50 member states; 41 responded. In the 38 responding countries that use a two-dose measles vaccination strategy, the age for administration of the second dose ranges from 3 to 14 years. Twenty-one countries in the region report ≥90% coverage with at least one dose of measles, eight report coverage of 80%–89%, nine indicate 50%–79% coverage, and three countries report coverage <50%. Regionwide, coverage of children aged 12–24 months with at least one dose of measles-containing vaccine is 82%.

The regional strategy to eliminate measles includes: establishing political commitment to measles elimination, developing measles elimination plans based on local epidemiologic data, achieving and maintaining high vaccination coverage, and strengthening surveillance. On the basis of their progress in measles control, European countries have been classified into three groups. Group 1 comprises six

countries that are close to eliminating the disease. These countries are characterized by;

- national reporting of suspected cases;
- laboratory testing of a high proportion of sporadic cases (at least one case tested per 100,000 population per year) *and* fewer than 10% of suspected cases confirmed for the past 5 years; and
- ≥95% measles vaccination coverage for the past 5 years *or* low prevalence of susceptibility to measles demonstrated by findings of serologic surveys.

The four countries in Group 2 have achieved good control of measles but are considered potentially at risk for measles outbreaks. These countries are characterized by

- national reporting of suspected cases;
- laboratory resources for confirmation of cases;
- ≥90% measles vaccination coverage for the past 5 years; and
- stable incidence of reported measles for the past 5 years *or* an interepidemic period ≥5 years.

Countries in Group 3 (31 countries) have poor control of measles and are characterized by

- <90% (or unknown) measles vaccination coverage; or
- no national reporting of suspected cases; or
- an interepidemic period <5 years.

UNICEF Urban Measles Control Initiative

UNICEF, in collaboration with WHO, is supporting an initiative to reduce deaths among young children (i.e., those aged <5 years) through urban measles control. The initiative is intended to catalyze improvements in child health activities in underserved urban areas. In such areas, where a substantial percentage of children is susceptible to the disease, measles circulates easily, affects infants, and is often exported to surrounding rural areas. The UNICEF/WHO strategy is to develop local partnerships to improve routine immunization services in poor urban areas, plan and carry out measles campaigns in high-risk areas, develop community-based measles surveillance, and promote child health and development. The proposed target age group is children aged 9–59 months, although the age group may vary on the basis of local epidemiologic findings. In addition to measles vaccination, campaigns undertaken as part of the initiative will include vitamin A supplementation. Vaccine will be administered with autodestruct syringes, and safety boxes will be provided for disposal of used injection equipment. Development of measles surveillance to evaluate the impact of immunization activities will be an integral part of the initiative.

Conclusions: Progress Toward Measles Elimination

- In countries where they have been fully implemented, the strategies adopted to eliminate measles (i.e., catch-up, keep-up, and follow-up) in the Western Hemisphere have substantially reduced or eliminated measles. 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. 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.
- Maintenance of high routine vaccination coverage and community-based surveillance (i.e., 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.
- In some countries (particularly in the Americas and the United Kingdom), most measles cases are 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.
- 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.
- Combining measles vaccination campaigns with other public health interventions (i.e., 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.

MEASLES SURVEILLANCE

In a measles elimination program, surveillance is intended to detect measles virus circulation in a timely manner (rather than to detect every single case), allowing public health authorities to undertake rapid ascertainment and investigation of suspected cases, determine risk factors for the disease, and implement outbreak control measures.

In Latin America and the English-speaking Caribbean, measles surveillance has been integrated with polio surveillance. Twenty thousand reporting units, at least one in each district or *municipio* (equivalent to a township or county), have been established in these countries. Weekly reporting is the norm, both for the occurrence of cases and the absence of cases (i.e., negative reporting). Cases are classified as "suspected," "discarded," or "confirmed." A suspected case is any illness that a health-care worker suspects might be caused by measles infection. Surveillance norms call for all suspected cases to be investigated thoroughly and promptly. Thorough investigation includes collection of a single serum specimen at the time of the patient's first contact with the health-care system and collection of appropriate specimens for virus isolation from every detected chain of transmission. A suspected case may be confirmed by a positive immunoglobulin M (IgM) antibody test of the serum specimen or by epidemiologic linkage to a case confirmed by such a laboratory test. Specimens are tested first with a commercial indirect IgM assay. Specimens that yield indeterminate results are tested with an IgM-capture enzyme immunoassay (EIA) developed by CDC (*3*) and are classified as confirmed if this more specific assay yields a positive result. A suspected case is discarded if a complete investigation fails to identify an epidemiologic link to a laboratory- confirmed case and a negative result is obtained from the IgM antibody test of the blood specimen. Suspected cases that are not completely investigated are classified as "clinically confirmed" and are considered to represent a failure of the surveillance system. During 1996, in the countries of Latin America and the Caribbean, a total of 10,144 suspected measles cases was completely investigated; laboratory tests in 90 (0.9%) cases were positive for measles.

Six surveillance indicators are being used in the Americas as of September, 1997:

- percent of surveillance sites reporting weekly;
- percent of reporting sites that report at least one suspected measles case per year;
- percent of suspected cases investigated within 48 hours of report;
- percent of suspected cases with adequate blood samples or epidemiologic linkage to a laboratory-confirmed case;
- percent of outbreaks with known source of infection; and
- percent of blood specimens with results reported within 7 days of receipt in the diagnostic laboratory.

During 1995–1997, PAHO conducted evaluations of surveillance systems in Brazil, El Salvador, Mexico, Nicaragua, Panama, and Venezuela. The evaluations included interviews with health workers; search of patient records at hospitals, health centers, schools, day care centers, and private clinics; and analysis of the indicators listed previously. The reviews concluded that surveillance systems in three of the countries had the capacity to detect cases rapidly but that surveillance systems in the other three did not. On the basis of these evaluations, PAHO concluded that its surveillance indicators were useful for continually monitoring the quality of the regional and national surveillance systems. PAHO recommended that every member country conduct periodic evaluations to ensure that its surveillance system is capable of timely detection of measles virus circulation.

Susceptibility profiles (i.e., estimates of the proportion of the population susceptible to measles by age) can be useful to help guide measles elimination strategies. In countries where measles virus continues to circulate, susceptibility profiles can be developed based on history of vaccination—whether with one or two doses of measles-containing vaccine—or history of disease, age distribution, and vaccination status of recent cases. As incidence declines, serologic surveys and mathematical modeling can be used to estimate susceptibility profiles. These profiles can, in turn, be used in deciding the timing of and age range for vaccination campaigns. Repeated serologic surveys are most useful if the incidence of measles is low and the quality of vaccination coverage data is poor.

Role of the Laboratory in Measles Surveillance

Recent field experience has demonstrated the usefulness and reliability of IgM EIAs for confirmation of suspected measles cases. Commercially available IgM EIAs can be done quickly, are sensitive and specific, and require only one serum specimen. The CDC antibody-capture EIA is used as a confirmatory test after initial testing with one of the commercially available assays, which are usually simpler and faster to perform (3). In tests of persons naturally infected with measles virus, the CDC test was positive in 77% of specimens obtained within 72 hours of rash onset and 100% of specimens obtained 4–11 days after rash onset; for 90% of these patients, second specimens obtained 28 days after rash onset were also IgM-positive (*4*).

The measles virus is a negative-stranded RNA virus with 15,894 nucleotides and six genes. Virus isolation and genotyping can be used to monitor changes in the genotypic pattern over time if genotyping is done before and after major control and elimination efforts. These molecular epidemiologic studies can be used to demonstrate interruption of measles virus transmission when it occurs. To facilitate communication among laboratories, a standard system of nomenclature to categorize the genotypes should be developed. In the interim, eight arbitrarily numbered genotypes—all of them isolated in North America during the period 1988–1997—have been identified. Group 1 includes all vaccine viruses regardless of geographic origin, several recently isolated wild viruses, and all wild viruses isolated from Europe and the United States during the 1950s and 1960s. Measles viruses isolated in Japan are mostly from Groups 2 and 3; viruses isolated in Europe are predominantly Groups 4 and 5. Group 6 viruses predominate in Africa and Group 8 in China and Vietnam. Group 7 viruses have a broad geographic distribution. The resurgence of measles in

the United States during 1988–1992 was caused almost entirely by Group 2 viruses. The absence of Group 2 virus from United States since 1993, except in one case imported from the Philippines, indicates that measles transmission was interrupted in the United States in 1993.

Conclusions: Measles Surveillance

Epidemiologic Aspects

- The disease burden of measles must be better documented by strengthening measles surveillance systems, both in developing and developed countries.
- Measles surveillance is an integral part of all efforts to control and eliminate the disease. The functions and requirements of a surveillance system must evolve as measles control progresses toward elimination of the disease. In countries and regions where control of the disease is the goal, surveillance should indicate patterns of transmission and identify areas or subpopulations where intensified vaccination activities are needed. As control of the disease is achieved and outbreak prevention or interruption of transmission become the goals of the program, the surveillance system should develop the capacity to a) detect measles virus circulation promptly, b) investigate outbreaks thoroughly to ascertain risk factors for measles, and c) identify areas or subpopulations where program failures may have occurred. Careful analysis of surveillance data, including findings of outbreak investigations, is needed to make decisions about control measures and to adjust programmatic strategies.
- In developing a surveillance system, simplicity in case investigation procedures is desireable, but should not be achieved at the expense of core data elements. The need for detailed data about each case evolves in parallel with programmatic progress toward elimination.
- Training is important to help workers know when and what to report. A case may enter the surveillance system either because it meets a clinical case definition (e.g., generalized rash accompanied by high fever and cough, coryza, or conjunctivitis) or because a health-care professional suspects that an illness is a case of measles.
- As measles incidence decreases, the surveillance system should acquire the capacity to assess risk for measles outbreaks based on the prevalence of measles susceptibility as measured by serologic markers of immunity, surveys of vaccination coverage, or both. These data should allow health authorities to predict outbreaks and to take action to prevent them.
- Monitoring of vaccination coverage achieved through routine activities or intensive campaigns should be conducted at the lowest geopolitical level (e.g., district or county) to identify local areas (e.g., villages or neighborhoods) or population groups where children remain unvaccinated. In evaluating vaccination coverage, countries using two-dose strategies should try to identify children who have received two doses, one dose, or no doses. These data are helpful in developing

mechanisms to rectify coverage shortcomings. The reported number of doses administered at the second-dose opportunity may not equate with the number of persons who actually received two doses because a first dose of vaccine may be administered to some children who were not vaccinated at the first dose opportunity.

- Monitoring the prevalence of susceptibility in a population may be useful for planning supplementary vaccination campaigns. Case surveillance or sero-surveillance data can help define age groups to be vaccinated in a catch-up or follow-up campaign.
- As disease incidence decreases, mathematical modeling may be necessary to obtain an accurate picture of the population prevalence of measles susceptibility. Data required for such modeling can include vaccination coverage, age-specific disease incidence, or prevalence of serologic markers of immunity from population surveys.
- In contrast to polio surveillance, no single indicator of the sensitivity of a measles surveillance system exists. PAHO has started using the proportion of reporting sites that report at least one suspected measles case per year as a measure of sensitivity. The European Regional Office of WHO has set a minimum level for the laboratory investigation of suspected cases of one per 100,000 total population per year. Other evaluations of sensitivity might include the proportion of outbreaks for which the source is known. Further experience with each of these approaches should be evaluated, and strategies should be adapted accordingly.

Laboratory Aspects

- In early stages of measles control, the function of the laboratory is to confirm outbreaks of the disease. Subsequently, as disease incidence declines to very low levels, laboratory confirmation of individual measles cases assumes increasing importance. In countries that are attempting to eliminate measles, all isolated cases of measles and at least one case from each chain of transmission should be confirmed by laboratory tests. In a country or region that is attempting to eliminate the disease, the occurrence of clinically confirmed cases (i.e., cases that are not confirmed by laboratory tests or linked to laboratory-confirmed cases by field epidemiologic investigation) should be regarded as a failure of the surveillance system.
- A network of laboratories is a requirement for successful implementation of a global measles elimination strategy. Such a network could be established by expanding on the existing global poliovirus laboratory network. Specific functions for national, regional, and reference laboratories should be established.
  - National laboratories should be able to confirm the diagnosis of measles, support measles virus isolation, provide quality assurance, and support epidemiologic surveys.

- — Regional laboratories should function as reference laboratories for serologic diagnosis of measles and virus isolation. In addition, they should fulfill training and quality assurance functions and conduct research.
- — Global reference laboratories should be responsible for quality control, proficiency testing, technical advice, research, and maintaining a reference bank of measles virus strains.
- — The network also should have the capacity to perform laboratory diagnosis of rubella and perhaps other rash illnesses that can be confused with measles.

- Laboratory tools are available to diagnose measles accurately by using EIA-IgM assays. Laboratory tools also are available to characterize and track virus isolates.
  - — The CDC antibody-capture IgM assay has been thoroughly evaluated and is highly sensitive and specific. The CDC assay remains the reference test in the Americas.
  - — Several commercial IgM assays are easier to perform than the CDC assay but offer comparable sensitivity and specificity. A comprehensive evaluation of these other assays is being performed.
  - — A radioimmunoassay (RIA) developed in the United Kingdom for detection of measles IgM in oral fluids is highly sensitive and specific and may be useful in countries capable of using RIA technology.
  - — Efforts have been undertaken to adapt the CDC antibody-capture EIA for use with oral fluids. If successfully adapted, oral fluid specimens could be used to confirm measles cases in laboratories that are not equipped to handle radioisotopes. The test would require a single specimen obtained at the time of the patient's first contact with the health-care system.
- Virologic surveillance, including isolation and genotyping of virus strains circulating in a country or region, is an important tool for routine surveillance and for evaluating progress toward measles elimination. Therefore, systematic efforts should be undertaken promptly to collect specimens for viral genotyping and to establish a global strain bank.
  - — As part of this effort, case investigations that include collection of specimens for viral isolation should be undertaken in countries before they initiate elimination activities as a means of documenting patterns of virus circulation. These data can be used to assess progress toward regional and global elimination of the disease.
  - — WHO should convene representatives of the laboratories performing measles genome sequencing to develop guidelines for isolation and sequencing of measles virus, as well as a standard system of nomenclature for measles viruses.

VACCINE SAFETY

Adverse events that occur after vaccination can be caused by the vaccine, occur coincidentally (i.e., the events may be temporally but not causally related), or result from programmatic errors. Adverse events caused by the vaccine include local and systemic reactions, febrile convulsions, allergic reactions, and anaphylaxis. Adverse events caused by programmatic errors include those resulting from unsafe injection practices (e.g., abscesses at the injection site, toxic shock syndrome, septicemia, and transmission of bloodborne viral infections, including hepatitis B or C and human immunodeficiency virus [HIV]), and illness or injury caused by administration of vaccine to persons for whom it is contraindicated. Unsafe injection practices can affect the vaccine recipient, the person administering the vaccine (e.g., through needle stick injuries), or other members of the community (e.g., because of improper disposal of needles and syringes).

Immunization activities represent about 10% of the global total of injections administered each year. Approximately 800 million injections were administered in routine EPI activities in the developing world in 1996, and another 240 million injections were administered in emergency vaccination campaigns. If the world's nations all adopt measles elimination strategies, 1.6 billion children could receive a single additional injection in measles catch-up vaccination campaigns and approximately 150 million could receive follow-up injections each year. Most of these vaccinations are likely to be administered by syringe because currently available jet injectors are not recommended for use in mass vaccination campaigns. New jet injectors are under development and will be field tested beginning in 1998, but their cost and suitability for use in developing countries are unknown.

The problems of using disposable needles and syringes for vaccination, whether for routine vaccination or in mass catch-up campaigns, are appreciable. Equipment shortages during mass campaigns or failure to dispose of used equipment after the campaign can increase risks for reuse of disposable syringes. Autodestruct syringes, by contrast, pose no risk for reuse during or after the campaign. Whether autodestruct syringes or disposable syringes are used, collection and incineration of used syringes and needles should be part of all mass vaccination campaigns.

Experience in the United Kingdom illustrates the importance of surveillance in establishing the background incidence of adverse events and monitoring their occurrence during and after a catch-up vaccination campaign. During a 1-month period in 1994, MR vaccine was administered to 92% of the United Kingdom's 8.4 million children aged 5–16 years. The surveillance system received 1,231 reports of 2,783 adverse events; included were 709 serious reactions affecting 557 children. More than half the reported events (e.g., allergic reactions, syncope, or convulsions) occurred within 24 hours after vaccination. A total of 120 reports were received of immediate allergic reactions or anaphylaxis. Approximately half of these children were referred to hospitals but few were admitted overnight; all recovered fully. Adrenaline was administered to fewer than half the children reported to have experienced anaphylaxis, indicating that the reported events may not have been true anaphylactic reactions. Investigation revealed that 24 of 29 reports of "convulsions" were episodes of syncope. Rates of most adverse events, including arthritis and facial palsy, were lower than background levels.

Conclusions: Vaccine Safety

- Unless field personnel are well trained and supervised and provided with the correct equipment, improper administration of injectable vaccines during mass vaccination campaigns can cause bacterial infections (e.g., abscesses, toxic shock syndrome, or septicemia) and transmit bloodborne diseases (e.g., hepatitis B, hepatitis C, HIV, syphilis, and malaria).
- Proper disposal of needles and syringes is an important component of routine immunization programs and mass measles vaccination campaigns.
  - Autodestruct syringes are the equipment of choice for mass vaccination campaigns and the preferred type of disposable equipment for routine administration of vaccines.
  - Puncture-resistant containers ("safety boxes") are required for collecting and disposing of used disposable and autodestruct syringes, needles, and other injection materials to reduce the risk to health staff and the general public from contaminated needles and syringes.
  - Training health-care workers in safe injection practices should be part of the planning and implementation of mass vaccination campaigns. Supervisors and senior managers should stress safe injection practices during the vaccination campaign. Evaluation of vaccination campaigns should include measures of observance of safe injection practices and disposal of used equipment.
  - Donors should be encouraged to supply vaccines in a bundle consisting of vaccine, autodestruct syringes, safety boxes, and training.
  - The development of safe and cost-effective alternative technologies suitable for administration of vaccines in mass immunization campaigns (e.g., a new generation of jet injectors) should be encouraged.
- Surveillance for adverse events after vaccination is important both for routine immunization programs and for mass immunization campaigns. Planning for campaigns should include establishing a mechanism to investigate and respond to reports of adverse events associated with administration of vaccines. At a minimum, the surveillance mechanism should be able to detect deaths and severe adverse events. Community-based surveillance systems can be used to detect adverse events that occur after vaccination as well as cases of measles.
- The number or rate of adverse events reported during mass immunization campaigns—whether vaccine-induced, coincidental, or caused by programmatic errors—should approximate the number or rate expected after administration of a similar number of vaccinations in routine immunization programs. The rate of vaccine-induced events may be lower than expected because many of those vaccinated are already immune and therefore not at risk. After mass vaccination campaigns, temporal clustering of adverse events apparently caused by the vaccine can cause substantial public concern. Knowledge of background rates of specific types of adverse events (e.g., anaphylaxis, febrile seizures, abscess at the injection site) can be very important in addressing public concern.

RESEARCH

Presentations during the meeting addressed research in three areas relevant to measles eradication: a) opportunities for research concerning measles immunology, b) development of alternative routes for administration of measles vaccine, and c) optimal age for measles vaccination. Measles virus and measles vaccinology offer unique opportunities for research in several areas—molecular and basic research, epidemiologic research, clinical disease and diagnostics, new vaccines, and new routes of administration. Studies have begun to examine measles-induced immune suppression, the pathogenesis of measles, alternative formulations and means of administration of measles vaccines, correlates of vaccine-induced cellular and humoral immunity, and the role of adjuvants in measles vaccines. Studies of immunocompromised persons infected with measles are particularly important because of the increasing incidence and prevalence of HIV infection. Particularly relevant to control and elimination of measles is research concerning persistent carriage of measles virus by immunocompromised persons.

Findings of several studies indicate that aerosol administration of measles vaccine is effective, particularly if Edmonston-Zagreb vaccine is used. Administering measles vaccine by the aerosol route is rapid, might be less costly than single-use needles and syringes, is nontraumatic, avoids risks for transmission of HIV and hepatitis B, and does not require medically trained personnel. Aerosols are easy to administer to school-aged children but are more difficult to administer to younger children and infants. The apparatus for administration of aerosol vaccines has limitations; it is cumbersome, requires crushed ice, and is not useful for single dose administration. Questions remain about possible effects on vaccinators of repeated exposure to aerosolized measles virus and potential adverse effects of aerosol vaccines, particularly among persons infected with HIV.

Factors that affect the optimal age for administering the first dose of measles vaccine include the risk for measles among infants, vaccination coverage among young children and infants, the prevalence in the target population of possible alterations in immunity caused by acquired conditions (e.g., HIV infection), and vaccine effectiveness, which is relatively low among infants because of maternally derived antibody but increases as children grow older. Factors that affect the optimal age range for inclusion in catch-up or follow-up measles vaccination activities include cost, the prevalence of measles susceptibility among young adults, and ease of access to unvaccinated persons.

Conclusions: Research

- Research on measles and measles immunization in immunocompromised persons should be conducted to clarify the potential for persistent carriage of measles virus. Measles virus infection is an important model for immunosuppression in the human host. Research concerning the pathogenesis of measles and immune responses of immunocompromised and immunologically normal persons to wild measles virus and vaccine viruses should continue.
- Aerosol administration of measles vaccine to school-aged children may be useful for catch-up campaigns but is less likely to be useful for routine vaccination of

young children. Additional research is necessary to determine its feasibility in field operations. Further research on alternative routes of vaccine administration should be encouraged. However, because introduction of new vaccines requires extensive testing and regulatory review, and because the safety and efficacy of presently licensed vaccines are well established, the introduction of new vaccines is unlikely to affect the feasibility of measles elimination or eradication.

ECONOMIC IMPLICATIONS OF MEASLES ELIMINATION

An economic evaluation presented at the meeting compared several options for future measles for a hypothetical western European country immunization policy, including the baseline case of no change in vaccination policy. All other options saved costs compared with the baseline. Optimal choices depended upon assumptions concerning past success in measles vaccination. If 70% of children aged ≤2 years were assumed to have been vaccinated, the optimal strategy would be to increase vaccination coverage with the first dose to ≥95%, adopt a two-dose vaccination policy, and conduct mass vaccination campaigns among persons in age groups with susceptibility levels ≥5%. In contrast, if past coverage among children aged ≤2 years were assumed to exceed 90%, increasing vaccination coverage with one dose of measles vaccine, without the addition of a second dose, would save costs compared with no change. In either situation, improving coverage with the first dose should be undertaken before adopting a two-dose vaccination schedule.

Also presented at the meeting were findings of an economic assessment that contrasted various global measles prevention strategies—control, elimination, and eradication. For each country, preliminary estimates were made of measles disease burden, vaccine needs, required financial resources, relative importance of economic and epidemiologic assumptions, and opportunity costs of investing in measles control rather than other selected health interventions. For each country, an estimate of age-specific measles susceptibility based on reported vaccination coverage, vaccine efficacy, reported age-specific attack rates, and case-fatality ratios was constructed. Costs of vaccination included direct vaccine and program costs, administration costs, costs of adverse events, and costs to treat measles cases that are not prevented. A 3% discount rate was used to estimate future costs in 1997 United States dollars. Present costs for vaccines, programs, and treatment of measles cases were estimated at $480 million annually. Findings of the analysis indicate that 80% of measles control program costs and disease treatment costs are paid by high-income countries (as categorized by the World Bank). However, of every 100 persons added each year to the global population that is susceptible to measles, 74 reside in low-income countries. The World Bank categorizes the world's most populous nations, India and China, as low-income countries. Under the assumptions used in this preliminary analysis, eradication would be cost-effective. The additional costs for vaccine and vaccination programs required to achieve eradication were estimated to be $4.7 billion, of which only $0.7–$1.8 billion would be required for low income countries.

Conclusions: Economic Implications of Measles Elimination

- 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 (i.e., physical capital and surveillance and management systems) and "human capital" (i.e., training of primary health-care personnel, front-line supervisors, and development of management resources). 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.

NEXT STEPS

Several lessons have been learned from previous efforts to eradicate communicable diseases (*5*). To eradicate a disease, medical scientists must have a thorough understanding of its natural history. To achieve consensus concerning the appropriate approach to eradication and sustained political commitment of resources, proponents of eradication should consult widely before embarking on the effort. National and international surveillance should be implemented early in the disease eradication program, and surveillance information should be used to guide program strategy. Implementation of the eradication strategy should emphasize flexibility and adaptation to the social, political, and public health circumstances of each country. A specific target date for eradication should be set to focus global efforts and maintain commitment to the goal of eradication.

In addition to these general considerations, factors to be considered in implementing measles eradication include the high short-term costs of the endeavor, the risk of failure (i.e., the probability of failure and the potential consequences of failure), and the need to strengthen comprehensive health services to achieve eradication. Among the factors that favor measles eradication are

- the perceived importance of the disease in less developed countries;
- the availability of highly effective vaccines and vaccination strategies;
- the likely favorable benefit:cost ratio;

- rapid communications developed over the last two decades; and
- the capabilities and know-how that are the legacy of smallpox and polio eradication efforts.

Factors that do not favor eradication include

- the high infectiousness of measles;
- increasing worldwide population density and urbanization (particularly in developing countries);
- increasing international travel;
- logistics questions, including the use of needles and syringes; and
- the potential competition for resources with other ongoing eradication efforts (i.e., efforts to eradicate polio and Guinea worm).

In discussions of next steps, speakers urged meeting participants to

- capitalize on lessons learned in previous global disease eradication campaigns, particularly the successful campaign to eradicate smallpox and lessons currently being learned in polio eradication activities;
- use surveillance information from ongoing measles control and elimination efforts to refine national and regional disease control strategies;
- discuss measles elimination at future international meetings on polio eradication;
- continue to increase routine measles vaccination coverage;
- use NIDs for measles as well as polio in countries where such efforts are feasible; and
- accelerate efforts to control measles virus in urban populations.

The next steps for measles control and elimination activities 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? Meeting participants 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.

Meeting participants pointed out that the more rapidly measles elimination activities proceed at the national and regional levels, the more easily measles eradication will be accomplished. Conversely, the more slowly elimination activities proceed, the more difficult eradication will be. Once measles transmission is interrupted in a

population, risks for virus importation and reestablishment of transmission increase over time. Conducting repeated follow-up vaccination campaigns is operationally difficult and expensive. Because routine vaccination and follow-up campaigns rarely succeed in vaccinating all susceptible persons in a population, and because the vaccine is not 100% effective, the prevalence of measles susceptibility in the population tends to increase over time. Thus, the more protracted the global measles eradication campaign, the greater the risk for reestablishment of measles in countries where transmission of the virus has been interrupted.

Participants also considered funding of measles eradication. Projects that attract donor support are successful (or have a high probability of success), are both politically and socially popular, 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, nongovernmental 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. Meeting participants considered consistency in messages about each aspect of measles eradication essential to the success of the advocacy strategy.

Conclusions: Next Steps

- Substantial progress has been made in controlling measles. Measles transmission has been interrupted in several countries, reinforcing the view that measles eradication is technically feasible using existing vaccines and intervention strategies.
- Three of the six WHO regions have established or are considering target dates for elimination of measles, indicating that the goal of eradication is likely to be adopted in the next 3–5 years.
- Although measles elimination has already begun in many areas, global eradication poses several additional challenges. Elimination activities must be integrated with development of the primary health-care system because that system will be crucial for maintenance of progress. Because they have few primary health-care resources, high measles incidence, and a substantial burden of infection with HIV, the countries of Africa are expected to present the greatest challenges to measles elimination. The most effective measles control strategies for these countries, which also contribute to strengthening their health-care systems, should be undertaken early in the process of eradication; the goal should be to demonstrate that measles transmission can be interrupted despite the substantial barriers to success that exist in Africa.

- Although perhaps not essential for interruption of measles virus transmission, effective routine immunization services facilitate achieving and maintaining measles elimination in a country or region.
- A renewed commitment to the goal of polio eradication is imperative, because much remains to be done to eradicate polio, particularly in the Indian subcontinent and Africa. Success in polio eradication will facilitate progress in measles elimination. Properly implemented, polio eradication and measles elimination activities can be mutually reinforcing and represent a natural joining of efforts. However, conjoining the efforts must not divert attention or resources from progress toward polio eradication. From a global perspective, measles eradication appropriately follows and builds on polio eradication activities. Nonetheless, planning for regional control, elimination, and ultimate eradication of measles should commence before polio eradication has been completed.
- Individual nations can and should accelerate measles control and, if high population immunity is achieved, can interrupt measles virus transmission. However, elimination of measles requires coordinated regional (i.e., multinational) efforts, and eradication requires coordinated global efforts. Sustaining interruption of measles transmission is difficult and expensive. Consequently, as the area from which measles has been eliminated increases, setting a goal of eradication and achieving it in a short period will become increasingly important.
- Estimates of additional resource commitments needed to achieve measles eradication should be developed using the best available information. These estimates should be used to develop partnerships and marshal support for eradication of the disease.
- Achieving measles eradication will require close and effective partnerships among official agencies, private and voluntary sectors, and external donors.

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