In the Literature

Halfway to 2015—But Less than Halfway to the Millennium Targets


We are now approximately halfway to the 2015 target date set by the United Nations in 2000 in the Millennium Declaration and the Millennium Development Goals. The United Nations has released a report assessing progress toward these goals. I will provide brief summaries of the assessments relevant to some specific infectious diseases.

Target: Reduce by two-thirds, between 1990 and 2015, the under-5 mortality rate. Measles is among the leading causes of childhood death due to vaccine-preventable diseases. As a consequence of improved provision of vaccination, the number of deaths due to measles decreased worldwide by >60% between 2000 and 2005, with Africa leading the way with a 75% decrease. Furthermore, measles vaccination campaigns have provided a structure for the provision of other measures, such as bed netting, deworming medicine, and vitamin A supplementation.

Target: To have halted by 2015 and to begin to reverse the spread of HIV/AIDS. The total number of AIDS-related deaths increased to 2.9 million in 2006, and in 2005, >15 million children had lost at least 1 parent to AIDS. The total number of people with HIV infection increased from 39.2 million in 2001 to 39.5 million in 2006, with the majority of cases occurring in sub-Saharan Africa. There were 4.3 million new infections in 2006, with the highest rates of increase of new infections in East Asia and the Commonwealth of Independent States. An estimated 2 million people in developing regions were receiving antiretroviral therapy as of December 2006—less than one-third of the 7.1 million people for whom it is currently indicated. Only approximately one-fourth of HIV-infected candidates for treatment in sub-Saharan Africa were receiving antiretroviral therapy. If current trends continue, the number of people in need of therapy will increase faster than the speed at which treatment services can be expanded. Only 11% of HIV-infected pregnant women in low- and middle-income countries were receiving services to prevent mother-to-infant transmission in 2005.

Target: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases. Although a number of African countries have made progress in the provision of insecticide-impregnated bed nets, this progress has been slow and uneven. Only 5% of children aged <5 years in sub-Saharan Africa sleep under such nets. Children in urban areas were 2.5 times more likely to be sleeping under impregnated bed nets than those in rural areas. Chloroquine continues to be commonly used to treat malaria in sub-Saharan Africa, despite plasmodial resistance to this drug.

The incidence of new cases of tuberculosis has begun to decrease in most regions. However, because of population growth, the absolute number of new cases was still slowly increasing. Of the estimated 8.8 million cases in 2005, 7.3 million occurred in sub-Saharan Africa and Asia. There were 1.6 million deaths due to tuberculosis in 2005, with approximately one-eighth occurring in individuals who were coinfected with HIV.

Target: Halve, by 2015, the proportion of the population without sustainable access to safe drinking water and basic sanitation. Poor hygiene, open defecation, and lack of safe drinking water together contribute to ~88% of deaths due to diarrheal illness in children aged <5 years. Unfortunately, only eastern, southeastern, and western Asia, together with northern Africa, Latin America, and the Caribbean, are on track to achieve the Millennium target. In fact, the number of people without access to sanitation increased by >100 million by the end of 2004.

This report indicates that progress in achieving the Millennium goals has been, at best, uneven. The most striking improvement in the area of infectious diseases has been the reduction in childhood mortality due to measles. No other area among the infectious-related disease goals can be considered to represent great progress, and some areas have gone backward, as in the cases of the availability of safe drinking water and sanitation in sub-Saharan Africa. An immediate and meaningful recommitment to the stated goals is necessary to have even a glimmer of hope that they will be achieved by 2015.

Breast-Feeding and HIV Transmission


It is estimated that as many as 360,000 infants were infected with HIV-1 worldwide as the result of breast-feeding in 2005. Seemingly paradoxically, results of secondary analyses of 2 studies of perinatal vitamin A supplementation in Africa included the finding that postnatal mother-to-infant HIV transmission, as well as overall mortality, were each lower when the infants were fed exclusively by breast-feeding than if they experienced partial breast-feeding or none at all. Coovadia and colleagues performed a prospective, observational study in South Africa to further evaluate the role of exclusive breastfeeding during the first 6 months of life.

The enrolled women were all provided with a single dose of nevirapine and received counseling during pregnancy. The
mothers subsequently received intensive infant feeding support. Exclusive breast-feeding was initiated at birth by 83% of 1372 infants born to HIV-infected mothers and continued for a median of 159 days. Two-thirds exclusively breast-fed for at least 3 months. Although 14.1% of the exclusively breast-fed infants were HIV infected by 6 weeks (presumably as the result of perinatal transmission), this proportion had increased to only 19.5% at 6 months. The risk of transmission was significantly associated with a birthweight <2500 g and a maternal CD4 cell count <200 cells/μL. The Kaplan-Meier estimated risk of postnatal transmission by 20–26 weeks of age among exclusively breast-fed infants who were HIV uninfected at 6 weeks of age was 4.04%, an incidence significantly lower than that for the other infants. Finally, exclusive breast-feeding was associated with a significantly lower cumulative mortality at 3 months of age (6.1% vs. 15.1%).

The competing biological tensions in the debate over breast-feeding when the mother is HIV infected arise from the knowledge that breast-feeding may transmit HIV infection, whereas a lack of breast-feeding is associated with an increased risk of other infections, particularly those that cause potentially fatal diarrheal illness. This study by Coovadia and colleagues appears to settle the issue of breast-feeding and HIV transmission. The results of this study are concordant with the current World Health Organization and UNICEF recommendations for sustaining exclusive breast-feeding for 6 months [1].

- Initiation of breast-feeding within the first hour of life
- Exclusive breast-feeding (i.e., the infant only receives breast milk, without any additional food or drink, including water)
- Breast-feeding on demand (i.e., as often as the child wants, day and night)
- No use of bottles, teats, or pacifiers

Predictable but Unintended Consequences: Dams and Malaria


Dam building has important benefits in underdeveloped countries, including energy production, flood control, provision of drinking water, improved river navigation, and provision of water for agricultural irrigation. On the other hand, dams may also increase the risk of malaria. Lautze and colleagues addressed the latter concern by examining the relationship of the distance of residence from the margin of the Koka reservoir in the Rift Valley of Ethiopia in 1994–2002.

The Koka dam was completed in 1961, making it the oldest dam in Ethiopia. Most people in the surrounding area live in mud huts, and few use bednetting. Malaria control was not considered in the management of the dam and was instead left to the local disease control authorities. In general, malaria control in Ethiopia involves indoor residual spraying with DDT or malathion in selected villages and as indicated.

Malaria diagnoses were obtained from malaria-control centers in towns near the reservoir. The investigators were unable to obtain information on possible cases in which self-treatment was administered. Individuals who lived closest to the reservoir had the highest incidence of malaria. Those living within 3 km had 1.47 times (95% CI, 1.41–1.52 times) the incidence of malaria of those living 3–6 km away and 2.31 times (95% CI, 2.24–2.39 times) the incidence of those living 6–9 km away. Transmission rates did not increase during the dry season. Logistic regression analysis found that the presence of the reservoir and interannual climate variation together accounted for >50% the observed variability in malaria case rates.

The reason for the increased risk of malaria in proximity to the reservoir cannot be stated with certainty, but the investigators list several possibilities related to vector enhancement. Puddles arise at the margins of the reservoir; in addition, the increase in adjacent groundwater levels could increase the number of nearby rainwater puddles. Furthermore, seepage under the dam has created a swamp area. These conditions are favorable to the regionally abundant Anopheles arabiensis, whose larvae thrive in vegetation-free puddles of turbid water. Given the apparent failure of indoor residual spraying, malaria control in this region is likely to necessitate additional measures, including control of these sources.

A number of previous studies provided evidence of an increased risk of malaria transmission as a consequence of damming rivers [1]. Dams continued to be built at a remarkable rate. The completion of the Three Gorges dam in China will permanently change the environment in areas home to many millions of people. Such projects must take into account the effects of the dramatic ecological changes on the health of humans, and those in areas where malaria is endemic must build extensive programs for the control of malaria transmission into the ongoing management of the dam [2].

References


Human Papillomavirus (HPV) and Cervical Cancer in Lesser Resourced Countries


Sixty paraffin-embedded tissues samples obtained by biopsy from patients with cervical cancer in Pakistan were examined for the presence of HPV DNA. HPV L1 gene was amplified by PCR with consensus primers and with primers specific for subtypes 16 and 18. HPV DNA could not be amplified from 1 sample, and the subtype could not be determined in 2 samples. Of the remaining 59 samples, HPV-16 DNA was amplified from 56 specimens, and 1 specimen yielded HPV-18 DNA. Almost 500,000 new cases of cervical
cancer are diagnosed each year throughout the world, more than replacing the 274,000 persons who die of cervical cancer during the same period. Thus, the introduction of Gardasil (Merck), a quadrivalent vaccine that includes the L1 capsid protein of the 2 most prevalent oncogenic HPV subtypes (16 and 18), has been rapidly accepted in the United States. Cervarix (GlaxoSmithKline), a bivalent vaccine that also contains the L1 protein of these subtypes, has been recommended for approval in Europe. These vaccines effectively prevent infection due to HPV-16 and HPV-18 and the high-grade cervical intraepithelial neoplasia that frequently results from infection.

Most deaths due to cervical cancer do not, however, occur in North America or Europe; >80% occur in lesser-resourced countries [1]. Cervical cancer is, in fact, a leading cause of years of life lost to cancer in those countries. The lesser risk, at least in the case of North America, is due to widespread screening for and treatment of cervical dysplasia, a strategy not available to the general populations of countries with limited resources. The incidence is likely to decrease further with the widespread acceptance of HPV vaccines, an approach that is also not currently accessible in the developing world.

The Strategic Advisory Group of Experts, which reports to the Director General of the World Health Organization, met in April 2007 to assess the potential benefit of HPV vaccines in lesser-resourced countries, as well as obstacles to their introduction [2]. The potential obstacles are biological, monetary, political, and social. Although HPV-16 and HPV-18 together account for up to 77% of cases of cervical cancer in developed countries, they account for a lower proportion of cases in lesser-resourced countries. The duration of protection remains undetermined, making cost-effectiveness analysis difficult, although mathematical modeling suggests it could be lifelong [3]. A major obstacle to introduction of HPV immunization is, of course, the high cost of the vaccine, which is in excess of $300 for all 3 doses in the United States. It has been estimated that, in contrast, the vaccine may need to be available at a cost per dose of as little as $1–$2 to make its use cost-effective and feasible in countries with annual per capita gross domestic products of <$1000 [1]. In an important first step, Merck announced on 1 October at the Clinton Global Initiative that it planned to donate at least 3 million doses of Gardasil for use in developing countries. Even if the cost problem were solved, there must be a supportive health care infrastructure with the ability to implement and maintain a vaccination program for the target population.

The Programme for Appropriate Technology has launched a 9-month pilot HPV vaccination study in 5 Ugandan districts aimed at girls aged 10–12 years through the school system [4]. One potential problem of using the schools, however, is the limited school attendance for girls in this age group; another is resistance from conservative religious groups. This pilot study may provide clues to the most promising ways of implementing national vaccination programs in countries with similar restraints.

References

Hepatitis B Virus (HBV) Control in China


More than a quarter million people die as a result of HBV-related liver disease each year in China, accounting for almost one-half of the worldwide mortality associated with this virus. Chronic HBV infection affects 9.8% of China’s population of ~1.3 billion. Most infections in China occur during infancy and early childhood, making early vaccination (beginning at birth) critical to control of the disease. HBV vaccine is administered within 24 h after birth and then again at the ages of 1 and 6 months.

Infant vaccination in China was limited because of high vaccine prices and fees charged to parents until 2002, when HBV vaccination was added to the national immunization program. In that same year, the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) began participation in a project with the Ministry of Health to make HBV vaccine available in some of the poorest areas of China. A national goal to reduce chronic HBV infection in children <5 years of age to <1% by 2010 was also established.

The resultant improvement in vaccine delivery was assessed by examination of national surveys conducted by the Ministry of Health in 1999 and 2004. The proportion receiving the “birth dose” of vaccine increased from 29.1% in children born in 1997 to 75.8% in those born in 2003, and the proportion receiving all 3 vaccine doses increased from 70.7% to 89.8%, respectively. The project involving the Ministry of Health and GAVI administered 3 doses of vaccine to ~1.5 million children in their target counties, resulting in the prevention of an estimated 1.47 million chronic HBV infections during 2003–2006. Nationally, ~42 million children were vaccinated during those years. In the poorer western provinces, vaccination rates also improved, although they remained significantly lower than the rates in other areas. The largest national deficit identified involved children born at home, who were less than one-half as likely to be vaccinated than those born in the hospital. In addition, vaccine coverage in children born in township hospitals was only two-thirds that of infants born in higher-level (i.e., county, provincial, or national) hospitals.

The increased vaccine coverage has been significant, but additional work is required to achieve the goal of reducing the incidence of HBV infection in children...
aged <5 years to <1%. A continued focus on the dose given at birth will be a key element in the attempt to achieve this goal, as it has been since 2002. The approaches used in this regard have included increasing the proportion of children born in the hospital and improving vaccine availability at both hospitals and township health facilities. The enhancement of effective collaborations between relevant agencies and facilities, increasing awareness in health care providers and parents, and provision of subsidies to village doctors will continue.

The Chinese accomplishments must be contrasted with the worldwide situation. The rate of global coverage of infants with 3 doses of vaccine, although having significantly improved over the previous 4 years, remained at only 55% in 2005, making the Chinese success to date all the more remarkable. Coverage rates ranged from 27% in Southeast Asia to 87% in the Western Pacific. Lessons learned in China will be helpful in many laggard regions of the world.