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Malaria vaccines: from laboratory to field

Introduction

The Global Malaria Control Strategy, discussed by WHO at inter-regional meetings (1991, 1992) and consolidated at the Ministerial Conference on Malaria held in Amsterdam in October 1992, has led to a commitment by the Governments to give priority to activities aimed at reducing morbidity and preventing mortality in populations at risk.[1] This strategy essentially translates into efforts to expand the coverage of malaria diagnosis and treatment by strengthening and providing training for the health service network, as well as for the referral system that handles severe cases and those resistant to the usual treatment. Knowledge of the characteristics and distribution of vectors, as well as of the environmental conditions that favor transmission, provides the basis for identifying and predicting areas of potential risk. Once again it has been noted that malaria control depends not only on the organization and management of programs at the institutional level, but, above all, on technological development aimed at finding new and more effective intervention strategies. In communicable disease control, vaccines are a cost-effective strategy. The development of a malaria vaccine can become one of the alternatives for supporting future malaria control efforts.

Malaria Immunity

Biological, clinical, and epidemiological studies of host-parasite interaction indicate that it is possible to develop concomitant immunity to malaria infection. In endemic high-transmission areas, such as certain regions in Africa where malaria is of perennial transmission, the population exposed to repeated bouts of infection progressively develops a natural immunity to the infection. Older children and adults have lower prevalence and levels of parasitemia and those with infection often either have very mild clinical symptoms or else are completely asymptomatic. The groups at greatest risk of developing severe malaria and, ultimately, dying are children under 5 who have not yet become immune, and pregnant women. In seasonally endemic, unstable, or low-transmission areas, individuals fail to acquire the same level of natural immunity or maintain a protective level of immunity due to the lack of continuous antigenic stimulation.[2]

During its life cycle, *Plasmodium* changes form, presenting its host with a broad antigenic repertory. In experimental models it has been possible to induce protection against infection and transmission through immunization with each of the different stages of the cycle. Immune response to the various biological stages of *Plasmodium* has also been seen with natural infection in humans.[3] Theoretically, a vaccine could act on any stage of the infective, disease or pathological process of malaria. However, the complex structure and morphological and antigenic variability of the parasite constitute the principal obstacles to the development of a protective vaccine.

The interest in learning about the mechanisms and antigens associated with natural immunity is justified in vaccine development because of the possibility that exposure to multiple infections in endemic areas could strengthen the immunity produced by the vaccine. The classical approach in immunization has been to increase the host's immunity to the parasite in order to control parasite density or eliminate signs and symptoms of the infection. Malaria vaccines could prevent or reduce infection, modify the severity of the disease or its course, and prevent or reduce transmission back to mosquitoes. Most recently, there have been studies aimed at the development of vaccines which reduce morbidity from a disease by suppressing the host's

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immunopathological response.[4] This type of vaccine would neutralize the parasite antigens that induce the excess production of cytokines--such as TNF and others, --which are related to the clinical severity of the disease.[5]

The strategy utilized in the quest for potential vaccines has been to identify and classify immunodominant antigens of *Plasmodium* sporozoites, merozoites, or sexual stages at the molecular level. Protein structures and their role in immune response in parasite-host interaction are being analyzed. The emphasis has been on vaccines for *Plasmodium falciparum*, because of the morbidity and mortality associated with that infection. Currently, two procedures are being used to obtain immunizing subunits: genetic engineering based on recombinant DNA technology using microbes as hosts' vectors; and chemical peptide synthesis. However, the lack of operational laboratory tests and the questionable usefulness of animal models for the understanding of the immunological basis for protecting humans against malaria are obstacles to the rapid development and evaluation of these immunizing agents.

Types of Malaria Vaccines

· **Pre-erythrocytic (sporozoite) vaccines.** The objective of this type of vaccine is to block intrahepatic infection, thus intercepting the parasite before hepatic infection is established. This kind of vaccine would be suitable for populations in endemic areas, especially groups of non-immune immigrants who would be unable to tolerate any level of infection. At the population level, these vaccines would reduce the incidence of infection, morbidity, and mortality from malaria. The first attempts to immunize individuals against malaria demonstrated that short-term immunity can be induced through intravenous inoculations of sporozoites attenuated by irradiation.[6] Repeated exposure to the bites of irradiated mosquitoes infected with *P. falciparum* also produced protection against artificial inoculations by infected, non-irradiated mosquitoes.[7]

The circumsporozoite (CS) protein that coats the surface of the sporozoite, which is common to several species of *Plasmodium*, has been identified as a strong stimulant of immune response. Advances in molecular biology have made it possible to determine and clone the sequence of amino acids in an immunodominant epitope of that protein (NANP in *P. falciparum*). Synthesis of the repeating peptide sequence has led to preparation of a synthetic vaccine, while genetic manipulation in *Escherichia coli* has produced a recombinant DNA vaccine. Although natural levels of antibodies to sporozoites do not confer protection against the infection, vaccines that stimulate a specific immune response could succeed in doing so.[8] However, the levels of protection and duration of immunity obtained in clinical trials with the synthetic vaccine $(NANP)_3$ adsorbed in tetanus toxoid and combined with aluminum hydroxide as an adjuvant,[9] as well as trials with recombinant DNA vaccine, have been discouraging.[10] It has been observed that the recombinant DNA vaccine is more immunogenic in individuals with prior exposure to the infection and natural antibody response to the sporozoites.[11]

Research in the field of pre-erythrocytic vaccines is directed to finding other functional antigens of the intrahepatic stage and protective epitopes related to cell-mediated immunity. We still lack a clear enough picture of the mechanisms involved in humoral and cellular immune response to sporozoites to predict the possible mechanisms of action for a vaccine against this stage.

· **Asexual blood-stage (merozoite) vaccines.** These vaccines are designed to prevent and control the infection of red blood cells which is the responsible for the phase of clinical and pathological manifestations of the disease, including death. An effective vaccine should produce clinical protection against serious forms and, as a result, reduce mortality. Its action on transmission would depend on how it affects the infectiveness of vaccinated individuals. Theoretically, there would be little or no change in the incidence of infection at the population level.

It has been demonstrated that it is possible to immunize animals with whole merozoites. These stages of the parasite are very complex antigenically, and a large number of antigens have already been classified, cloned, and evaluated as possible vaccines. Monoclonal antibodies against the glycoprotein (MSA1) detectable as the parasite matures from merozoite to schizont induce protective immunity in animals and inhibit *in vitro* growth of *P. falciparum*.[3]

An erythrocyte surface antigen (Pf155/RESA) of the *P. falciparum* parasite was found to inhibit *in vitro* growth and confer partial protection in *Aotus* monkeys [12]. In a longitudinal study carried out in the Gambia, the immunological profile of children who developed clinical malaria was compared with that of children who had asymptomatic parasitemia. It was concluded that antibodies to Pf155/RESA appeared to contribute to clinical immunity to *P. falciparum* malaria, although no association was found between tests of cellular immunity (proliferation and production of interferon) and presence of T-cell receptors for the antigen.[13] Tests in *Aotus trivirgatus* have been used to evaluate different hybrid proteins and molecules resulting from peptide synthesis. Based on these findings a polymeric multistage molecule composed of peptide sequences 55kD, 83kD, and 35kD of the merozoite, combined with the repeating NANP sequence of the CS protein of the sporozoite (SPf66), has been evaluated with promising results.[14]

· **Gametocyte transmission-blocking vaccines.** There are also vaccines that target the parasite stages

that transmit the infection from man to mosquito. These vaccines do not protect the immunized individual, but indirectly confer protection on the population by keeping the infection from developing in the mosquito after it has bitten an infected individual. Their public health role is to reduce malaria transmission in endemic areas. The effectiveness of this type of vaccine should be determined indirectly through functional tests that evaluate the reduction in the infectiveness for mosquitoes that have ingested parasites and blood from vaccinated individuals.

It has been demonstrated that, during infection, individuals produce antibodies against the sexual stages of the parasite that can block the subsequent infection of mosquitoes. Various surface proteins of the gametes, zygotes or ookinetes of *P. falciparum* can produce immunity that blocks transmission. Gamete 45kD antigen has produced transmission-blocking immunity in experimental models. Immunity to transmission in mice was demonstrated through the use of a recombinant DNA vaccine of ookinete Pfs25 antigen.[3]

Clinical and Epidemiological Evaluation of Vaccines

The principal objective in evaluating a vaccine is to determine its potential usefulness in controlling the disease in question. Evaluation of the degree of protection conferred on vaccinated individuals should precede any assessment of the vaccine's impact on transmission. Before any vaccine can be approved by health regulatory authorities and implemented as a public health measure, increasingly complex clinical and epidemiological trials must be conducted that use appropriate methodologies to verify its safety and effectiveness. The World Health Organization has prepared specific guidelines for evaluating all types of malaria vaccine.[15-17] These guidelines include recommendations for field trials that address questions of design, selection of study populations, execution of the trials, and data analysis. These trials must adhere to the ethical principles outlined in the Helsinki Declaration (1984) with regard to safety, protection, and benefits for individuals. The clinical evaluation of any vaccine is expected to include the following phases:

· **Phase I.** The first phase consists of clinical trials of toxicity and immunogenicity that are carried out after the initial stages of experimentation on animal models (phase 0) have been completed. The phase I trials are carried out on a small number of non-immune adult male volunteers from outside the endemic area, and their objective is to determine the optimal dosage and immunization schedule in order to obtain an appropriate balance between localized and systemic side effects and immune response. These studies may include a comparison group of individuals injected with the vaccine eluent or adjuvant or with a placebo.

· **Phase II.** Once evidence has been obtained of the vaccine's immunogenicity and safety, then its protective effect is evaluated through artificial infections or challenges (phase IIa). The effectiveness of the vaccine in protecting vaccinated individuals against the infection or disease is compared with the responses of an unvaccinated control group. These studies are carried out in non-immune individuals who are hospitalized and kept under strict medical control at specialized centers. Phase IIb evaluates the protective effect of the vaccine under conditions of natural infection in endemic areas in a selected group of individuals.

· **Phase III.** The fundamental objective of this phase is to evaluate the protective effect of the vaccine under controlled conditions in a population targeted for future vaccination. The trials are carried out in endemic areas with populations exposed to natural transmission. The most appropriate methodology for these cases is double-blind placebo-controlled clinical trials. The trials should include hundreds or thousands of volunteers (depending on malaria incidence in the area and the length of the study) who are randomly assigned to receive the vaccine or a placebo. The aspects to be compared (end points of comparison) between the study groups are defined ahead of time; for example: incidence of parasitemia, incidence of clinical disease, number of malarious episodes per group, time elapsed before the first episode, etc. In addition, there is an evaluation of the more unusual side effects that were not identified in the phase I and II trials with their smaller number of volunteers.

During this phase it is considered necessary to design "extended phase III" trials with a larger number of participants in order to evaluate other measures of the vaccine's effectiveness that could not be evaluated in the previous trials. These field trials in an open population can be designed to assess the duration of the protection provided by the vaccine, the vaccine's impact on mortality, the relationship between immune response and protection, the vaccine's protective efficacy under field conditions in different population groups and different epidemiological situations, mathematical models to predict impact on the population and on transmission, operational aspects of alternative surveillance strategies, rate of sporozoites in the mosquitoes (for sexual-stage vaccines), etc.

· **Phase IV.** This phase involves evaluations of the vaccine's epidemiological impact after its registration and routine introduction into control programs for the exposed population. Only during this phase is it possible to evaluate the real effect of the intervention in controlling the disease. Towards this end, case-control studies are conducted which compare the proportion of vaccinated individuals among malaria cases diagnosed in the service with the proportion of vaccinated individuals in a group of healthy controls selected from the same population, based on specific criteria. If the vaccination protects against the disease, the proportion of vaccinated

individuals among the diagnosed cases should be lower than among the controls. In addition, when the vaccine is progressively introduced into endemic communities, it is possible to evaluate its impact on the incidence of the disease by comparing vaccinated and unvaccinated populations,[18] or by conducting "before-and-after" studies of epidemiological trends.

It is important to point out that the value of any clinical or epidemiological trial depends fundamentally on the quality of the protocol, as well as on the rigorous implementation of the actual research project.[19] Studies which fail to include solid planning and/or which are weak in terms of baseline epidemiological data will find it difficult to come up with any conclusive findings. Research funding agencies usually appoint independent monitors to follow all phases of the clinical trials in order to ensure adherence to the agreed-upon protocol. These monitors have the job of keeping track of the codes of the products used (both vaccines and placebos), and of deciding when a study should be interrupted for established reasons of safety or effectiveness.

The validity of research to evaluate a vaccine, and the acceptance of research findings by health regulatory authorities, is influenced by the scientific quality and independent observations of the trials. The products to be tested, protocols for the clinical trials, ethical standards, and quality control of information must adhere to the current minimum guidelines established by WHO i.e., WHO good manufacturing practices (GMP)[20] and good clinical practices (GCP),[21] as well as any local requirements and ethical standards.

Measures of Protective Efficacy

The *protective efficacy (PE)* of a vaccine is measured by comparing attack rates in the vaccinated versus the placebo group, as expressed by the formula $PE = 100\,x\,(Iuv\text{-}Iv)/Iuv\%$, where *Iuv* = incidence of the disease in unvaccinated individuals and *Iv* = incidence of the disease in vaccinated individuals. The value obtained is the proportion of the disease's incidence that is prevented by the intervention (protective efficacy). This measurement is aimed at quantifying the extent to which the intervention reduces the incidence of the disease, and thus shows the intervention's potential impact on public health.[19] Protective efficacy can also be estimated as $PE = 100\,x\,(1\text{-}RR)$, where $RR = (Iv/Iuv)$, or the relative risk of the disease occurring in vaccinated as opposed to unvaccinated individuals. Of interest to public health is the *attributable proportion*, defined as the proportion of cases of the disease in the *total population* that can be prevented with the intervention. Obviously, this proportion will depend on vaccination coverage in the population, the vaccine's protective efficacy, and the incidence of the disease. This proportion is expressed as $[P(1\text{-}RR)*100]$, where *P* equals coverage by the vaccine in the exposed population.

In evaluating the effect of a malaria vaccine, different *end points* of comparison can be used to describe its impact. End points of comparison can include incidence of parasitemia (symptomatic or asymptomatic), febrile clinical episodes, severe cases of malaria, levels of parasitemia, time elapsed before the first clinical episode, and deaths, within varying periods of time after vaccination, and within groups other than the study population. A distinction is made between the proportion of protected individuals and the proportion of malarious episodes prevented. In addition, statistical procedures should be used in these comparisons (person-time incidence or survival rate) that take into account the loss of participants to follow-up, as commonly occurs in prospective population-based studies. Theoretical mathematical models have been proposed to quantify the direct and indirect effects of malaria vaccines.[22]

Field Trials with the Colombian SPf66 Vaccine

The SPf66 vaccine, designed by Dr. Manuel E. Patarroyo of the Immunology Institute, San Juan de Dios Hospital, Bogotá, Colombia, consists of a chemically synthesized polymeric protein hybrid made up of three different epitopes, 35.1, 55.1, 83.1 measured in kD, of *P. falciparum* merozoite proteins, intercalated with the repeating sequence *Asn-Ala-Asn-Pro* (NANP) from the CS protein of the sporozoite. Of the various proteins that had been identified and purified from strains of *P. falciparum* isolated from malaria patients, these induced the most promising protective immune response in *Aotus* monkeys.[14] The initial phase I/IIa trials conducted in Colombian military personnel demonstrated that the vaccine is well tolerated, stimulates the production of antibodies to molecule SPf66, and could confer protection against artificial challenges with parasitized red blood cells drawn from infected individuals.[23] Subsequent studies on a larger group of volunteers in the region of Tumaco, Colombia,[24,25] confirmed the vaccine's safety, and classified individuals as either high, intermediate or low responders in terms of antibody production. Subsequently, a possible association was demonstrated between alleles HLA DR4 and deficient production of antibodies to SPf66.[26] Based on these field studies, it was concluded that the optimal immunization schedule was 3 doses, administered subcutaneously on days 0, 30, and 180, each dose consisting of 2mg of the synthetic peptide adsorbed in alumen.[27] Protective efficacy against *P. falciparum* infection was roughly estimated at 82.8%, and against *P.vivax* infection at 60.6%. However, there was still no confirmed correlation between the immune response and clinical protection.[23] In another field trial it was observed that 4.3% of the 9,957 individuals vaccinated with 3 doses presented minor localized reactions such as localized hardening and erythema.

Seven cases of temporary bronchospasm were reported.[28] The vaccine was also shown to be safe in children aged 1-14.[29] Phase III trials followed in Latin America, and have already been concluded in Venezuela, Colombia, and Ecuador, as summarized below. The findings reported in these studies have motivated other groups of researchers in Africa, Europe, the United States, and Asia to evaluate SPf66 vaccine in hyper-endemic geographical areas and populations with higher susceptibility to infection (children aged 1-15).

Venezuela

In an open, non-controlled study in 13 communities in the state of Bolivar, Venezuela, 1,420 vaccinated individuals (who received vaccine on days 0, 30, and 120) and 938 unvaccinated controls were followed over an 18-month period. Monthly visits were made to all the participants and samples were taken every 8-10 weeks. According to the analysis, the vaccine was safe and immunogenic, and offered protection against *P. vivax* and *P. falciparum* infection. Nearly 7% of the vaccinated individuals reported minor side effects, which occurred most commonly after the 2nd and 3rd doses. ELISA tests revealed positive titers for antibodies to SPf66 in 25.6% of the individuals examined before vaccination, 53.6% after the 2nd dose, and 76.6% after the 3rd dose. The antibodies lasted for 1 year after the 3rd dose was administered. The vaccine's protective efficacy was assessed by comparing cumulative incidence rates based on person-time exposure for the 12 months after vaccination, taking into account any differences in incidence between the study groups reported before the vaccination. The protective efficacy of the vaccine was estimated at 55% for *P. falciparum* (95% confidence interval: 21% to 75%), and 41% for *P. vivax* (19% to 57%). Of the individuals who were initially seronegative, 24% showed no seroconversion. This study is considered to be the first trial with the SPf66 vaccine in a general population in endemic areas.[30]

Colombia

In a double-blind placebo-controlled study in La Tola, Colombia, 1548 volunteers assigned to two study groups were vaccinated (738 with SPf66 vaccine and 810 with a placebo) on days 0, 30, and 180.[31] A system of active and passive surveillance to diagnose cases was implemented until 12 months after the 3rd dose was administered. Close to 1% of the individuals experienced mild side effects after vaccination. Seroconversion with low antibody titers was present in 28% of the vaccinated individuals. The vaccine's protective efficacy was calculated from the ratio of rates of disease based on estimated person-time of exposure, yielding an estimated figure of 33.6% (95 % CI: 18% to 46%). The protective effect was greatest in children from 1-4 (77%) and the adult population >45 years of age (67%). Several methodological issues have been raised regarding the calculations of protective efficacy. There is some discussion over whether effectiveness should be calculated in terms of malarious episodes prevented or proportion of individuals protected. The interpretation is different from a public health standpoint.

Ecuador

In the community of La T, in Esmeraldas, Ecuador, 537 volunteers assigned randomly to two study groups (230 in the SPf66 vaccine group and 238 in the placebo group) were vaccinated on days 0, 30, and 180. Active and passive surveillance was carried out until 12 months after the 3rd dose of vaccine was administered, with all study participants being visited every two months. A health unit equipped to diagnose and treat malaria was kept in operation. Minor localized side effects were observed, mainly after the 2nd dose, in 19% of the SPf66 group and 3.7% of the control group. Thirty days after the 3rd dose, the prevalence of antibodies to SPf66 was 57% in the vaccinated group and 8.8% in the placebo group. During the monitoring process, 4 cases of *P. falciparum* malaria were diagnosed in the vaccinated group (incidence = 1.7/1,000 person-months) and 12 cases in the placebo group (incidence = 5.1/1,000). The protective efficacy of the vaccine was estimated at 66.8% (95 % CI: - 2.7% to 89.3%).[32]

Observations about the Trials in Latin America

Regarding the trials conducted in Latin America, it has been observed that, even by itself, the implementation of prompt medical treatment and epidemiological monitoring in the study areas was enough to bring about a significant reduction in malaria incidence. This was confirmed in La T (Ecuador), Las Majadas (Venezuela), and especially Aripao (Venezuela), where the study was discontinued because malaria transmission had been interrupted in the area. In two more study areas in Colombia (Rio Rosario, Nariño; and Vigia del Fuerte, Antioquia), where trials are currently underway to test SPf66 vaccine, it has been decided to extend epidemiological monitoring by 2 years due to the low incidence of malaria (Patarroyo, M.E. and Restrepo M., personal communication). Because of the variability and instability of malaria, especially in low-transmission areas, it is considered important to carry out preliminary baseline studies of malaria incidence under the surveillance conditions that are to be introduced in the course of the trials. This will make it possible to evaluate the role of epidemiological monitoring in the reduction of transmission.

The conflicting results regarding the protective effect of SPf66 vaccine [35,36] have been attributed to technical problems in the preparation of the initial lots of vaccine.[31]

The controversy over the clinical findings of the Colombian studies with SPf66 vaccine resulted from weaknesses in the design of the initial clinical trials carried out in several communities in the area of Tumaco, Colombia.

Variability and lack of precision in the findings of the various phase III trials described can be explained, in part, by flaws in the design and execution of the trials. In general, the following problems have been recognized: lack of baseline information on incidence prior to the trials; use of study areas with low incidence; wide variation between expected and observed incidence; low compliance by participants in adhering to the 3-dose vaccine/placebo schedule; too-small samples to allow precise estimates or analysis of subgroups; lack of a standardized approach for assessing immune response in the different studies; lack of a precise analytical plan; insufficient monitoring of self-medication; excessive use of antimalarial medication for treatment of presumptive malaria cases; irregular assignment to treatment; and an inadequate vaccine/placebo coding system.

Phase III Trials underway in other Regions

Tanzania

With support and monitoring from the Special Program for Research and Training in Tropical Diseases-TDR/WHO, the Ifakara Center in Tanzania is conducting a controlled double-blind clinical trial with SPf66 vaccine in a group of 600 children 1-5 years of age living in a high-transmission area. The objective is to evaluate the vaccine's effect on prevalence, level of parasitemia, and incidence of acute cases of malaria. Two weeks before the administration of the vaccine all the participants are treated with sulfadoxine-pyrimethamine (Fansidar) to prevent the possible immunosuppressive effects associated with parasitemia. Monitoring, programmed for 18 months and thus ending 12 months after the 3rd dose is given, will end in December 1994, at which time the codes will be released so that the data can be analyzed. This study is a collaboration between the Swiss Tropical Institute, Basel, Switzerland; the National Institute for Medical Research, Tanzania; the Consejo Superior de Investigaciones Cientícas de España [Spanish Higher Council for Scientific Research]; and the London School of Hygiene and Tropical Medicine.[33]

Thailand

Working in coordination with and receiving technical assistance from the Immunology Institute of Bogotá, the Walter Reed Army Institute of Research has produced and formulated SPf66 vaccine in the United States in a processing plant that complied with Food and Drug Administration regulations (GMP) for clinical trials. After studies of safety and immunogenicity in adults and children living in transmission-free areas and endemic areas were satisfactorily concluded, a phase IIb double-blind trial was designed to be carried out in a refugee camp in the community of Shoklo, Thailand. The study includes 1,500 children, ages 8-15, randomly assigned to one of two groups: a group receiving SPf66 and a group given recombinant hepatitis B vaccine. Monitoring and case-finding will be carried out through daily visits to the participants over a period lasting 18 months (through June 1995). Protective efficacy will be determined by comparing the length of time between the administration of the 3rd dose of vaccine and the appearance of the first episode of clinical *P. falciparum* malaria in the vaccinated group and in the control group.[34]

The Gambia

With the support of the UK Medical Research Council Laboratories in Fajara, Gambia, and the London School of Hygiene and Tropical Medicine, a Phase III trial is being carried out with 600 children ages 6-11 months, who have been randomly assigned to receive SPf66 or injectable polio vaccine in 3 doses. The vaccine's effectiveness in preventing parasitemia and clinical malaria episodes will be evaluated.[34]

The TDR/WHO Steering Committee on Immunology of Malaria (IMMAL) suggests that the findings of independent studies now being carried out in several regions of the world will be essential for reaching any definitive conclusions about the protective efficacy of SPf66 vaccine. October 1995 has been set as the critical date for consolidating the information from clinical trials and defining strategies for future development of the vaccine. However, it is important to remember that a vaccine's effect can vary greatly depending on the conditions that define the burden of infection. The indirect effect of immunization in reducing the number of parasitized individuals, and the principle of dependent effects on the dynamics of disease transmission, can lead to inconsistent results in areas with different patterns of transmission. WHO/TDR/IMMAL estimates that it will take at least 5 to 12 years for a vaccine found to be successful in phase III trials to be routinely adopted in malaria control programs.

During the 46th World Health Assembly in Geneva, Dr. Patarroyo, speaking on behalf of the Government of Colombia, offered the patent rights to SPf66 vaccine to the World Health Organization in order to ensure that, if this vaccine comes into use as a public health tool, it will be available to the neediest citizens at an affordable cost.

Malaria Vaccines in Control Programs

Although the use of malaria vaccines to control the disease is not envisioned as a likely short-term prospect,

there are still some aspects that need to be considered. The decision to introduce vaccines into a control program depends basically on assessments of cost-effectiveness and social acceptability. The available alternatives or a combination of them need to be compared in terms of expected impact and cost. It is important to look at direct benefits (deaths prevented, cases prevented, individuals protected) and indirect ones (opportunity for multiple vaccination, primary health care activities, health education, maternal and child health care, etc.), as well as the direct and indirect costs of immunization. Cost-opportunity analysis will make it possible to evaluate the best alternatives for investment in health protection.

As with any other public health measure, it is necessary to evaluate the intervention's feasibility in terms of compliance and coverage of the population (particularly if multiple doses are required); sustainability (human, material, and physical resources); and production scale and vaccine availability. In field operations it is important to recognize issues such as duration of useful protection, need for revaccination, the vaccine distribution system, stratification of the risk area, identification of the most vulnerable communities, and the possibility of conducting selective or mass immunizations.

One of the risks that cannot be overlooked when introducing malaria vaccines in high-transmission areas is the possibility that the immunological profile and natural immunity of the exposed populations might be altered, leaving them vulnerable to more severe forms of the disease or epidemics.

Finally, it must be recognized that the introduction of a malaria vaccine as another control method will be viable only to the extent that living conditions and the general health of the population are improved and the capacity of the basic health services network for the diagnosis, treatment, and epidemiological surveillance of disease is strengthened.

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Source: Communicable Diseases Program, Division of Communicable Disease Prevention and Control, HCT/HPC, PAHO.

International Epidemic Intelligence Service Course

The School of Public Health of the Emory University and the Centers for Disease Control and Prevention (CDC) are offering an International course on International Epidemic Intelligence Service. The course will be held from 3-28 of October, 1994 in Atlanta, Georgia, United States of America.

The International Course is a four-week program patterned after CDC's annual Epidemic Intelligence Service (EIS) course. The overall objective of the program, which is conducted in English, is to provide participants with basic skills they will need to use epidemiology in their work.

The course consists of:

- Presentations and discussion on epidemiologic principles and basic statistical analysis; public health surveillance; field investigations, surveys and sampling, and epidemiological aspects of current major problems in international health.
- Problem sets, discussed in small groups, based on actual epidemiologic investigations.
- Presentations by participants of epidemiologic data from their own countries.
- A field exercise, involving data collection and analysis.
- Computer training in the use of Epi Info 5, a software developed at CDC and WHO for epidemiologists that combines word processing, data management, analysis, and graphics.
- Presentations on the organization and work of the CDC in International Health.

The deadline for receiving all completed information is June 1, 1994.

All application materials and inquiries regarding the International EIS Course should be directed to:

Philip S. Brachman, M.D.
School of Public Health
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Demographic Transition in the Americas

The population of Latin America increased from 11 million in 1700 to 30 million in 1850, with an annual growth rate of 0.6%. It had risen to 61 million by 1900 and to 165 million by 1950; by 1995 it is estimated that the Latin American population will total 482 million, which signifies annual growth rates of 1.4% between 1850 and 1900, 2.0% between 1900 and 1950, and 2.4% during the second half of the present century.

Inasmuch as the size, growth, and age structure of a country's population are the result of the interaction of three basic factors--mortality, fertility, and migration--any attempt to explain population dynamics in the medium and long term must first establish an interpretive model that relates these variables with one another and with other variables of economic and social development. The rapid population growth that has occurred worldwide in this century provided the basis for the theory of demographic transition, which grew out of the historical experience of the western countries, especially those of Europe, and viewed population growth as a feature of contemporary development. This theory attempts to formulate a generalized explanation of the process of declining mortality and fertility observed in the developed countries of Europe (excluding from the model, except in isolated cases, the role of the migration). It postulates a close relationship between the rate of population growth and the level of socioeconomic development. Although in individual cases it cannot always be maintained that less population growth is synonymous with more development, in general there appears to an inverse relationship between these two processes.

As the trend toward lower mortality in the early years of life continues, the age distribution of the population will also change, as will the most prevalent health problems in most countries of the Region of the Americas. These changes, together with the clear reduction in fertility observed in recent years, will undoubtedly result in an intensification of the trend toward aging in the medium and long terms. With a growing proportion of the population entering adulthood and old age, the epidemiological profiles of the countries of Latin America will tend increasingly to reflect diseases and health problems of adults and the elderly rather than those of children. In some countries--Chile, Costa Rica, Cuba, Barbados, Bahamas--this process has been hastened in recent decades by rapid declines in infant and child mortality. These demographic and epidemiological changes are occurring at different rates, depending on existing fertility and mortality levels, as well as on the distribution of risk factors that contribute to the appearance of diseases, the resources available, the accessibility of health services, and their effectiveness in responding promptly to these changes. Regardless of whether or not one accepts the validity of theories that attempt to explain demographic and epidemiological changes in light of socioeconomic and political changes, the fact that such changes have taken place cannot be denied. Moreover, it seems highly likely that most of these changes cannot be reversed.

"Demographic transition" is understood to mean a series of stages characterized by successive reductions in mortality and fertility. In order to define these stages, the artificial indicators of mortality and fertility will be used: life expectancy at birth (LEB) and total fertility rate (TFR). It will thus be possible to eliminate the influence of age distribution, a problem that arises when crude death and birth rates are used. Owing to lack of generalized information, the variable "migration" will not be considered, although it is recognized that it is impossible to study population dynamics in various countries of the Americas without taking into account migratory movements. As a clear illustration of the importance of migration it suffices to point out that of the 54 million emigrants who left Europe between 1815 and 1930, 50 million settled in the Americas, 32.6 million of them in the United States, 6.4 million in Argentina, 4.7 million in Canada, 4.3 million in Brazil, and a large number in Uruguay and Cuba, as well.

Adapting L. Tabah's presentation of the subject in "World Population at the Turn of the Century" (United Nations, New York, 1989, ST/THAT/SER.A/111), this article will separate the demographic transition into 5 stages with the following levels of mortality and fertility:

Stage one (1,1):
High mortality and high fertility.
LEB of under 45 years and TFR of more than 6.5.

Stage two (2,2):
Both mortality and fertility begin to decline, although the decline in mortality takes place first.
LEB of between 45 and 55 years and TFR of between 5 and 6.5.

Stage three (3,3):
The declines in mortality and fertility accelerate.
LEB of between 55 and 65 years and TFR of between 3.5 and 5.

Stage four (4,4):
Low levels of mortality and fertility.
LEB of between 65 and 75 and TFR of between 2 and 3.5.

Stage five (5,5):
Very low mortality and fertility, below replacement level.
LEB of 75 or more years and TFR of under 2.

Table 1

Demographic transition in the Americas:

Total fertility rate, life expectancy of birth, and stages in the transition, by country, 1950-55, 2020-2025

COUNTRY	1950-1955			1970-1975			1990-1995			2020-2025		
	TFR	LEB	SDT	TFR	LEB	SDT	TFR	LEB	SDT	TFR	LEB	SDT
ARGENTINA	3.15	62.5	(4,3)	3.15	67.2	(4,4)	2.79	71.3	(4,4)	2.24	74.1	(4,4)
BAHAMAS	4.22	59.8	(3,3)	2.99	66.6	(4,4)	2.01	72.2	(4,4)	1.85	77.6	(5,5)
BARBADOS	4.67	57.2	(3,3)	2.74	69.4	(4,4)	1.80	75.6	(5,5)	1.85	79.3	(5,5)
BOLIVIA	6.75	40.4	(1,1)	6.50	46.7	(2,2)	4.56	61.2	(3,3)	2.55	72.5	(4,4)
BRAZIL	6.15	51.0	(2,2)	4.70	59.8	(3,3)	2.75	66.2	(4,4)	2.00	72.1	(5,4)
CANADA	3.70	69.0	(3,4)	1.97	71.3	(5,4)	1.78	77.4	(5,5)	1.80	80.7	(5,5)
CHILE	5.10	53.7	(2,2)	3.63	63.6	(3,3)	2.66	72.0	(4,4)	2.25	74.6	(4,4)
COLOMBIA	6.76	50.6	(1,2)	4.66	61.7	(3,3)	2.67	69.3	(4,4)	2.09	74.6	(4,4)
COSTA RICA	6.72	57.3	(1,3)	4.33	68.1	(3,4)	3.14	76.3	(4,5)	2.34	79.4	(4,5)
CUBA	4.10	59.4	(3,3)	3.55	70.9	(3,4)	1.87	75.7	(5,5)	2.00	77.0	(5,5)
ECUADOR	6.90	48.4	(1,2)	6.05	58.9	(2,3)	3.62	66.6	(4,4)	2.13	72.5	(4,4)
EL SALVADOR	6.46	45.3	(2,2)	6.10	58.7	(2,3)	4.04	66.4	(3,4)	2.31	74.1	(4,4)
GUADELOUPE	5.61	56.5	(2,3)	4.49	67.8	(3,4)	2.16	74.6	(4,4)	1.85	78.8	(5,5)
GUATEMALA	7.09	42.1	(1,1)	6.45	54.0	(2,2)	5.36	64.8	(2,3)	2.92	72.3	(4,4)
GUYANA	6.68	52.3	(1,2)	4.90	60.0	(3,3)	2.55	65.2	(4,4)	2.10	72.8	(4,4)
HAITI	6.30	37.6	(2,1)	5.76	48.5	(2,2)	4.79	56.6	(3,3)	3.67	66.1	(3,4)
HONDURAS	7.05	42.3	(1,1)	7.38	54.0	(1,2)	4.94	65.8	(3,4)	2.69	73.6	(4,4)
JAMAICA	4.22	57.2	(3,3)	5.00	68.6	(3,4)	2.38	73.6	(4,4)	2.10	78.3	(4,5)
MARTINIQUE	5.71	56.5	(2,3)	4.08	69.2	(3,4)	1.99	76.2	(5,5)	1.85	79.8	(5,5)
MEXICO	6.75	50.8	(1,2)	6.37	62.9	(2,3)	3.16	70.3	(4,4)	2.03	75.3	(4,5)
NICARAGUA	7.43	42.3	(1,1)	6.79	55.3	(1,3)	5.04	66.7	(2,4)	2.55	74.1	(4,4)
PANAMA	5.68	55.3	(2,3)	4.94	66.3	(3,4)	2.87	72.7	(4,4)	2.12	74.3	(4,4)
PARAGUAY	6.80	62.6	(1,3)	5.65	65.6	(2,4)	4.34	67.3	(3,4)	3.10	69.6	(4,4)
PERU	6.85	43.9	(1,1)	6.00	55.5	(2,3)	3.57	64.6	(3,3)	2.23	72.0	(4,4)
PUERTO RICO	5.02	64.8	(2,3)	2.99	72.5	(4,4)	2.16	75.0	(4,5)	2.10	78.0	(4,5)
DOMINICAN REPUBLIC	7.40	46.0	(1,2)	5.63	59.9	(2,3)	3.34	67.5	(4,4)	2.19	73.6	(4,4)
TRINIDAD & TOBAGO	5.30	58.2	(2,3)	3.45	65.7	(4,4)	2.74	71.3	(4,4)	2.10	77.2	(4,5)
URUGUAY	2.73	66.1	(4,4)	3.00	68.8	(4,4)	2.33	72.5	(4,4)	2.09	74.6	(4,4)
USA	3.45	69.0	(4,4)	2.02	71.3	(4,4)	2.07	75.9	(4,5)	1.80	79.7	(5,5)
VENEZUELA	6.46	55.2	(2,3)	4.96	66.2	(3,4)	3.12	70.3	(4,4)	2.12	73.7	(4,4)

TFR = Total Fertility Rate
LEB = Life Expectancy at Birth
SDT = Stage of Demographic Transition (the first number in parenthesis refers to the fertility level and the second one to the mortality level; 1 indicates a high level of mortality or fertility, and 5 indicates very low mortality or fertility levels).

Table 1 shows the values of LEB and TFR for the various countries in the region for 1950-1955, 1970-1975, 1990-1995, and the estimates for 2020-2025. The countries are also classified by stage of demographic transition (SDT) in accordance with the preceding definitions of fertility and mortality levels 1-5. Accordingly, a value of 3,4 represents a fertility level of 3, or 3.5-5 children per woman, and a mortality level of 4, that is, life expectancy at birth of 65-75 years. Based on the general trends of the values corresponding to the subregion, it is possible to distinguish 3 phases in the demographic transition: an initial phase of significant gains in LEB accompanied by slower reductions in fertility, followed by an intermediate phase in which the reductions in fertility are more pronounced than the gains in LEB, and a final phase in which reductions in fertility slow but LEB continues to increase.

Often couples will seek to increase family size because, given the prevailing levels of productivity and mortality (with LEB of under 45 years, only half of those born will reach the age of 15) the economic contribution of the children who do survive is essential, as is support for old age. Hence, in order for the demographic transition to begin and for progress to be made to successive stages of the process, mortality must be reduced sufficiently to allow a decline in fertility to take place. This explains why transitional progress, with rare exceptions, is always greater in terms of mortality than in terms of fertility.

In the period 1950-1955, only six of the 31 countries considered--Bolivia, Guatemala, Haiti, Honduras, Nicaragua, and Peru--were in the first stage, which might be called the pretransitional stage, with life expectancy at birth of under 45 years and fertility of 6.5 children or more per woman. By 1970-1975 these countries had clearly moved on to another demographic stage. Mortality had fallen appreciably, with LEB increasing between 6 and 13 years, while fertility decreased more slowly or remained essentially unchanged. It can thus be stated that in most of the countries the demographic transition was under way before 1950, and several countries--namely, Canada, the United States, and Uruguay--were in advanced stages by that year. It should be noted that the latter country, Uruguay, remained at the same stage over the entire period examined (1950-1995) and is expected to be at that stage even within 30 years: (4,4).

At present, in the period 1990-1995, most of the countries are in advanced stages of demographic transition, with mortality and fertility levels of 4 or 5, excepting the aforementioned countries, plus El Salvador and Paraguay. Only in Haiti is LEB under 60 years. Twenty of the remaining thirty countries have already attained LEB of more than 70 years. By 2020-2025, it is expected that only Haiti and Paraguay will not belong to this group, and in several of the countries, namely, Bahamas, Barbados, Canada, Cuba, and the United States, as well as the French Overseas Departments of Guadeloupe and Martinique, LEB will exceed 80 years, while fertility rates will have fallen to below the population replacement level.

Table 2
Demographic changes in Latin America

Indicators	Around 1950	Around 1995
Birth Rate (x 1000)	42.5	25.7
Mortality (x 1000)	15.4	6.9
Natural growth	27.1	18.8
Migration (x 1000)	0.6	-0.8
Life Expectancy at birth (LEB):		
- Total	51.3	67.9
- Male	49.8	65.2
- Female	53.1	70.9
Proportion reaching:		
- at age 15:	80%	94%
- at age 65:	45%	70%
Total Fertility Rate (TFR):	5.86	3.13
Net Reproduction Rate (NRR):	2.15	1.51
Population aged under 15 (%):	40.46	33.81
Population aged 65 and over (%):	3.45	5.11
Urban Population (%):	41.7	74.5
Pop. in cities of >1 million (total percentage of population):	10.0	30.0
Median age:	19.7	23.2
Proportion of dependents:	78.3	63.7
Infant Mortality Rate (IMR):	125	47
Deaths in > 5 age group (%):	45*	26**
Deaths in > 65 and over (%):	19*	36**

* 1960-65
** 1985-90

Table 2 summarizes the changes associated with demographic transition in Latin America over the period 1950-1995, during which the region went from fertility and mortality levels of 2,2 in 1950-1955 to 2,3 in 1960-1965 and 1970-1975, reaching 3,3 in 1980-1985 and 4,4 in 1990-1995.

The convergence of LEB and TFR as they move from values of around 1,1 or 1,2 toward values of around 4,4; 4,5; or 5,5 can be seen in the course followed by some countries. Bolivia, for example, went from 1,1 to 2,2 and 3,3 between 1950-1955 and 1990-1995, and it is expected to reach levels of 4,4 in 2020-2025. A similar evolution is observed in the cases of Ecuador, Guatemala, Haiti, Honduras, and Nicaragua, countries that were in the pretransitional stage at the beginning of the period examined. Other countries which had already begun the transition evolved similarly, with some variations, all due to a lag in the decline of fertility with respect to mortality in the early stages.

Another way to perceive the convergence is through a comparison over time of the ranges of variation in LEB and TFR between countries. Whereas in 1950-1955 the range of variation in LEB was 31.4 years (from 69 in Canada and the United States to 37.6 in Haiti), for 1990-1995 it has dropped to 20.8 (Canada 77.4, Haiti 56.6) and it is estimated that by 2020-2025 it will have decreased to 14.6 (Canada 80.6, Haiti 66.1). As for fertility, the range has diminished from 4.7 children in 1950-1955 (Uruguay 2.73, Nicaragua 7.43) to 3.26 in 1990-95 (Canada 1.78, Nicaragua 5.04), and it is estimated that by 2020-2025 it will be 1.87 (Canada and the United States, 1.80, Haiti 3.67).

If "demographic lag" is defined as a difference of 2 between mortality and fertility levels, an examination of the data reveals that such a lag occurred only at the beginning of the period under study, during 1950-1955, when both Paraguay and Suriname showed a mortality level of 3, indicating that evident strides had already been made in reducing mortality--especially in Paraguay--while fertility remained at more than 6.5 children per woman.

The differential behavior of the two components was noted above in connection with the observations regarding the trends in the various countries, in which the decline in mortality generally preceded the decline in fertility in the early stages of the demographic transition, the time lag between the two phenomena varying depending on the country. In the last decade, however, there has been a notable reduction in fertility--greater than had been expected. While 1988 United Nations projections of life expectancy at birth for the countries of the Region during 1990-1995 differ very little from 1992 projections (an exception being Bolivia, which showed a 5-year increase), the same cannot be said of the projected total fertility rates. Taking into account census findings, especially in countries that had high fertility (although not only in those countries, as evidenced by the case of Brazil), it is possible to predict an acceleration of the demographic transition as a result of a marked reduction in fertility in the coming decades.

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Source: Health Situation Analysis Program, HDA/HDP, PAHO.

Cholera Situation in the Americas

During the 19th century, the Americas experienced the full force of the first five pandemics of cholera, with tens of thousands of cases and thousands of deaths affecting all countries of the region. Apparently because of the installation of water and sewage disposal systems in many of large cities, cholera disappeared from the Americas toward the end of the century and did not reappear during the sixth pandemic early in the 20th century. This fortunate situation continued through the first 30 years of the seventh pandemic, which began in 1961, even when cholera reached and spread throughout Africa between 1970 and 1973. It was, therefore, alarming when epidemic cholera appeared in January 1991 along the northern coast of Peru.

Cholera cases were first detected in Chancay, near Lima, and the cause was confirmed to be toxigenic *Vibrio cholerae* O1 El Tor Inaba. Within a matter of days, additional cases were reported from several communities along the 1200 km coast north of Lima. From there, the epidemic continued to spread rapidly, peaking with over 20,000 cases per week at the end of March and reaching all departments of the country by the end of the year. The impact of the epidemic, which totaled over 320,000 cases with nearly 120,000 hospitalizations, was tremendous and placed enormous demands on already overextended health services. Fortunately, the country was able to respond, with considerable external assistance, and succeeded in limiting deaths to 2,900 or less than 1% of cases (Table).

In January 1992, Peru again began to see an increase in cases above the 2,000 to 4,000 per week observed in the second half of 1991, with the greatest increase occurring in and near Lima. After March, cases again declined gradually to about 1000 per week during September 1992. In late 1992 and early 1993, cases again increased, affecting all parts of the country. In the second half of 1993, Peru saw further declines in cholera incidence, though most regions continued to report cases. Between 1991 and 1993, Peru had an 88% reduction in total cases.

The second country to be affected by the epidemic was Ecuador, with disease entering on the coast at the border with Peru, apparently introduced by fisherman. There was a rapid increase in cases peaking in April 1991, after which the incidence declined but the disease continued to spread along major communication routes, reaching both mountain and coastal areas. As in Peru, cases began to increase again in the last quarter of 1991 and peaked in March 1992, after which an appreciable decline was observed. The most affected area during 1992 was the major coastal city of Guayaquil, which accounted for one third of all cases in Ecuador that year. In 1993, Ecuador had much less cholera than in the previous two years, with only 14% of the number of cases reported in 1991.

Colombia was also infected in March 1991, initially on the southern Pacific coast, but the disease spread slowly up the coast and to the interior, ultimately infecting the entire country. Though disease incidence in Colombia remained up in 1992, it declined by 98% in 1993. Brazil was first infected in April 1991, at the point where the Amazon River enters from Peru and Colombia. Cholera remained in that area for several weeks before spreading eastward along the Amazon. A major epidemic in Brazil began in the last quarter of 1991, reaching the city of Belem on the Atlantic coast by the end of the year. During 1992, the epidemic in Brazil affected most of the northern regions and produced over 30,000 cases. In 1993, disease incidence increased by 66% and extended through most of the northern regions of the country.

Cholera was expected to spread contiguously in South America, and its appearance in a small community in central Mexico in June 1991 was surprising. In spite of vigorous efforts, Mexico was unable to confine the infection, which eventually reached much of the country, with the highest rates along the southern Gulf coast and the states bordering Guatemala. Outbreaks persisted in 1992, with cases peaking in August. In 1993, Mexico had even more cases in a similar seasonal pattern and geographical distribution, and outbreaks occurred in the capital and major cities such as Puebla.

Disease inevitably spread southeast from Mexico to Central America and northwest from Colombia to Panama. After modest outbreaks in the last quarter of 1991, both Guatemala and El Salvador had large epidemics in the middle of 1992, coincident with the normal diarrheal disease season. Guatemala had an increase in cases in the second half of 1993, with a total that year 99% higher than in 1992. El Salvador had smaller outbreaks in the first half of 1993 but experienced a large outbreak beginning in December 1993, with nearly 2000 cases per week, which appeared to be related to travel during the holiday season. The greatest number of cases occurred in the metropolitan area of San Salvador, especially among poor persons living in marginal urban zones.

Panama was seriously affected in 1991, primarily in Darien Province, and had the third highest case rate in the Americas that year. The rate more than doubled in 1992 but fell by 99% in 1993. Nicaragua detected its first case in November 1991 but had little disease until April 1992, when a major epidemic affecting all of the south and west of the country began. In 1993, cholera spread to the more remote central and Atlantic regions and produced 111% more cases than in 1992. In the second half of 1993,

Honduras also began to experience significantly more cases than in the previous two years. By contrast, Costa Rica had only limited numbers of cases in both 1992 and 1993.

In spite of its long border with Peru, Bolivia did not detect cases until August 1991, seven months after cases first appeared in Peru. Even then, infection remained confined to areas around La Paz until February 1992, when infection spread to low-lying, tropical regions and produced over 22,000 cases in 1992. Disease spilled into Argentina and eventually Paraguay, with epidemics continuing in southern Bolivia and northern Argentina in 1993. In the meantime, cholera continued to spread along the Atlantic coast of South America, passing through Venezuela and reaching the three Guyanas. Fortunately, Venezuela, Guyana, and French Guyana had fewer cases in 1993 than 1992, and Suriname had none in 1993.

By the end of 1991, cholera had infected 15 countries, with transmission extending from Mexico in the north to Chile in the south and from the Pacific coast of Peru to the Atlantic coast of Brazil. An additional 5 countries were involved in 1992. Only one country in continental Latin America, Uruguay, was not infected at some time during the 3 years 1991-1993. Interestingly, none of the island states and territories of the Caribbean detected cases, while all maintained heightened surveillance. The overall pattern of disease in the Americas was set by that in Peru, which accounted for 82% of total reported cases in 1991 and 60% in 1992 but only 36% in 1993. The Americas produced 67% of all cases reported worldwide from 1991 to 1993, the years with the highest number of reported cases in the seventh pandemic of cholera.

While numbers of cases indicate the impact of cholera on society and the health services, comparisons between countries are better made with incidence rates. In 1991, the rates in Peru and Ecuador far exceeded those in other countries, with 1.5% of the population in Peru suffering cholera-like illness. Case rates were also relatively high in Panama and Central America. Rates in those three countries remained elevated in 1992, but in that year Bolivia had the second highest rate in the Americas after Peru. Rates in 1993 were highest in Peru and Guatemala (32 cases per 10,000 population), followed by Nicaragua, El Salvador and Bolivia (16, 12, and 12 cases per 10,000 population, respectively).

In spite of efforts to promote a uniform case definition for cholera and consistency of reporting between countries, different definitions were used and different criteria were applied for reporting. It is also true that quality of reporting varied even within countries. Therefore, comparisons of incidence rates should be made with these differences in mind.

The 8,622 deaths attributed to cholera in the first 36 months of the epidemic seems relatively minor when compared with the estimated 150,000 deaths from diarrheal disease estimated to occur each year among children under 5 years of age. However, one must recall that untreated cholera is associated with a mortality rat of 30 to 50 percent. All of the 941,000 cholera cases reported in the Americas between 1991 and 1993 received treatment at a medical facility, and more than half required hospitalization. These numbers placed a tremendous demand on the health services, and it can be conservatively estimated that at least 100,000 lives were saved of persons who would have died without adequate treatment.

Indeed, it is just this achievement that was most remarkable. In Peru, except at the very beginning of the epidemic, the case fatality rate was kept below 1%. In most other countries, death rates were below 2%, though higher rates were seen at some of the earlier stages of the epidemic in several. Later elevations in case fatality rates, as were seen in Bolivia, Panama, and Nicaragua, created renewed concern about the proper management of cases.

In all affected countries, cholera was predominantly a disease of adults, with more than 75% of cases occurring in persons over 5 years of age, in contrast to other acute diarrheal illness, 75% of which normally occurs in children under 5. In some countries, there was a predominance of males among reported cases, but whether this was due to greater exposure among males or a greater tendency to seek treatment for male patients is not known. The risk of death from cholera did r appear to be associated with age or sex. Where the, were evaluated, cholera deaths were related to access and use of health services, those dying usually not seeking care or arriving late at health facilities. While overall death rates from cholera were low, there are large differences within countries, with more remote and less accessible areas having rates 10 to 20 times higher than the capital cities, where the best hospitals are within easy reach. It is precisely this issue which was of major concern to Nicaragua, which saw its case fatality rate rise to 5% in mid-1993 as the disease entered populations which were difficult to reach because of their remoteness or the presence of civil strife. The increase in the regional case fatality rate to 1.8% for 1993 may be related to several factors, including underreporting of cases that survived, presence of disease in less accessible areas, and improper management of cases.

Disappointingly few investigations were carried out in Latin America to identify specific modes of transmission and risk factors for cholera. Many that were done were supported by staff of the Centers for Disease Control and Prevention of the United States Government. In Latin America, as elsewhere, cholera was a disease almost exclusively of the poor. In some of the larger cities of Peru, drinking unboiled municipal water was an important risk factor, and heavily contaminated wat

Cholera in the Americas
Reported cases and deaths* per country and year
1991 - 1993

COUNTRY	First reported case	Cases 1991	Cases 1992	Cases 1993	Total Cases	Deaths 1991	Deaths 1992	Deaths 1993	Total Deaths	Case fatality ratio 1991-1993
South America										
Argentina	02/05/92	0	553	2,070	2,623	0	15	33	48	1.83
Bolivia	08/26/91	206	22,260	9,189	31,655	12	383	230	625	1.97
Brazil	04/08/91	2,101	30,054	49,956	82,111	26	359	535	920	1.12
Chile	04/12/91	41	73	28	142	2	1	0	3	2.11
Colombia	03/10/91	11,979	15,129	230	27,338	207	158	4	369	1.34
Ecuador	03/01/91	46,320	31,870	6,347	84,537	697	208	55	960	1.13
French Guyana	12/14/91	1	16	2	19	0	0	0	0	0
Guyana	11/05/92	0	556	66	622	0	8	2	10	1.60
Paraguay	01/25/93	0	0	3	3	0	0	0	0	0
Peru	01/23/91	322,562	212,642	71,448	606,652	2,909	727	575	4,211	0.69
·iname	03/06/92	0	12	0	12	0	1	0	1	8.33
Venezuela	11/29/91	13	2,842	409	3,264	2	68	10	80	2.45
Mexico and Central America										
Belice	01/09/92	0	159	135	294	0	4	3	7	2.38
Costa Rica	01/03/92	0	12	14	26	0	0	0	0	0
El Salvador	08/19/91	947	8,106	6,573	15,626	34	45	27	106	0.68
Guatemala	07/24/91	3,674	15,395	30,604	49,673	50	207	306	563	1.13
Honduras	10/13/91	11	384	1,925	2,320	0	17	27	44	1.90
Mexico	06/13/91	2,690	8,162	10,712	21,564	34	99	193	326	1.51
Nicaragua	11/12/91	1	3,067	6,473	9,541	0	46	220	266	2.79
Panama	09/10/91	1,178	2,416	42	3,636	29	49	4	82	2.25
USA	04/09/91	26	103	18	147	0	1	0	1	0.68
Total		391,750	353,811	196,244	941,805	4,002	2,396	2,224	8,622	0.92

* Up to December 31st. 1993.
Source: PAHO/WHO/CDD.

distributed in badly decaying systems probably played an important role in the rapid and extensive spread of cholera. Even in that country, those with some resources quickly learned how to decontaminate their water or obtain clean water, and cholera became a disease of those without means and knowledge.

In all countries, food which was improperly prepared, handled or stored, allowing its contamination with cholera organisms, was a major source of infection. In some, seafood obtained from contaminated water and not fully cooked was shown to be causally linked to cholera cases.

Throughout Latin America and the Caribbean, sewage is usually discharged without treatment into rivers, lakes and oceans. Not infrequently, it is diverted for irrigating crops, especially those, such as vegetables, which require large amounts of water and fertilizer. The risk of contaminating these crops is obvious, though it has not been proven that this practice is associated with the transmission of cholera. When cholera deaths occurred in Santiago, Chile, authorities destroyed fields using such irrigation practices and banned the sale of uncooked vegetables and salads in restaurants. Cholera cases ceased in 1991 after the ban but recurred in 1992 and 1993. Unfortunately, no case-control studies were performed to confirm whether or not disease was associated with consumption of these foods.

In contrast to what was apparently experienced in the 19th century, cholera in the Americas in the 1990s has been a predominantly rural disease in several countries. Some of the larger cities such as Lima and Guayaquil were seriously affected, but in all countries the rural poor, who lack water and sanitation services, suffered a major burden of disease. The recent appearance of cholera in some of the largest cities of the Region, including Mexico City, Sao Paulo and Rio de Janeiro, indicates that the most densely populated and poor areas may be at risk of potentially explosive epidemics. Nonetheless, it is likely that cholera will persist among the rural poor, presenting a continuing challenge for treatment and prevention.

For the three years 1991 to 1993, the countries of the region and the Pan American Sanitary Bureau approached the cholera epidemic as an emergency. Intensive efforts were made to establish and improve surveillance and to disseminate information about the epidemic. Health care providers were instructed in proper case management to prevent deaths and complications, with emphasis on the provision and use of oral rehydration salts. Laboratory capacity for diagnostic confirmation of cases, antibiotic sensitivity testing and identification of vibrios in food and water was strengthened in all countries. Methods for providing disinfected water, disposing of human excreta and handling foods to prevent contamination were developed and implemented in thousands of communities. Efforts at prevention relied heavily on social communication strategies for health education. To assist with the implementation of these emergency measures, the Pan American Health Organization (PAHO) mobilized over US$21 million from the international community. That these measures had a positive impact is shown by declines in cholera incidence in several countries, in *Salmonella typhi* infection in Chile, and in non-cholera diarrhea in Costa Rica, Nicaragua, Mexico, and several other coutries.

During the past 15 or more years, health and environmental services, including water and sanitation systems, deteriorated seriously without maintenance or investment to meet increasing needs. PAHO has estimated that investments in environment and health totalling over 210 billion dollars during the next 10 years are needed to correct deficiencies and return the Americas to a situation in which it is no longer susceptible t epidemic cholera. Until these major investments can be made, it seems likely that cholera will persist in many countries of the Region. In Peru, Ecuador and some countries of Central America, a seasonal pattern for cholera appears to have emerged, suggesting that the infection may already be endemic. The prevention efforts mentioned above will need to be continued and expanded in order to limit the impact of cholera, until deficiencies in health and environmental services can be corrected.

Source: Division of Communicable Disease Prevention and Control, HPC, Health Situation Analysis Program, HDP/HDA, and Expanded Program for the Control of Diarrheal Diseases CDD.

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