Measles Battle Loses Potent Weapon

Use of an experimental vaccine that showed promise in tackling the disease in the Third World has been halted because it has been associated with excess mortality in some countries

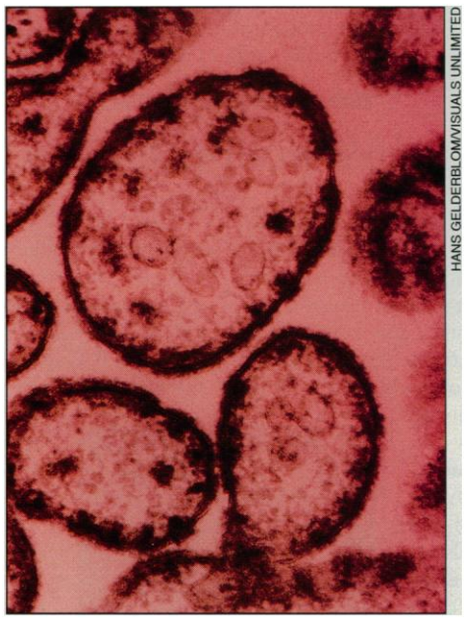
In a disheartening finale to a decade of promising clinical trials, the World Health Organization (WHO) this month suspended all use of the most effective measles vaccine ever developed. The difficult decision followed a review of studies that reached a baffling conclusion: Children in some Third World countries inoculated with the potent formulation—called the high-titer Edmonston-Zagreb vaccine—remain well protected from measles but have an increased risk of dying from a variety of other diseases in the years following vaccination. And, to add to the mystery, girls who had been given the vaccine seem to be more at risk than boys.

The vaccine's loss constitutes a significant setback for developing countries, where measles remains the number one infectious killer. The disease strikes about 44 million children a year and kills 1.5 million of them. Public health officials had been hoping that the new vaccine would make a dent in those horrifying statistics in the 1990s. Its key advantage compared to the standard vaccine is that it can be used much earlier in infancy, a time when millions of children in developing countries contract the disease.

The impact will be less immediate in countries like the United States, where measles tends to strike later in childhood. But that doesn't mean domestic officials are unconcerned. Researchers are at a loss to explain the excess mortality linked to the new vaccine, although they suspect it may be a result of immune suppression. And that lack of knowledge points up a key problem: Measles research has lagged badly in recent years. Moreover, large-scale measles outbreaks have appeared in 3 out of the past 4 years in the United States, with as many as one-third of the cases in some cities occurring in children already vaccinated with the standard vaccine. Still reeling from the reemergence of tuberculosis, experts are concerned that the country could be caught off guard by another highly infectious slumbering giant (see box).

"Much of the work on measles was done between 1954 and 1966, and everything went wonderfully," says Duke University pediatrician Samuel Katz, chairman of the Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices. Indeed, measles research may have been a victim of its own success. The first vaccine was approved in 1963, and within 5 years, Katz notes, the U.S. incidence of measles dropped by an incredible 95%. "The attractiveness of the field declined and funding became skimpy," Katz says. "Today, you can count on one hand, almost, the number of people who are doing basic research with the measles virus."

But while interest and money waned, the measles problem had hardly been solved, especially in developing countries. Aside from the difficulty of reaching enough people in poor countries with any vaccine program,



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Black box. Little is known about the inner workings of the measles virus.

the standard vaccine, made from live attenuated viruses, has a serious drawback: It is generally ineffective in the presence of maternal antibodies, which remain in the blood for about the first 9 months of life. In developing countries, where measles is often "hyperendemic," as many as one in three infants catch the disease within their first 9 months. (In developed countries, where the disease is less common, young infants run little risk of exposure to the virus and vaccination can be postponed until 12 or even 15 months of age.)

Hopes for a better vaccine rose in 1983 when a preparation made from a nonstandard measles strain, called Edmonston-Zagreb, proved immunogenic in Mexican infants 4 to 6 months old when given in doses 10 to 100 times the usual concentration. Studies in Guinea-Bissau and Haiti confirmed the vaccine's effectiveness in this critical age group, and in 1990 WHO recommended that the high-titer Edmonston-Zagreb vaccine be used in areas where measles in younger infants was a major health problem.

It wasn't long before the bubble burst, however. By late that same year, researchers in Guinea-Bissau reported that children who had been inoculated with the high-titer vaccine were dying at higher than expected rates from a spectrum of ailments already common to the region, including pneumonia, diarrhea, and parasitic diseases. In February 1991 Senegal reported the same problem. In one key study, children who received the high-titer formulation had a mortality rate in the first few years after inoculation that was 80% higher than that of their counterparts who received the standard inoculum. But these studies were preliminary and WHO allowed trials to continue while gathering more data.

By June of this year, however, when a WHO task force met in Atlanta to discuss the vaccine, similar data were coming in from Haiti; the link seemed irrefutable, with an average increased risk of mortality of about 20%. After the meeting, WHO recommended that use of the vaccine be halted temporarily pending further review. Last week, at a meeting held in Indonesia, the Global Advisory Board of WHO's Expanded Programme on Immunization officially ratified that suspension, effectively killing further trials of the formulation. (Standard doses of the Edmonston-Zagreb strain have been used safely for years in some parts of the world and are still allowed, however.) The agency is expected to publish its findings and recommendations in its weekly report within the next few weeks.

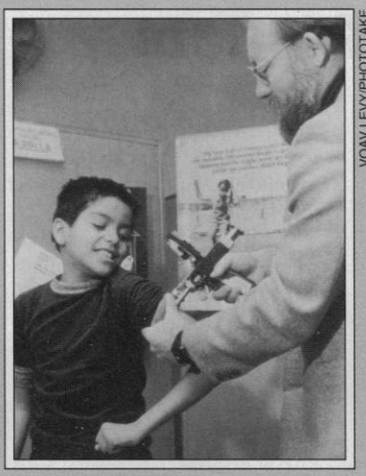
Although immunologists and virologists are mystified by the high-dose vaccine's ill effects, they are focusing on the possibility of immune suppression. Indeed, the measles virus itself is known for its ability to cause a transient, generalized immune suppression even as it triggers long-lasting specific immunity. "It's well known that infection with the wild-type measles virus can suppress the immune system, as evidenced by a weakened delayed hypersensitivity response to tuberculin skin tests," says Johns Hopkins virologist Diane Griffin. "A high-dose vaccine may just mimic, in an amplified way, what happens with natural measles."

Unfortunately, Griffin says, scientists

U.S. Epidemics: The Price of Neglect?

It was science at its best: In the 5 years following the introduction of a measles vaccine in 1963, the number of domestic measles cases dropped dramatically from 458,000 to 22,000; by 1983 the number had fallen to an all-time low of fewer than 1500. But incidence has increased annually since then. More than 18,000 cases occurred during the epidemic of 1989, and epidemics recurred in 1990 and 1991.

Public health officials blame most of the recent U.S. upswing on parents' growing failure to vaccinate their children. A recent survey of eight major U.S. cities by the Centers for Disease Control found vaccination rates ranging from 52% to 71%. But beyond the problem of coverage, it has also become clear that up to 5% of those who do get vaccinated fail to develop antibodies, and an even greater percentage may lose their protection years later. To remedy the situation, U.S. officials began recommending a two-dose measles regimen in 1989, with the first dose to be given at 12 months followed by a booster several years later.



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Scattershot. Measles is making a comeback as vaccination lags.

Antibody development and persistence should increase with the new dose schedule, but some experts worry that compliance will be even worse than with the one-dose schedule. A better solution, they say, would be to develop a single-dose vaccine that could be given at a few months of age, when other vaccines are also being given. Public health officials had hoped that the high-titer Edmonston-Zagreb vaccine (see main story) might fill that role, but last week's permanent suspension of its use now has scientists going back to their drawing boards.

Unfortunately, the U.S. research establishment is hardly in a position to make up for the loss quickly. "We've had a relatively good vaccine for 25 or 30 years," says Kenneth Bart, director of the National Vaccine Program Office in Rockville, Maryland. "So research has virtually ground to a halt." Indeed, the National Institute of Allergy and Infectious Diseases currently funds only two projects relating to measles. It recently invited grant proposals in the area, but no new money has been allocated. That means that any new projects will have to cannibalize resources from the existing virology budget.

–R.W.

know very little about how the measles virus interacts with the immune system. "We know a lot more about viral immunology now than we did when measles vaccines were first developed," Griffin says. "There is hope for figuring it all out, but first we're going to have to understand what this immune suppression really is. If we could find out what causes it, we could figure out what not to do in a vaccine."

As equally baffling as the increased mortality itself is a mysterious gender bias. In several countries, like Guinea-Bissau and Senegal, girls were found to be much more likely to suffer from the vaccine-related delayed mortality. "Why on Earth should this vaccine effect be gender related?" asks John Clements, medical officer for WHO's vaccine program in Geneva. "It was totally unexpected." Some infectious diseases do cause higher mortality in one sex or the other, although no such bias has been recognized for naturally occurring measles. But in those cases, it's usually the girls who are better at fighting off pathogens. That has led at least one immunologist, E. Richard Stiehm at the University of California, Los Angeles, to propose that in fact girls do mount a superior immune response to the measles vaccine—and then go on to suffer from a generalized hypersensitivity that leaves them at an immunological disadvantage later on.

Some find the vaccine's gender correlation so counterintuitive they suspect it has sociological, rather than biological, roots. Kenneth Bart, director of the National Vaccine Program Office in Rockville, Maryland, suspects that equal numbers of boys and girls may get sick in the few years after vaccination, but that girls receive less adequate medical care and so die at higher rates. But Lauri Markowitz, a medical epidemiologist with CDC's Division of Immunization, counters that workers in West Africa have told her there is no evidence that boys in the trials were treated better than girls. "The whole thing is so strange," she says. "I don't think people really have a clue about what's going on." To shed light on the vaccine's mechanisms of immune suppression and gender bias, a research team headed by Markowitz plans to measure antibody levels and immune cell counts in 100 boys and girls in the Los Angeles area who received the high-titer Edmonston-Zagreb vaccine in clinical trials in the past 2 years.

One lingering worry is that any live virus measles vaccine potent enough to induce immunity in infants with maternal antibodies may cause long-term immunosuppression. "Given that possibility," asks Bart, "is it even ethical to continue tests of [measles] vaccines that are immunogenic in the presence of maternal antibodies, or should we be going back to animal models?" An advisory group to the National Vaccine Program will discuss ethical issues and other aspects of the high-titer vaccine at a conference on the National Institutes of Health campus next week.

One option sure to come under consideration is to move beyond live attenuated vaccines altogether. A killed measles virus vaccine was used for several years in the United States but was pulled from the market in 1967 when it was shown to increase the odds of getting a severe form of the disease called atypical measles. To this day nobody knows whether the problem is inherent to killed measles viruses or whether it might disappear if the vaccine were processed differently.

Virologists say that ideally they'd like to come up with an engineered vaccine containing protective viral elements and none of the components that cause immune suppression. But given the rather primitive state of knowledge about the measles genome, they concede, it will be years before such an effort has any hope of success.

"Meanwhile," says WHO's Clements, looking on the brighter side, "we still have a very good vaccine for children older than 9 months, and we need to increase coverage." More than 20% of the world's children remain beyond the reach of WHO's measles vaccination program, he says. And much could be gained by simply improving the distribution of the standard vaccine, which by itself has already reduced childhood mortality in Haiti, Guinea-Bissau, and other countries.

"That vaccine has saved millions of lives," Clements says. And in a comment unintentionally ironic for its combination of optimism and disappointment, he adds: "It will continue to be the pillar of measles control throughout the world."

–Rick Weiss

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