Dehydration is the loss of fluids and electrolytes that, depending on extent, can compromise the health and well-being of an individual and in extreme cases, prove fatal. Dehydration can be caused by many events from the simple failure of an individual to take adequate quantities of fluids to replace physiologic needs to situations such as heat exposure, extreme physical exertion, and diarrhea. The most common pediatric condition worldwide leading to dehydration is acute gastroenteritis and in fact, the severity of disease is partially measured by the degree of dehydration it produces (Table 1).

In children, the severity of dehydration can be quantified in clinical terms and correlated directly with the percent of body weight lost. Using these criteria elaborated by the World Health Organization (WHO), a child is considered to be severely, moderately or mildly dehydrated if he or she loses greater than 10%, 5% to 9%, or 2% to 5% of body weight, respectively. At each level of dehydration, the associated symptoms have been graded and a child with severe dehydration may present with an altered state of consciousness (or in coma or shock), low blood pressure, dry mouth and eyes, sunken fontanelles, and a failure to urinate.

Because acute gastroenteritis is the prime cause of dehydration and death among children in developing countries, this review of the disease burden of dehydration will focus on the burden linked to acute gastroenteritis from a wide variety of causes.

A REVIEW OF STUDIES

A critical awareness of the problem of diarrheal diseases occurred when investigators first tried to identify the causes of mortality among children of less than 5 years of age in developing countries (Table 2). Puffer and Serano reviewing studies in Latin America identified and grouped a large number of conditions causing gastroenteritis under the heading of diarrheal disease deaths. This designation remained and in 1979, the WHO expanded its activities on cholera to include all diarrheal diseases with a focus on prevention and control. In 1982, a background paper commissioned for the Diarrheal Disease Control Program reviewed published studies from the global literature that addressed mortality from diarrheal diseases in an effort to
TABLE 1. Diarrhea treatment chart

<table>
<thead>
<tr>
<th>Degree of dehydration</th>
<th>Signs*</th>
<th>Rehydration therapy (within 4 hr)</th>
<th>Replacement of stool fluid losses</th>
<th>Dietary therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (3%-5%)</td>
<td>Slightly dry buccal mucous membranes, increased thirst</td>
<td>ORS 50 mL/kg</td>
<td>10 mL/kg or 1/2–1 cup of ORS for each diarrheal stool</td>
<td>Human milk feeding or half- or full-strength lactose-containing milk or undiluted lactose-free formula</td>
</tr>
<tr>
<td>Moderate (6%-9%)</td>
<td>Sunken eyes, sunken fontanelle, loss of skin turgor, dry buccal mucous membranes</td>
<td>ORS 100 mL/kg</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Severe (≥10%)</td>
<td>Signs of moderate dehydration with one of the following: rapid thready pulse, cyanosis, cold extremities, rapid breathing, lethargy, coma</td>
<td>Intravenous fluids (Ringer's lactate), 20 mL/kg/hr until pulse, perfusion, and mental status return to normal; then 50–100 mL/kg of ORS</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

*If no signs of dehydration are present, rehydration therapy is not required. Proceed with maintenance therapy and replacement of stool losses.

*Infants and children who receive solid food can continue their usual diet, but foods high in simple sugars and fats should be avoided.

From Duggan et al. (7).

establish the high priority with which these conditions should be treated. From their review of studies published before 1980 where active surveillance had led to an assessment of diarrheal deaths, they estimated that 4.6 million children younger than 5 years old would die annually of a diarrheal disease. This study helped set the priority for investment in diarrheal disease interventions, and has been confirmed and remained a priority that has been maintained through a number of subsequent reviews.

In the 20 years since this first publication, at least six other groups have examined

TABLE 2. Diarrhea mortality estimates

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Year</th>
<th>Deaths per year (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snyder and Merson (17)</td>
<td>1982</td>
<td>4.6</td>
</tr>
<tr>
<td>Institute of Medicine (9)</td>
<td>1986</td>
<td>3.5</td>
</tr>
<tr>
<td>Martines et al. (19)</td>
<td>1990</td>
<td>3.2</td>
</tr>
<tr>
<td>Bern et al. (1)</td>
<td>1992</td>
<td>3.3</td>
</tr>
<tr>
<td>World Dev Report (18)</td>
<td>1993</td>
<td>2.5</td>
</tr>
<tr>
<td>Murray and Lopez (12)</td>
<td>1997</td>
<td>2.4–2.9</td>
</tr>
<tr>
<td>Bacon (17)</td>
<td>2002</td>
<td>2.5</td>
</tr>
<tr>
<td>Parashar (14)</td>
<td>2002</td>
<td>1.7–3.0</td>
</tr>
</tbody>
</table>
and updated estimates of the mortality associated with diarrheal diseases. These studies have differed slightly in their methods, but have generally sought data from published studies in the English medical literature and tried to combine data from the best studies to identify a general target figure rather than establish any exact quantification, which would be impossible. Early estimates did not include data from China and therefore probably underestimated the true numbers. Nonetheless, several trends seem important from the data—the estimated number of diarrheal deaths worldwide has been reduced by half over the past 20 years in line with the decline in deaths among children younger than 5 years old, and the percentage of diarrheal deaths has remained at approximately 20% of all deaths among these children.

While these reviews have provided cogent targets for interventions and investments, they all suffer from systematic weaknesses that are difficult to correct given the studies available for review. In most of the studies, the cause of death was determined by verbal autopsy, that is, an in-depth interview with the parent or caregiver after the death occurred. In the absence of good pathologic and laboratory evidence, the interviewer is recovering second-hand symptoms and signs and trying to convert these to a coded diagnosis. The quality of this data depends on the quality and interest of the interviewer. Many diarrheal deaths in hospitals often occur among patients with substantial medical problems, making it difficult to unravel whether the diarrhea was the "cause" of the death or merely an ancillary or contributing event. Other disease conditions, such as measles or human immunodeficiency virus infections, can set a child up for a subsequent diarrheal illness that might be more severe. Deciding whether a diarrheal death is primary or secondary can further complicate the matter. In short, despite the many reviews of the importance of diarrhea as a cause of childhood deaths, and despite the evidence that the number of deaths may be increasing substantially, the true number remains problematic.

Enteric infections have a broad range of presentations, from the most common and asymptomatic infections to diarrhea that can range from being mild and inconsequential to moderate, requiring medical intervention and oral therapy; to severe disease with dehydration that can be fatal (Fig. 1). The distribution of these presentations can be visualized as a pyramid of diarrheal illnesses with the most common and least severe at the base and the least common fatal cases at the apex. The size and the shape of this pyramid provide important insights to a child’s individual risk or a countries medical experience in dealing with diarrheal diseases. Differences in the shape of this pyramid can help visualize differences occurring between children in developed and developing countries. Differences in a child’s exposure to gastrointestinal infections further reflects both their exposures to different pathogens as well as the pathogen’s access to different routes of transmission.

Several differences in the shape of the diarrhea pyramid are evident. First, in developing countries, the pyramid of gastrointestinal infections has a very broad base reflecting the high incidence of gastroenteritis each year—three or more per year— for their first 5 years of life—15 or more episodes by the age of 5. This contrasts to the 1.5 episodes per year among children in developed countries. While information about the risk of a child seeking health care for mild or moderate disease
is limited and, subject to issues of local access, mortality at the peak of the pyramid is strikingly different. From studies in many developing countries, an estimated 2.5 million diarrheal deaths occur each year among children younger than 5 years old in a birth cohort of approximately 125 million children. This means that approximately one child in 60 will die of an acute diarrheal illness by the age of 5, making diarrhea the second leading cause of death responsible for 20% to 25% of the 10 to 12 million deaths each year among children younger than 5 years old in the developing world. With development, mortality drops dramatically and in the United States, an estimated 300 children younger than 5 years old die each year with diarrhea coded on their death certificates from an annual birth cohort of 3.5 million. In other words, a newborn in the United States has only one chance in 10,000 of dying from diarrhea before the age of 5, which represents less than 3% of all deaths among children this age.

While we have some estimates of the total incidence of and mortality from diarrheal diseases worldwide, the distribution of disease of intermediate severity leading to clinic or medical visits is highly dependent on access to and availability of treatment. Healthcare statistics are much more abundant in industrialized settings and this can indirectly reflect severity of illness although it is dependent on access to care. In developing countries, the number of prospective longitudinal studies providing information on severity is limited and often site-specific. Furthermore, those longitudinal studies in which field workers visit homes regularly to monitor events often provide mothers with appropriate therapy so that mild disease might be prevented from becoming more severe. Consequently, the shape of the middle of the pyramid is site-specific and our database to estimate the range of these values is quite large.

CONTRASTING CHARACTERISTICS OF GASTROINTESTINAL DISEASES IN CHILDREN

The shape and size of the gastrointestinal pyramid depends on many factors that have only been recently described and understood. In the past, gastrointestinal illnesses were considered to be problems of poverty—of poor children growing up in
an environment coated with a fecal veneer who suffered with inadequate access to clean food, water, sanitation, and hygiene. The irony is that as countries improve and develop, gastrointestinal infections remain among the most common problems of children even though all of the necessary changes in sanitation, food hygiene, and water have been made. A number of factors contribute to understanding this apparent paradox.

**Etiologic Agents**

Gastroenteritis is a collection of symptoms that we now know can be caused by a large number of infections agents and toxins (Fig. 2). Perhaps the greatest advance in the past 30 years has been the elucidation that these illnesses were, for the most part, infectious in origin. With the discovery of many new enteric pathogens, we can now make an etiologic diagnosis of most illnesses. When we contrast the etiologies of diarrheal illnesses between children in developed and developing countries, we find some interesting differences that provide insights into questions of prevention and control.

In developing countries, the wide diversity and abundance of bacterial, viral, and parasitic agents illustrate the many breaks in hygiene that allow these organisms to persist and spread. With development and improvements in water, food, and sanitation, most of the bacterial and parasitic diseases such as cholera, shigellosis, amebiasis, and cryptosporidiosis have become uncommon leaving the viruses to persist and predominate. In the United States or Finland, children will rarely have a bacterial or parasitic infection, and when they do, their risk can often be traced to an outbreak

![Graph](image-url)

**FIG. 2.** Hospitalizations for diarrhea by etiology among children in developing countries.
in a daycare setting where many children are exposed from a single individual. In contrast, the major viral pathogens—rotavirus, enteric adenoviruses, astrovirus, and caliciviruses including both the Norwalk-like and Sapporo-like groups remain with an incidence that may vary little by setting. Furthermore, some diseases have become problems in industrialized countries because of changes in food technology. For example, salmonellosis from contaminated chickens and eggs increased with intensive production methods and is a problem in the United States and United Kingdom, while it remains a rare disease in Bangladeshi children.

Modes of Transmission

The change in the distribution of gastrointestinal pathogens reflects changes in the modes of their transmission. Many enteric infections are spread uniquely by the fecal-oral route through vehicles of contaminated water, food, or environmental surfaces. Improvements in food and water hygiene including chlorination, refrigeration, and sanitation have brought a reduction in those organisms transmitted by these routes and vehicles. In Mexico, for example, the cholera epidemic of the early 1990s brought massive efforts to chlorinate water supplies and separate sewage from drinking water. The effort not only led to a marked reduction in diarrheal mortality, but a sharp decline in the number of deaths occurring in the summer season, but not the winter season. This suggests that those pathogens spread by contaminated water, including cholera, could be controlled when these interventions were effective. At the same time, the residual deaths in winter are likely due to rotavirus indicating that the mode of spread for this agent must be independent of contaminated food or water.

For this reason, efforts to control rotavirus, the most common cause of severe diarrhea in children worldwide, have relied on the development of vaccines rather than improvements in water and food hygiene.
Nutritional Status

A major determinant of the severity of diarrheal illness is the nutritional status of the child (Table 3). The interaction between nutrition and infection is complex. Diarrheal illnesses have long been associated with nutritional insults in children, and early longitudinal studies indicated that each infection can compromise a child’s ability to maintain his position on the growth curve. Conversely, malnutrition appears to be a major determinant of severe and fatal diarrhea. A critical question for public health has been to explain why children in developing countries in whom diarrhea develops die from their disease while children in industrialized countries do not. Nutritional status appears to be the principal risk factor to explain this difference. A recent review of studies examining diarrheal mortality by nutritional status found that in all studies, the risk of fatal diarrhea increased up significantly with a decrease in the nutritional status of the child. Based on this collection of studies, it has been estimated that as much as half of the diarrheal mortality could be averted if the nutritional status of children could be improved.

Malnutrition can take many forms. Children who have inadequate food intake and a low weight for age may simply not have enough residual to survive a severe dehydrating diarrhea in which they lose 1 L of fluid in 24 hours. Alternatively, these children can have micronutrient malnutrition due to deficits of zinc, vitamin A, or other micronutrients that can predispose them to more severe disease. The role of zinc has become a major focus of attention because preliminary field trials suggest that supplementing malnourished children with zinc can lower their risk of death from diarrhea and other infections. Because zinc is a component of more than 100 enzymes in the body including some central to developing a proper immune response, some researchers have suggested that zinc alone may be the magic bullet that could decrease the severity of diarrhea among children in developing countries. This hypothesis is currently being tested in large-scale field trials. The results could alter our current understanding and approach to the prevention of severe and fatal enteric infections in children.

PRESENTATION OF GASTROINTESTINAL INFECTIONS

Gastrointestinal infections can present as many different syndromes, from the acute diarrheal events to dysentery—the passing of stool with blood and mucous—to
chronic diarrhea lasting more than 2 weeks. Each of these extracts its toll and the distribution of these events varies greatly by setting. Both chronic diarrhea and dysentery, when present, are particularly severe leading both to prolonged nutritional loss, invasive disease with marked cytokine responses, and more severe sequelae. Some acute diarrheal diseases can cause chronic or distant pathology as well. Some campylobacter infections have been associated with Guillain Barré syndrome. Escherichia coli O157 infections have been linked to the hemolytic-uremic syndrome, and amebiasis can lead to liver abscesses, while diarrhea and dysentery are most common.

TREATMENT

Over the past two decades, the estimates of the number of children dying of diarrheal illnesses in developing countries have been reduced dramatically. While this observation has been made in many surveys of the literature, the methods used to arrive at this conclusion are weak and the explanations uncertain. One explanation posited to have made the greatest impact on the reduction in diarrheal deaths has been the globalization of the Diarrheal Disease Control Program of WHO that promotes the use of oral rehydration therapy (ORT). Global efforts have brought ORT to more than 50% of mothers in the developing world. The impact of this should clearly be to decrease the severity of diarrheal illness in children and reduction in the number of deaths and hospitalizations. The WHO claims that nearly one million deaths per year are prevented with ORT by mothers and clinics. In fact, while this is possible, it remains difficult to prove. What is evident in the United States is that the number of diarrheal deaths has been reduced greatly between 1970 and 1985, suggesting that the management of cases and the access to patients has likely played a role. Since 1985, neither the number of diarrheal deaths nor hospitalizations have declined.

CONCLUSION

In conclusion, the past two decades have witnessed major improvements in our understanding of the agents of diarrhea, their modes of transmission, and interventions, including a global program to provide Oral Rehydration Therapy to prevent severe and fatal cases of diarrhea. These have led to a substantial decrease in the estimated numbers of diarrheal deaths worldwide. At the same time, diarrhea still ranks as the number two cause of death among children in developing countries, responsible for 20% to 25% of all deaths among those <5 years of age with approximately 2.5 million deaths per year. Much work remains to improve these estimates and identify additional interventions to decrease this continuing burden among children including interventions targeting childhood nutritional deficiencies, the introduction of vaccines for rotavirus, and infrastructure changes that will ensure food and water free of fecal contaminants and enteric pathogens.
REFERENCES


DISCUSSION

Dr. George A. Bray: A very interesting presentation for those of us who don’t deal with diarrheal diseases, except in our own grandchildren. The one we hear about most in the US is E. coli O157. Is that something that occurs elsewhere in the world or is that just a meat-processing problem that we pick up in the developed countries as opposed to the underdeveloped ones?

Dr. Roger Glass: George, I think it’s an interesting question, because when I came from the bacterial enterics group at CDC, we spent most of our time studying salmonella, which was the result of the food processing industry where millions of chickens are produced in
high-rise apartments and the chickens on the 10th floor poop on the chickens on the 9th floor, on the chickens on the 8th floor etc., and you can imagine you only have to introduce 1 salmonella to have it amplified into a million chickens, and so our chickens are uniformly contaminated. In Bangladesh, every family has its own 2 or 3 chickens and if a single chicken has an epidemic of salmonella, it never spreads beyond the chickens of that family or the next family. I think the E. coli O157 is a similar problem. The bugs occur worldwide, just like salmonella does, but the ability to amplify them as an emerging pathogen through animal husbandry, through mixing of meat. Remember that the original E. coli O157 outbreak was called The Big Mac Attack. It occurred in a McDonald’s outlet, because hamburger was processed centrally and became contaminated and was distributed, and then it was also rapidly propagated, because those contaminated hamburgers were served at lunchtime on grills that were busy. The hamburgers that were infectious were those hamburgers then placed on the outside of the grill that never reached the proper temperature to decontaminate. So I think that a lot of the problems we have in the United States with diarrheal diseases are emerging pathogens, because of food processing and the way we handle our foods, just like the problems we have with new pathogens like cyclospora that come in from foods produced in developing countries, where sewage can be used to irrigate raspberries and other crops. The bugs are worldwide, but their importance is a function of how we treat our foods and hygiene and where it comes from.

Dr. Anne Ballinger: I wanted to ask 2 questions. Firstly, are the benefits of zinc supplementa-
tion only seen in children who are zinc deficient or do normal zinc levels in zinc supplementa-
tion also have a benefit? And secondly, what’s the mechanism of zinc in decreasing morbidity
and mortality?

Dr. Roger Glass: Anne, I appreciate your question. I’m here among nutritionists and gastro-
enterologists who know a lot more about zinc than I do. To my understanding, it’s very hard
to measure background levels of zinc. In fact, by giving it and seeing the impact, you’re
measuring it as an assessment. Zinc, also to my understanding, affects over 100 enzymes in
the body, and I’m not aware of which system is specifically influenced. Perhaps someone
else who’s worked on zinc, maybe Dr. Molla could answer that one better than I could.

Dr. Eva Micskey: You didn’t mention probiotics at all in the prevention of diarrhea. Don’t
you trust them?

Dr. Roger Glass: I don’t have any experience with probiotics, so I’d love to learn more
about them. It’s clearly an area that’s received a lot of research. I just have no personal
experience in the diseases that I’ve dealt with. Perhaps others can address that better in the
coffee session.

Dr. Michael J.G. Farthing: Could I just briefly comment. I think the concept of probiotics
has been with us for at least a century, Pastor, Mechinikov, they’re all very interested. The
difficulty is that I don’t see a lot of data, hard data that would support widespread implementa-
tion. I think there are some one, or two, or three good studies that suggest an impact. If
you’ve got some new information that probiotics are good for the prevention of acute and
persistent diarrheal disease, then I think it would be very useful to air it at this workshop,
but I think the difficulty is that the evidence is at the moment uncertain.

Dr. Wolf Endres: There are a lot of studies using probiotics, lactobacilli and bifidobacteria
in the prevention and therapy of diarrheal diseases. Concerning therapy of diarrhea, there has
been an impressive ESPGHAN study carried out in 11 cities from 10 countries showing
beneficial effects of Lactobacillus GG (1). There are also studies published by Saavedra et
al. (2-3) and Chouraqui et al. (4) using Bifidobacterium lactis and Streptococcus thermophilus
which demonstrate preventive effects in infants and young children with respect to diarrhea, diaper rash and constipation.

Dr. Mohammed Juffrie: If your strategy to reduce the morbidity of diarrhea is vaccine, could you give me information about the rotavirus vaccine?

Dr. Roger Glass: The first rotavirus vaccine was licensed in the United States in 1998. Nearly a million children were immunized in the first 9 months, about 20% coverage of US children, and then intussusception was identified as a rare complication. The result was that vaccine, after lots of study, was removed, and we’re still unclear about the rate of intussusception following vaccination, whether natural rotavirus causes intussusception or what the attributable risk really would be in the United States, or would have been in developing countries. That vaccine and the company behind it have disappeared. Currently, both Merck and Glaxo, and Smith Kline are testing vaccines in South America, The United States and Europe, and there’s a vaccine that’s licensed for rotavirus in China and vaccines under development here in India and Indonesia. All of these are live oral vaccines. They would be given in multiple doses to children at the time of their routine childhood immunization. And the hope is that these will protect against severe rotavirus disease, which is responsible for a 1/4 to 1/5th of total diarrheal mortality. Like many other viral diseases of children, this is a universal infection. We call it a democratic disease, because it affects rich and poor, blacks and whites, everyone and so it’s a vaccine that would have a market world-wide. Our hope is that within 5 years we would have new rotavirus vaccines and they would enter immunization programs.

Dr. Marcello Giovannini: From your experience, what do you know about exclusive vaccination exposed to the risks of basic dehydration in the first weeks of life?

What is the risk of this dehydration in the first two weeks of life with exclusive breastfeeding? What kind of measures are to be adopted to prevent this problem?

Dr. Roger Glass: You know, you’re asking me a good question, and I’m really not a neonatologist. I don’t have experience of this. In fact, in the United States, we define diarrhea by code only after the first month of life, so I defer to a neonatologist.

Dr. Mirdula Chatterjee: Actually we have conducted one study on the incidence of diarrheal disease and have taken certain factors like the function of safe drinking water, the social-economic status of the family, the habit of filtration and the literacy rate of the mother, and we found that the last factor, that is the literacy rate of the mother, is the most important one. Given the other factors constant, if the literacy rate of the mother is high, the incidence of diarrheal disease is low and visa-versa.

Dr. Roger Glass: We spotted that because we’ve done studies in the United States when I came back from Bangladesh. We asked the question, why do American children die of diarrhea? We live in a country with clean water and clean food and access to care. Who are the children who die? And we found that the number one risk factor for an American child dying of diarrhea was to have a mother who is under 20, who had not finished high school, who is alone and unmarried. So they’re basically women who don’t have either mother-craft skills or the bottom of the educational literacy level. It’s a nice parallel to your study, but in the United States.

Dr. George Fuchs: I was just going to comment on the question of why do breastfed children, any of them, have malnutrition or diarrhea in the first two weeks of life, and I think it’s probably a question of definition. If you look at the children, who are supposedly breastfeeding and have diarrheal disease the first two weeks of life, they’re not generally exclusively breastfeeding, and other non-breast milk, foods, or even water, are introduced and so their exposure to pathogens is actually increased.

Dr. Deba Prasad Banerjee: Since you have worked a lot on rotavirus diarrhea, I would
like to know what was the average duration of diarrhea in those cases and how was the response to ORS in these cases?

*Dr. Roger Glass:* The duration in rotavirus in these cases can be from 3-7 days duration and these children do respond to ORS. They can be treated, even if they vomit, but I think a main cause of mothers not pushing ORS is that the children will vomit, but the volume of vomit is supposed to be low and this explains why mothers don't persist. I think in a health care facility, you can still rehydrate these children orally.

*Dr. S. K. Mittal:* When considering this identification of low birth weight in young infants as the high risk factor in diarrheal disease, should we not change our strategy for management of diarrheal diseases in this age group from just fluid and nutrition to the control of systemic infection, early detection and management of the stomach infection? This seems to be the major cause of death in this young age.

*Dr. Roger Glass:* That's a really good question. My wife's a neonatologist, so I'm very interested in what happens to low birth weight infants and young infants. It seems now that as global infant mortality has come down, that fraction that is due to neonatal mortality has increased, and about half of infant mortality is now in the neonatal period. Interventions to stop mortality in this age group have not really been well worked out. We spent a lot of time in the post-neonatal period, but not much in the neonatal period or in the low birth weight infant, so I think that we need special strategies and that's got to be tackled head on. I don't think we have adequate strategies right now.

*Dr. Chun-Yan Yeung:* In our country, salmonella remains the major pathogen in bacterial enterocolitis and more than half of them have resistance to first line antibiotics such as Ampicillin, Chloramphenicol and Trimethoprim & sulfamethoxazole. Last year we encountered about 6 strains with resistance to the third generation cephalosporins, Ceftriaxone. And in another hospital there were strains with resistance to Ciprofloxacine. I would like to know what the situation is in your country and for you to comment if you have to use antibiotics. In the cases of Salmonella gastroenteritis, what antibiotics do you prefer, if you have to decide before the antibiotics susceptibility is available? And what is the resistant rate in your country and in other countries?

*Dr. Rogers Glass:* For the diarrheal diseases, we generally don't use antibiotics at all, even for salmonella, unless it's a shigella dysentery or unless we find a parasite, an amoeba or giardia. So I'm not sure that's an issue.

*Dr. Chun-Yan Yeung:* Yes, I agree with you that in most cases we don't need antibiotics, but in some cases with invasive infections such as septicemia or GI tract perforation, we have to use them. So if you have to use them, which kind of antibiotics would you prefer to use as the first line antibiotics?

*Dr. Roger Glass:* I don't think I'm really qualified to respond to that one here, because I think it really depends upon the condition, the choice, the sensitivity and the profile in your hospital. In the US, we have hospital infection committees, which monitor antibiotic uses and control the antibiotics that are distributed, so it's a whole different set of activities. I don't think I have a proper response for that.

*Dr. Y. K. Amdekar:* I think in many developing countries the cultural factors can be . . . of the professionals and the contribution of industry causes the perpetuation of diarrhea. For example there's a culture of starving children with diarrhea. There is a professional practice of over-use of antibiotics fueled by the fear that the bacterial infections are more common in developing countries and the industrial contribution would be probiotics, among which, any of the Lactobacilli is arguably the best. I think there are other factors, which should concern
us about perpetuating diarrheas, leading to recurrent or persistent or chronic malnourishing diarrheas.

Dr. Roger Glass: That is a really good point, and I think that point underscores the need to feed during diarrhea, which has been a major change in thinking over the last 15-20 years, that you feed children and don't starve them and withhold antibiotics, except in those cases of dysentery. So I think there are areas of improved management of diarrhea that we can implement right now to decrease the severity of mortality.

Dr. Abdul Majid Molla: Most of the etiology of acute diarrhea has been worked out in the developing countries. For the developed countries, like yours, what is the situation of the non-infectious etiology of acute diarrhea? By that I mean acute diarrhea in children due to allergy, any food allergy or diarrhea caused by the overuse of antibiotics.

Dr. Roger Glass: Twenty-five years ago we thought that most diarrheas were due to food allergies, weanling foods, idiopathic causes, malnutrition, we didn't know what they were. Now our group has really been looking for 15 years at new viruses to fill in the pie diagram, and to date we can fill in most of the pie diagram segment with infectious agents, so that the segment remaining to be filled in with allergies, foods or antibiotics is really relatively limited. I don't know the fraction for that, but I know in the community diarrheas, it would be relatively small.

Dr. M.K.C. Nair: In India we have developed a lot of expedients managing diarrhea with ORS, and wherever the program has been done properly and successfully, the results have been extremely good. In hospital-settings where mortality was very high, now you don't even have one per year that particularly related to diarrhea dehydration. Similar good success stories exist all over India, although as a country, we have not achieved that much. Number two, the high risk group of low birth weight babies has not got attention and that probably needs a slightly different strategy, as we need to look particularly at the nutritional aspect in that group. Number three, we may have a different group with the immunodeficiency becoming a problem, so there may be a smaller group, where you need to develop a third strategy.

Dr. Roger Glass: I think the advances in India in treating diarrheal disease have been enormous within the hospitals and the challenge is to convey these lessons to children, who don't make it into health care, and to identify who fails. There have been studies of doing verbal autopsies to try to identify, and we've tried these in the United States as well, to identify a child who dies of diarrhea and figure out where in the process of the illness things went wrong. In fact, we found in American Indians who have had a high mortality from diarrheal diseases that 90% of them, go to a physician before they die. So it's not access to care, but rather the care that they're given after that first interaction or their willingness to come back, if they're severe. So I think the challenge is really to figure out who fails and how to extend services beyond the clinics in the health care setting.

Dr. Michael J.G. Farthing: Roger, just a quick question about rotavirus vaccine. You were quite upbeat that within 5 to 6 years we're going to have a vaccine that's going to be useful worldwide. I just want to challenge that. We had a rotavirus vaccine that was working in a number of countries in the developing world that seems to have faltered in the USA and I have two questions. One you know: are we going to be able to sustain a vaccine development strategy that is going get a useful vaccine that's going to work worldwide or are well-nourished children in the developed world going to always, if you like, "overreact" to these vaccines? Then, in the same way that we've got different vaccine strategies for oral Polio for the developed and the developing world, are we going to have to rethink the whole strategy with rotavirus vaccine? Now I have to say that I'm less optimistic than you.

Dr. Roger Glass: Michael, I think the global strategy is that the vaccines being made now
in China, India, Indonesia are being developed in those countries as well as by multi-nationals. About half the children who die of diarrhea die in China, India, Indonesia and the same countries, so our hope is that in 5 to 7 years, those vaccines will be available for children in the countries, which have half the mortality. Also, by having a strategy of multiple vaccines in the process of development, should we have a glitch in the development process like we had with intussusception, which was entirely unexpected, we won’t have a 5-year delay, before the next vaccine comes forward. So I’m optimistic on several fronts. I’m optimistic, because the first vaccines demonstrated that live oral vaccines could really work to protect against rotavirus and were easily implemented, showing that live orals are good. I’m also optimistic, because we don’t have a single candidate going forward, but we have at least 5 that are in the development process so they can be available. And I’m optimistic that in the time frame of 5 to 7 years we will have something to use in a global strategy. But we’ll see. We can have a meeting on that, Michael. That’s one of our ideas for 7 years, okay?

Dr. Narendra Kumar Arora: If I can ask the last question and this is again about rotavirus. As we understand, it is the fecal contamination of food and water, which spurs on the diarrheal disease. Yet, while the availability of clean, portable water and environmental hygiene have improved in developing countries, why does rotavirus still exist even in developed countries, where 1 to 2 diarrheal episodes per child per year are occurring?

Dr. Roger Glass: I think that’s a wonderful issue in epidemiology. Most of those bacterial pathogens and parasitic pathogens are spread by food- and water- borne transmission. They’re in contaminated food and contaminated water and it’s through the control of improvements in food and water that you can get rid of them. For the viruses, we really don’t know how they are spread. We know they’re spread by contact, person to person contact. They might be spread by air-borne droplets, because they have a winter seasonality. We don’t really know how they are spread, but the fact that they affect children in the United States and in European countries, even in Chile, suggests that improvements in food and water are not going to make a difference and that’s why we are really looking for vaccines as a way to protect and prevent against these diseases.

REFERENCES