THE EPIDEMIOLOGIC BASIS OF CHOLERA CONTROL[1]

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It is vitally important that cholera control programs emphasize optimum treatment of cases, surveillance, and identification of transmission pathways by epidemiologic investigation. This position is persuasively supported by the following detailed review of past research, recent experience, and commonly used control measures.

Introduction

In virtually all newly-infected countries excessive control measures are adopted, largely because the medical profession and the public are unprepared for the emergency. Information that is misleading and often erroneous is conveyed by health and lay authorities to the news media, and this information may in turn be further distorted as it is conveyed to the public. This causes people at all levels to overreact, a situation that has been aptly referred to as "cholera hysteria," and in some cases panic may ensue. The press becomes critical and even hostile, further complicating the situation. In such an atmosphere measures are often taken that are unnecessary, expensive, and even counterproductive. Therefore, to understand which measures are appropriate and which are not, it is important that health authorities and all members of the medical profession be familiar with cholera.

How Is Cholera Transmitted?

The Discoveries of Pacini and Snow

Cholera occupies a unique position in the history of bacteriology and epidemiology. Three decades before Robert Koch isolated *Vibrio cholerae* in 1883, Filippo Pacini, the famous Italian anatomist, published the first description of the etiologic agent of cholera and was the first to use the name *Vibrio cholerae.* The organism is host-specific for man; i.e., there is no known reservoir except man.

In the same year that Pacini published his work another significant contribution was made by Dr. John Snow, an English anesthesiologist who studied cholera in London. It is relevant in 1974 to note what John Snow wrote about cholera in 1854; for he recorded his observations with great precision, lucidly and persuasively describing his conclusions in a classic study that marks the beginning of the science of epidemiology (*Snow on Cholera,* 1936).

London, at that time, was a congested city with juxtaposed houses whose water was provided by two competing companies. Snow described the setting:

"The pipes of each company go down all streets and enter nearly all quarters and alleys. A few houses are supplied by one company and a few by the other according to the decision of the owner or occupier at that time when the water companies were in active competition. In many cases a single house has a supply different from that on either side. Each company supplies both rich and poor, both large houses and small, there is no difference either in the conditions or occupation of the person receiving water from different companies. As there is no difference whatever, either in the houses or the people receiving the supply of the two water companies or in any of the physical conditions with which they are surrounded, it is obvious that no experiment could have been

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devised which would more thoroughly test the effect of water supply on the progress of cholera than this which circumstances placed ready made before the observer. The experiment too was on the grandest scale. No fewer than 300,000 people of both sexes, of every age and occupation, and of every rank and station from gentle folks down to the very poor were divided into two groups without their choice and in most cases without their knowledge; one group being supplied with water containing the sewage of London and amongst it whatever might have come from cholera patients, the other group having water quite free from such impurity."

Snow then demonstrated that the cholera death rate was six times higher among persons who used the impure water of the Southwalk and Vauxhall Company than among those who used the purer water of the Lambeth Company (see Table 1).

As a result of this investigation, Snow recommended a highly specific control measure, the removal of the Broad Street Pump. This latter event was of great importance to the science of epidemiology, not only because it clearly demonstrated that water was a vehicle of cholera transmission, but also because it showed so dramatically that a very simple, inexpensive, and highly specific control measure—removal of a pump handle—could play a key part in epidemic control if it were based upon careful epidemiologic investigation.

John Snow is remembered primarily for these observations, but it is not generally appreciated that he made an equally important observation that tells us how cholera is *not* transmitted. He wrote: "These houses (supplied by the Lambeth Company) although intimately mixed with those of the Southwalk and Vauxhall Company which experienced such a great mortality, did not suffer even so much as the rest of London." This simple astute observation indicates that Snow recognized that person-to-person or contact transmission does not play an important role in the spread of cholera.

As a result of Snow's work, which has been corroborated on many occasions, but to which little has been added, we have come to recognize two types of epidemic situations; namely, the explosive and the protracted types.

Typically, an explosive epidemic and its connection with a common source or common vehicle are easily recognized. In this situation a large number of cases appear in a community over a short period of time. This was the type of epidemic Snow described.

However, sometimes cholera presents a more protracted pattern, with only a few cases per day or per week for several weeks. It is tempting to dismiss these latter as representative of contact spread, but in fact whenever one studies such outbreaks one also finds that a common source, usually drinking water or water used in the marketing or processing of foods, is responsible. Careful investigation in affected communities often reveals numerous inapparent infections, occurring particularly in family groups exposed to common food and water supplies.

In the Philippine outbreak of 1961 both types of epidemic spread were reported (Joseph, P.R., *et al.*, 1965). The epidemic curve representing the outbreak in Israel in 1970 began with a protracted pattern and then assumed an explosive character; there is evi-

TABLE 1—Attack rates of cholera by district and by source of water supply.

	Population in 1851	Death by Cholera in 14 weeks ending 14 October	Deaths per 10,000 living
Houses supplied by the Southwalk and Vauxhall Co.	266,516	4,093	153
Houses supplied by the Lambeth Co.	173,748	461	26

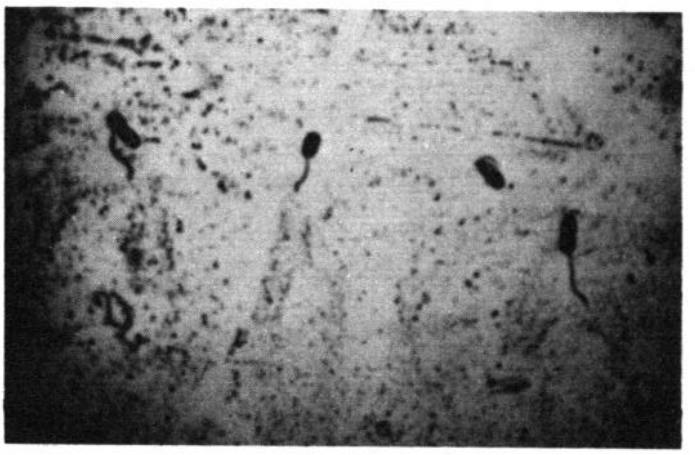
$X^2 = 1{,}658; p < .00001$.
Source: John Snow, *Snow on Cholera* (*12*).

dence supporting the conclusion that transmission via ingestion of raw leafy vegetables was responsible for this outbreak (Cohen, *et al.*, 1971). In 1971 a large explosive outbreak occurred in Istanbul; that was traced to contamination of part of the city's drinking water (Akyol, 1971). The Italian epidemic of 1973 was caused by the use of contaminated water to "freshen" shellfish; that epidemic was also explosive in character (Baine, *et al.*, 1973). In each of these outbreaks drinking water or water used in the marketing of seafoods and leafy vegetables was incriminated, pointing up the central role of water in transmission and the continued validity of Snow's conclusions after 120 years.

There has been a striking absence of any data that prove or even suggest that person-to-person or contact spread is of any importance in transmitting cholera, although in every newly infected country exaggerated fear of such transmission has shown up clearly in the control measures adopted.

Research Developments

Clinical studies conducted with volunteers at the University of Maryland help explain why cholera transmission is so uniquely dependent upon water and why contact transmission does not occur under ordinary circumstances. Table 2 summarizes data collected in a series of experiments over a ten-year period (Dupont and Hornick, 1973). It compares the infecting doses of major enteric pathogens that are needed to cause disease. Note that *V. cholerae* requires the highest inoculum, 4 logs higher than *Salmonella typhi* and 7 logs higher than *Shigella* Spp. The table also correlates the type of transmission with inoculum size. The enteric infections that depend upon large doses to cause disease are transmitted by water, in contrast to the contact spread that is the usual but not exclusive means of transmission of enteric pathogens capable of causing disease in low doses.



Cholera is caused by intestinal infection with *V. cholerae*, a mobile, rod-shaped, gram-negative bacteria with a single polar flagellum. This photomicrograph shows several *V. cholerae* obtained in an intestinal biopsy from a cholera patient.

Hornick and his colleagues demonstrated that a major determinant of the inoculum size required is the subject's gastric acid (Hornick, *et al.*, 1971). Neutralization of gastric acid by $NaHCO_3$ markedly reduced the dose of *V. cholerae* needed to cause disease. This observation underscores the validity of epidemiologic data collected in Israel, and more recently in Italy, showing that persons with prior gastric surgery are particularly susceptible to cholera. The same principle applies generally to other enteric diseases.

TABLE 2–Infecting dosages and modes of transmission of the bacteria responsible for principal enteric diseases.

Etiologic agents	Approximate dose (No. of organisms) required to cause disease	Type of transmission
Vibrio cholerae	10^9	Water (food)
Salmonella typhi	10^5	Water (food)
Salmonella typhimurium	10^{3-4}	Contact, water, or food
Shigella Spp.	10^2	Contact, water, or food

This picture from the Indian subcontinent shows relatives of a patient suffering from cholera gravis. Rectal cultures have shown all of them to be infected with *V. cholerae*, but all have only mild diarrhea or are completely asymptomatic. Infection with the El Tor strain of *V. cholerae* typically produces many hard-to-diagnose cases of this kind.

These clinical and epidemiologic studies demonstrate that cholera is not a highly contagious disease, a point that has important implications for determining which control measures are appropriate and which are not.

In addition to man's natural gastric acid defense barrier, nature has provided him with others that are equally important. It is well-known that bacteria normally inhabiting our intestinal tract create an important barrier by a variety of mechanisms collectively referred to as bacterial antagonism. Studies have shown that one way of predisposing animals to cholera is to give them an antibiotic drug that will eliminate their intestinal flora. Animals thus pre-treated with an antibiotic and allowed to excrete it are more susceptible to a cholera challenge than animals untreated with antibiotics (Freter, 1955). Although the relevance of this observation to man is unclear, these data have obvious implications for use of chemoprophylaxis as a control measure, a point we will deal with later.

Still another natural defense is normal intestinal motility, which acts as a cleansing mechanism. Recent studies conducted by Dupont and Hornick (1973) have demonstrated very clearly that drugs which inhibit normal intestinal peristalsis have deleterious effects. These workers showed that diphenoxylate (Lomotil®), a synthetic opiate-like drug, delays the recovery of shigellosis patients even when appropriate antibiotics are given. Other workers have reported the occasional occurrence of salmonella bacteremia when patients with gastroenteritis are treated with opiates (Sprinz, 1969). Moreover, animals treated with opiates are much more susceptible to a variety of enteric pathogens than are untreated controls. The message is clear: diarrhea is nature's attempt to clear the intestine of noxious and harmful agents; it is a protective mechanism that prevents the localization and multiplication of pathogens in the intestine.

Should Cholera Patients be Isolated?

The studies cited above illustrate that cholera is not a highly contagious disease. Moreover, if it is treated as a highly contagious disease an

erroneous impression is created that reinforces the dread and fear often accompanying cholera epidemics, thereby contributing to cholera hysteria.

Cholera patients should be managed like typhoid patients. Any hospital that cares for typhoid patients should be able to treat cholera patients. Normal enteric precautions are of course indicated, but it is unnecessary and undesirable to confine or isolate cholera patients in a hospital ward, and to use masks (as if respiratory spread were possible) or gloves (as if the patient were infectious to the touch). It is an established fact that physicians, nurses, attendants, laboratory workers, and others who come in close personal contact with cholera patients and their excreta are not in jeopardy if handwashing and careful disposition of the patients' excreta are enforced.

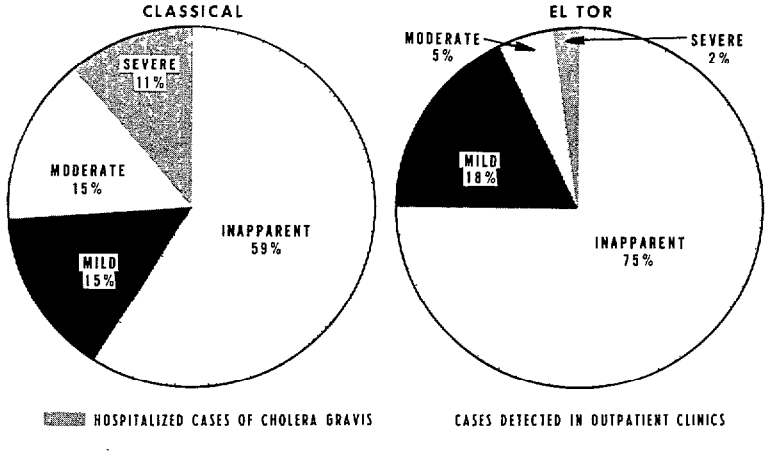
Is Quarantine Appropriate?

Quarantine has been used to varying degrees by many countries in the current pandemic. Iran and Russia tried to contain cholera with military quarantines, initially on their borders and subsequently around infected areas. There is good evidence that such drastic measures accomplish nothing and only contribute to the cholera hysteria.

One may find the reasons why by analyzing the clinical spectrum of cholera. Figure 1 shows that in contrast to people infected with the classical cholera vibrio, only a small percentage of those infected with the El Tor vibrio will present clinical features readily distinguishable as cholera. The diagnosis of such overt cases is relatively easy; but infection with the El Tor vibrio more often (about 75 per cent of the time) causes no symptoms or is so mild (about 18 per cent of the time) that it cannot be readily differentiated from other acute enteric illnesses. The case-to-infection ratio in classical cholera is about 1:7; in contrast there may be 25, 50, or even 100 mild or asymptomatic infections in the community for each severe El Tor case.

These asymptomatic persons, some of whom may be incubating the disease, and other persons with mild symptoms, may travel and take the disease with them, thus establishing new foci. Unfortunately, there is no practical way to intercept or detect such carriers. The cycle of transmission is completed when the vibrios shed by these carriers find their way to water that is used for drinking purposes or used to "freshen" other foods that are not customarily cooked, such as vegetables (as in Israel) or seafood (as in Italy). So by the time the first

FIGURE 1—Clinical spectra of El Tor and classical cholera, showing the percentage distribution of symptoms for individuals infected with each type.



indigenous cases are recognized there are often numerous excretors, not only in the immediate community, but also in other communities that have had economic and social intercourse with the overtly affected one.

Thus, quarantine doesn't work; quarantine represents the proverbial situation of closing the barn door after the horse has run away. Quarantine has been attempted in many countries in this and previous pandemics, and there is no evidence that it has ever been successful in containing cholera. In fact, there is abundant evidence of quarantine failure, inasmuch as costly economic consequences and social upheaval have been apparent whenever it has been used.

It should be also noted that vibrios will not survive when dried; thus fomites (that is, inanimate objects) are not important in transmission; and for this reason there is no epidemiologic evidence to support the measures that are often taken to prohibit the movement of a variety of goods within a country or from one country to another.

What is the Appropriate Role of Vaccine in a Cholera Control Program?

Cholera vaccine is of low potency and the limited protection induced by vaccine is of short duration. Proponents of the vaccine usually cite two reasons for its use as a control measure: first, its use is supported by public opinion; and second, even if the vaccine provides only 50 to 60 per cent protection, that protection is worth the effort needed for its administration.

Most students of this disease take exception to these arguments. Our own position is that an *informed* public and medical profession will not demand vaccine when they are given the facts concerning its limitations. Emphasis is on the word "informed" because the public appeal of the vaccine is greatly influenced by the mass media. If the press gives the public the impression that vaccination is the answer to cholera control, as has happened repeatedly, the public will understandably panic when it finds that vaccine is not available in what is likely to be interpreted as a life-or-death situation.

With regard to vaccine efficacy, the 50 to 60 per cent levels of protection reported in controlled field trials should not be taken at face value. These trials were conducted under circumstances that are not applicable to newly or recently infected areas. That is, the vaccines were tested in populations with high levels of natural immunity, in which vaccine-induced immunity was further reinforced by abundant current transmission. Moreover, such field tests have been conducted using vaccines of optimal potency. Under these most favorable circumstances vaccine-induced immunity is indeed achieved about 50-60 per cent of the time; but there are no data on the effectiveness of cholera vaccine in newly infected areas (where the populations may be regarded as virgin with respect to cholera immunity) and in situations where unselected vaccines are employed.

A recent study sponsored by the World Health Organization showed most vaccines to have low potency and some to have no measurable potency.[3] Moreover, in some countries vaccine has been produced that was highly reactive and difficult to deliver because of increased viscosity. Thus, in newly infected areas the effectiveness of the vaccine is likely to be considerably less than the levels of protection achieved in field trials.

In addition to the limited effectiveness of currently available vaccines in disease prevention, it is important to emphasize that cholera vaccine does not prevent transmission of the organism or eliminate the carrier state. Although the vaccine does not carry a risk of serious reactions, almost all who receive it will develop a sore arm, and some will develop mild to moderate constitutional symptoms—such as malaise, generalized aches, and slight fever—lasting 24 to 48 hours and often requiring absence from work. Finally, and most distressing of all, administration of the vaccine conveys a false sense of security to those who receive it and may inadvertently encourage consumption of unsafe food or water; it also

[3]WHO Document BD/Cholera 71.5.

conveys a false sense of accomplishment to those who administer it.

Nevertheless, there may be some members of the community who insist upon receiving vaccine. The vaccine should not be denied those who insist upon receiving it, but such demand should be met through existing health delivery systems, while public health authorities address themselves to more productive and meaningful tasks.

There is good evidence that the administration of antimicrobial agents, particularly tetracycline, can prevent cholera in households where a cholera case has occurred (McCormack, *et al.*, 1968). But in the community at large, as contrasted with the infected household, individual risk of acquiring the disease is much lower, considerably harder to define, and generally spread over a longer period of time. Thus it may be necessary to treat between 200 and 500 persons to prevent a single case, whereas in an infected household prophylaxis of ten persons or less will achieve the same results. Under these circumstances, one needs to carefully weigh the possible benefits from reduced cholera morbidity against the cost in money and the risk of adverse drug reactions which might result from mass chemoprophylaxis.

The limited scientific evidence that is available appears to cast serious doubt on the likelihood that net benefit would accrue. The long-acting sulfonamide sulfadoxine (Fanasil), which is given in a single dose, has been advocated for such use (Lepeyssonie, 1971) and has been widely employed, particularly in some West African countries. Despite the claims of its proponents, however, evidence from other areas raises considerable doubt about the suitability of this drug—because of the development of sulfonamide resistance, the relatively low efficacy of this drug as compared to others in clinical trials, and the uncommon but serious desquamating skin reactions that may occur. Mass chemoprophylaxis with chloramphenicol was employed in Iran in 1965 in a desperate but futile attempt to contain the disease, and tetracyclines have been extensively used in other countries with results that were questionable at best.

In general, where mass chemoprophylaxis has been employed as a cholera control measure, persons sometimes receive excessive doses of the drugs used—either because of popular misconceptions (if one dose is good, ten must be better) or because of multiple visits to different health facilities that cannot be cross-checked. No one can deny the danger of such indiscriminate drug use, especially when such potentially dangerous compounds as long-acting sulfa drugs and chloramphenicol are administered without close supervision. There is also the risk that tetracycline or related drugs may be administered to persons suffering from kidney failure, to pregnant women, to children, etc. Finally, there is the real possibility, as noted earlier, that elimination of the normal bowel flora may encourage superinfection, not only with vibrios but with other enteric pathogens as well. Considering these dangers in addition to the difficulties of administering such a program, justification of mass chemoprophylaxis is difficult indeed.

What Control Measures Are Appropriate?

The key to a successful control program is surveillance. The term surveillance means different things to different people; but in public health it usually means the continuous appraisal of the status of a disease in a community, based upon an analysis of information on the occurrence of cases of that disease. Surveillance is essential to a cholera program because it gives meaningful direction to public health efforts. That is, it consists of systematic reporting and investigation of cases and analysis of the data obtained in order to provide a basis for action. The success of a surveillance program in a community will depend on both the reporting of disease cases and the investigation of those cases, especially ones which are clustered.

Three essential factors influence reporting—the attitudes of health authorities toward cholera, the availability and reputation of treatment facilities, and the efficiency of laboratory services.

Reporting is greatly inhibited if repressive measures are taken when cases are identified.

Repressive measures can take many forms, such as quarantining of a family, hospital, community, or area; imposing a military cordon; or restricting movement of people or goods into or out of infected areas.

Measures that limit the movement of people or compromise the economy of an area by indiscriminate restrictions on shipments of goods or foods are never necessary. Such measures contribute to hysteria among the people and perpetuate misconceptions regarding the severity, infectivity, and spread of the disease. In so doing, they tend to hinder surveillance by discouraging the reporting of cases.

The first priority in controlling cholera is to save lives. Fear and even panic grip communities where cholera deaths occur. If cases can be recognized promptly and proper treatment instituted without delay, fear will abate and families will not be reluctant to report their cases. As already noted, modern treatment with intravenous and oral fluids should insure survival in over 99 per cent of all cases, including those of children and pregnant women. For these reasons one of the best investments in cholera control is for health and lay authorities to establish the logistics necessary to insure that all suspect cases are promptly accommodated in optimum treatment facilities.

Treatment centers should not be quarantined. Reluctance to report cases and fear of the disease can be overcome by permitting one or a few parents or relatives free access to visit patients. In pediatric cases, one parent or relative should be permitted to stay with the patient to assist in oral fluid treatment and nursing. These measures are important because they emphasize the basically benign nature of the disease and dispel fears that it will be transmitted by contact.

Cases may be missed if physicians do not have or do not use the laboratory facilities available in a community. Laboratory diagnosis is not important for the clinical management of cholera patients, but it is essential for surveillance. All cases of diarrheal disease in a cholera epidemic or in a cholera-threatened area should be cultured. Where laboratory facilities are not readily available, any one of a variety of cholera transport media (or simple blotting paper immersed in stool) should be employed to transport specimens to the laboratory. Community surveillance—by the systematic sampling of sewage using the Moore swab technique—is strongly recommended for all areas threatened by cholera or actually infected (Moore, 1948).

Prompt investigation of all cases is essential to an effective surveillance program. These investigations should be conducted by health workers who are thoroughly familiar with the epidemiologic concepts of time, place, and person. Past experience has shown the results of such investigations to be extremely rewarding in terms of providing a basis for specific control measures. This point deserves special emphasis, because the specific control measures needed will vary in each outbreak, depending on the results of the investigations.

It should be stressed that surveillance involves a two-way flow of information. Those responsible for reporting cases need to know how their data are being used. This is best accomplished by issuing a surveillance report. Such a report need not be elaborate; a simple, brief, informative newsletter published weekly or monthly will help substantially in gaining the support and cooperation of physicians and health workers in the community. The inclusion of brief and timely anecdotes and vignettes concerning laboratory, clinical, and public health topics will enhance both the usefulness and interest of these reports.

Each autonomous area within a country should develop a surveillance system. The details of setting up such a system and other information about organization and logistics are provided by a chapter on surveillance (Gangarosa and Mosley, 1974) in *Cholera*, by Barua and Burrows. It is important to emphasize that existing medical channels should be maintained. However, local resources should be reinforced with staff and facilities from the central government during epidemics and epidemic investigations; and the Pan American Health Organization's resources and support for epidemic investigations should be fully utilized.

SUMMARY

This paper discusses an epidemiologic basis for cholera control. The reasons why newly infected countries often overreact in the emergency that arises in cholera epidemics are presented. The paper traces historically the development of rational control measures and identifies the significant clinical and epidemiologic studies that have been conducted in the current pandemic that relate to the question of how cholera is being transmitted. Finally, these points are interrelated in a critical review of commonly used cholera control measures.

This presentation emphasizes that it is inappropriate to isolate cholera patients in treatment facilities, indicates why quarantine and chemoprophylaxis are useless and even counter-productive, and shows why cholera vaccine has such limited value in containing a cholera epidemic.

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