V. EPIDEMIOLOGY OF CHOLERA

by

W.H. Mosley, M.D.
Chief, Epidemiology Section,
Pakistan-SEATO, Cholera Research Laboratory

Introduction

This lecture is not intended to be a comprehensive review of all aspects of the epidemiology of cholera but is meant to cover broadly both areas of knowledge and of ignorance in understanding this disease. It is my intention that this lecture will serve as a stimulus for subsequent discussion over the next few days, particularly as the problems of the control of the spread of cholera are considered. In this lecture, the epidemiological patterns of cholera will be taken up looking first at time, place, person, and then the role of water in transmission, the possibility of person to person spread by contact, the role of carriers and unrecognized cases and of fomites and a brief consideration of non-cholera vibrios or NAGS and the effectiveness and usefulness of cholera vaccines and antibiotics prophylaxis in the field.

1. Time

a. Seasonal pattern: Cholera, like essentially all other infectious diseases, will have a characteristic seasonal pattern. This has proven to be true for both endemic as well as epidemic cholera, however, the cholera season for any particular locality cannot be predicted but will only be defined by observation. In Dacca, East Pakistan, over the past three years, the cholera season has reached its peak at the end of the monsoon during the months of November, December and January and has disappeared as the hot dry months of March, April and May arrived. On the other hand, in Calcutta, 125 miles to the south, the cholera season characteristically rises to its peak during the hot dry season and ends with the monsoon rains. In the Philippines, the cholera season in some areas has tended to reach its peak with the rainy season. The cause of this seasonal appearance and disappearance of cholera is unknown.

The initial introduction of cholera into an un-infected area may occur at any time of the year but once the infection is established, seasonal recurrences of the disease are likely. For example, in Hong-Kong, the first epidemic was

from August through November 1961. Subsequently, there were no cases and no evidence of infection within the colony until the following year when there was a recurrence from August through October 1962. Again the disease seemingly disappeared only to recur from June through August 1963 and again from April through June 1964. It was of interest that in Hong-Kong extensive bacteriological sampling of nightsoil collections from all areas of the city between seasons were entirely negative, however, when cases began to appear in a few localities, nightsoil samples taken from most of the districts in the colony, were positive for V. cholerae (El Tor). Subsequently, with the disappearance of cases, the nightsoil samples were negative.

Even in the endemic area of East Pakistan, the seasonal pattern is quite distinct. For example, in our vaccine field trial area in Matlab Bazar in rural East Pakistan, during the peak of the cholera season in the months of December and January, there were over 150 cholera cases. Subsequently, during the months of May to September there were no cholera cases and an extensive rectal swab survey of all diarrhoea cases (4 000 per month) in a population of 60 000 over this five-month period, yielded no evidence of vibrio cholera. Thus endemic cholera, is actually characterized by recurrent epidemics with the virtual absence of cases between the epidemic seasons.

It is important to recognize this seasonal characteristic of the disease and realize that the waning of the disease may not be due to control measures but merely due to the seasonal pattern and furthermore, that a recurrent epidemic the following year is not unlikely.

b. The pattern of spread: Koch described two types of epidemics over seventy-five years ago: an explosive epidemic and a protracted one. The explosive epidemic is easily recognized and can usually clearly be related to as a common source or common vehicle. Classic illustrations are water in the Broad Street Pump epidemic, described by John Snow in London in the nineteenth century or food, such as the explosive epidemic in Negros Occidental, due to the ingestion of small raw shrimps described by Joseph and co-workers in the Philippines in 1962. Thus, whenever an explosive outbreak of cholera occurs with a large number of cases appearing in an area within one week, one should look for a common source of spread. This is usually almost invariably water or water related. A person to person spread of the disease will not produce

the explosive epidemic.

Cholera may also appear in a protracted pattern with only a few cases per day or per week or over several weeks. The mechanism of spread in this instance is not always well defined. In East Pakistan, this pattern of occurrence of cases has been shown also to be due primarily to transmission by water. In these instances, it is usually a large body of water such as a river, tank or canal, which, because of the dilution, has a low level of contamination and thus is only exposing the community to a relatively low dose which is only occasionally reaching a susceptible person and producing a case. This protracted pattern may also be due to "contact" spread, particularly where there may well be a large number of inapparent infections such as has been suggested with El Tor cholera in the Philippines or Hong-Kong, however, to-date, there has been no conclusive demonstration of "contact" spread of cholera.

c. Time of onset: Cholera characteristically has the onset of symptoms at night or in the early morning. The pathophysiology of these phenomena is unknown. Epidemiologically this pattern of onset is important in that not infrequently a patient with onset of his illness at night may not be able to reach a treatment centre because of lack of transport facilities; or if death occurs during the night it may not be recognized by the members of the community as cholera. From the view point of the cholera treatment centre, most of the cholera cases will appear at the hospital in the morning.

d. Incubation period

The incubation period is variable and can range from one to ten days although it is usually about 48 hours. Incubatory carriers have been described in the literature for as long as seventeen days prior to the onset of symptoms. Here at the Cholera Research Laboratory we have seen incubatory carriers as long as eight days prior to the onset of the disease. The time of incubation is probably influenced by the dose of the infectious organisms initially ingested and is certainly influenced by the pattern of nocturnal onset of symptoms. An illustration of this, is the laboratory technician who was infected in Washington D.C. in 1965. He was symptom-free for two days after handling the organisms and subsequently had nocturnal diarrhoea for three successive nights before finally having enough symptoms to warrant further investigation. During this period he had travelled to New York city and back!

2. Place

This can be covered briefly by saying that cholera may occur any place. It usually tends to involve predominantly the lower socio-economic strata of the society, most likely because of the sanitary facilities that exist there. The introduction of the disease is often in the largest cities such as seen in Bangkok, Hong-Kong and Manila and sea ports following the routes of trade as has been classically described.

3. Person

Both sexes are equally susceptible. John Snow, in the nineteenth century, noted however, that the earliest cases in an epidemic were often predominantly males and he attributed this to more mobility of the male population and thus, more exposure to potential sources of infection. Once the disease has been seeded in the community, the case rate will be equal for both sexes. An illustration of the predominance of males in the introduction of the disease was seen with the introduction of cholera into Negros Occidental in 1961. This was attributed to the ingestion of small raw shrimps which was a characteristic habit of adult males. The subsequent epidemic wave in Negros Occidental affected both sexes.

4. Age

Epidemic cholera is characteristically a disease of adults. It has been observed by Dizon in the Philippines that the best surveillance for cholera is to maintain a watch for adult deaths reported to be due to diarrhoea, gastroenteritis or food poisoning. Ordinarily, these entities do not cause death in adults. The reason for the high case rate in adults is related to unknown factors influencing host susceptibility to clinical disease once infection is acquired. This is illustrated by the studies of Yen in Taiwan in 1962 in observing the carrier: case ratios. He noted that in children under ten, there was an average of four carriers detected for every case whereas in adults this ratio shifted markedly to only three carriers to every case. This indicates that if all age groups of a susceptible population were uniformly exposed, children would be more likely to have only inapparent infection or mild diarrhoea while adults would be more likely to have severe disease and be seen in cholera treatment centres.

The same pattern of milder disease in children and severe disease in adults has been demonstrated in our field study area in Matlab Bazar. Here, if we look at the hospital experience only, we see that a large proportion of the cases are adults. However, in our field surveillance with daily house-to-house visits and rectal swab cultures of all diarrhoeas, it was found that the mild cholera cases detected in the field were primarily in children. It is of interest to observe, however, that clinical cholera is very infrequent in infants below the age of one year although this age group is commonly found infected. In addition, the case rate is lower in adolescence than in younger children or adults. The host factors responsible for this pattern of disease in the population are unknown.

In summary, epidemic cholera is manifested primarily by adult cases of the disease although in the community there will be milder cases and carriers which are more frequent in children.

The age pattern in endemic cholera is quite distinct. Burnet observed that one difference between endemic and epidemic cholera was the age distribution of cases. In endemic cholera, more cases were in children whereas in epidemic cholera, there were more cases in adults. He suggested that acquired immunity played the role in this pattern. We have confirmed this observation in East Pakistan, particularly in the Matlab vaccine trial area. There, the case rate has been shown to be ten times higher in children than in adults. Further a serological survey in that population has demonstrated that indeed there is an increasing immunity with age, the adults having a much higher antibody level than the children. Thus, the fall in the case rate with age in this endemic area correlates with the higher level of immunity found with increasing age. This immunity is presumably due to a recurrent exposure to the organism with prolonged residence in this locality.

5. Role of water

Water has been incriminated in the transmission of cholera since the classical studies of John Snow over one hundred years ago and a little more needs to be added. There remain two major points that are not entirely resolved however:

1. Is water a reservoir for cholera in an endemic area or merely a vehicle for transmission of the disease?

Much of the older literature speaks of tanks or ponds of the Ganges delta being a permanent source of infection. In addition, many workers have tried to incriminate various fish, most notably the Hilsha fish as a reservoir for cholera. Our studies over the past two years indicate that water is not a reservoir of infection. Water sources have only shown positive cultures at the time that cases or carriers are present which could serve as a source of contamination. After removal of the cases or carriers, cultures of the water become negative within a few days. All the evidence available to-date indicates that man is the only reservoir of infection with water serving only as a transient vehicle.

2. Is water the only mechanism of spread?

This cannot be answered with certainty. In East Pakistan, it is not possible to disassociate water from other means of spread because of the intimate relationship of the population with surface water. We have demonstrated that cholera is not easily spread by contact both by repeated examination of the attendants of the cholera cases on our ward as well as by the bacteriological examinations of intimate neighbourhood contacts of cases in Rayer Bazar and other congested areas in different community outbreaks. Further in a longitudinal study in the Rayer Bazar community, it has been demonstrated that although diarrhoea occurs throughout the entire community, only the area in contact with contaminated water sources has had cholera cases. If much contact spread occurred, one would expect wide dissemination of cholera with the generally unsanitary conditions existing in that community.

Another illustration of the low frequency of contact spread is given by the beautiful description of J. Snow, of cholera, in the houses served by the Southwalk and Vauxhall Water Company as compared to those served by Lambeth Company. He states "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 the occupier at that time when 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 and small houses; there is no difference either in the conditions or occupation of the person receiving water from different companies. As there is no difference whatsoever, either in the houses or people receiving the supply of both water companies or in any of the physical conditions with which they are surrounded, it is obvious that no experiment could have been 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, of every rank and station, from gentle folks 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 sewage of London and amongst it whatever might have come from cholera patients, the other group having water quite free from such impurity". Snow goes on to present data which indicate that the fatality rate for cholera in these districts were: " Southwalk and Vauxhall 71 per 10 000, Lambeth 5 per 10 000. Cholera was therefore fourteen times as fatal at this period amongst persons having the impure water of Southwalk and Vauxhall Company than amongst those having the purer water from Thames Ditton". As regard contact spread of cholera, Snow goes on to state"... it follows, therefore, that these houses (supplied by Lambeth) although intimately mixed with those of the Southwalk and Vauxhall Company, in which so great a proportion of mortality occurred, did not suffer even so much as the rest of London which was not so situated." From this description, it is obvious that the classical studies of Snow on the water-borne spread of cholera could never have been accomplished had there been significant contact spread of the disease. Our small scale studies in Rayer Bazar, have only confirmed these classic observations.

6. Role of carriers

Chronic convalescent carriers of the El Tor sub-type have been reported with high frequency both in the Philippines and in Iran, one persisting as long as three years. It is of interest to note that over the past three years, in spite of a variety of approaches in a search for chronic carriers

in East Pakistan, by the Cholera Research Centre including the weekly swabbing of convalescent patients for eighteen months and the purging of over 100 convalescent cases, we have not yet demonstrated a single cnronic carrier of V. cholerae. It is not unlikely that the high frequency of persistent carriers of infection represents a major epidemiological difference between endemic cholera such as seen here in East Pakistan and epidemic cholera that has spread throughout the Far and Middle East.

7. Role of unrecognized cases

This factor cannot be understimated in the spread of cholera. In the studies in the Philippines that I had an opportunity to participate in, in 1962, it was shown that the route dissemination in the communities could be related to unrecognized cases and unrecognized deaths due to cholera. In our vaccine field trial area here in rural East Pakistan, by daily house-to-house surveillance of all diarrhoeas, we have shown that during a cholera season over 50% of the total cholera cases detected had only mild diarrhoea which did not require them to seek hospitalization. These unrecognized cases coupled with the totally inapparent infections indicate that to follow the progress of an epidemic only by looking at hospital admissions, is like trying to define the extent of an iceberg by merely examining that part which is above the surface.

8. The role of fomites and other vehicles in the spread of the disease

Most fomites and even most foodstuffs are probably not of great importance in the spread of cholera except whether they would involve the transmission or ingestion of raw water such as the eating of raw fish. Certainly there is no epidemiological evidence to support the measures often taken to prohibit the importation of a great variety of goods from one country to another, from stamped envelopes to lumber.

9. Non-cholera vibrios or NAGS

Much confusion has arisen regarding the non-agglutinating vibrios as being related to cholera. At this time, it can be categorically stated that the non-agglutinating vibrios are not cholera vibrios; they are different organisms. There is as yet no convincing evidence that mutation from a non-agglutinating vibrio to V. cholera occurs under laboratory conditions much less in nature as a cause of cholera epidemics. The frequent reports of non-agglutinating vibri being found for the first time in the face of a cholera epidemic primarily

represents an alertness by the laboratory to identify these organisms since the usual bacteriological techniques for enteric pathogens would tend to group non-cholera vibrios with the paracolon group or other unidentified organisms.

10. Vaccines

Studies both in East Pakistan and in the Philippines have demonstrated that cholera vaccine can reduce the case rate by 50 to 75%. Further observations here have demonstrated that the level of protection induced by vaccine correlates with the antibody titre produced by the vaccine. The discouraging aspect of cholera vaccines so far, as demonstrated in the Philippines trial, is that the vaccine in a non-endemic area may only give six months' protection or less. In an endemic area the protection has been shown to last over two years.

Serological studies have shown that in the endemic population, cholera vaccine injections actually produce a booster response in a highly immune population and thus, one sees both a sustained protection after vaccination and we have been able to demonstrate a sustained high level of antibody. On the other hand, as an illustration of what happens to a population that does not live in an endemic area, we have obtained serological specimens from Americans six months after their cholera booster injections and have shown that the antibody titre is almost completely lost. Presumably, the population living in the endemic area is continually being re-immunized by repeated natural infection.

At this time with the current vaccines available, in order to produce a sustained protection in a population, regular boosters at six months' intervals would seem to be indicated. The evidence to date both from the Philippines trial and our studies in East Pakistan indicate that while vaccine does protect the individual from developing the disease, it does not prevent or reduce significantly the carrier rate. Thus, vaccination is not a useful quarantine measure in preventing the spread of disease by carriers.

11. The role of antibiotics

The place of antibiotics in the control of cholera from the epidemiological standpoint has not yet been established. Observations in the Cholera Research Laboratory ward have demonstrated that an adequate course of tetracycline can eliminate the infection, however, an adequate course appears to require at least five days of therapy. Recent observations by Gangarosa in Iran, suggest that several days' therapy with chloramphemicol is not sufficient as many convalescents

were subsequently demonstrated to have positive cultures by purging. Thus the usefulness of antibiotics in mass prophylactic programmes remains open to question from the theoretical as well as from the practical standpoint.

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