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**WHO EXPERT COMMITTEE
ON CHOLERA**

Second Report

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WORLD HEALTH ORGANIZATION

GENEVA

1967

WHO EXPERT COMMITTEE ON CHOLERA

Manila, 13-19 September 1966

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WHO EXPERT COMMITTEE ON CHOLERA

Second Report

1. INTRODUCTION

The second WHO Expert Committee on Cholera met in Manila, Philippines, from 13 to 19 September 1966, fifteen years after the meeting of the first committee.¹

On behalf of the Director-General, Dr Francisco J. Dy, WHO Regional Director for the Western Pacific, opened the meeting and expressed the hope that the deliberations of the Committee would provide a useful guide to public health workers in the fight against cholera.

He pointed out that after a rapid decline in the incidence of cholera and its retreat to the endemic foci in South-East Asia in the 1950s, epidemic waves of cholera, beginning in 1961 when the El Tor biotypes of the cholera vibrio invaded countries of the Western Pacific, had gradually reached pandemic proportions. Recently, cholera had invaded large areas in Asia from the Caspian Sea to the Pacific Ocean.

These new pandemic trends of cholera have raised fresh problems and emphasized the need for new approaches and intensified activity in order to combat cholera more effectively.

2. TERMINOLOGY AND CLASSIFICATION

2.1 Terminology

The following terms and definitions have been adopted in this report :

(a) *Cholera* is a disease typically characterized by an acute severe dehydrating diarrhoea with rice-water stools, a consequence of infection with *Vibrio cholerae*. This syndrome may be associated with infection by other vibrios, but frequently no pathogenic agent can be isolated. Occasionally, a similar syndrome is produced by infection with other known pathogens, e.g. shigellae or salmonellae, or as a complication of some other infections and intoxications.

¹ Wld Hlth Org. techn. Rep. Ser., 1952, 52.

In this report, the term "cholera" indicates infection by *Vibrio cholerae*, i.e., vibrios, agglutinated by O group 1 serum. This includes not only the "classical" cholera vibrio but also the biotypes resistant to group IV cholera-phage and to polymyxin B, which agglutinate chicken erythrocytes and may produce haemolysin, i.e., the El Tor biotypes.

To ensure that only the infectious disease caused by *V. cholerae* was reported as cholera would require bacteriological facilities and skills adequate for the study of every incident of dehydrating diarrhoea. Such facilities are only now being developed in the areas of poor sanitation where this disease occurs. Where there is no laboratory support, cholera is often not reported or reporting is based on clinical criteria alone. Since even experienced clinicians cannot, with certainty, differentiate cases due to *V. cholerae* from those with an unknown cause, particularly in patients who die shortly after admission to hospital, cases of "cholera" reported only on clinical grounds include other types of dehydrating diarrhoea.

(b) The term "cholera infection" indicates a condition in which *V. cholerae* multiply in an individual. The spectrum of infection ranges from a dramatic, severe, dehydrating diarrhoeal disease resulting in death within a few hours, through less severe illnesses (including diarrhoea with no dehydration), to asymptomatic infections. For each typical clinical cholera case there is probably at least one patient with milder diarrhoea due to *V. cholerae*; the number of asymptomatic infections varies in different localities and population groups from five to ten or more per typical cholera case. In endemic areas mild diarrhoea due to *V. cholerae* is more often found in children than in adults.

Cholera infections are usually self-limiting, vibrios disappearing within two weeks after the attack. Occasionally, a focus is established, probably in the biliary tract of the patient; in one case, the organisms persisted there for over four years. The stool in such individuals is frequently free of vibrios, although the duodenal contents are positive. The term "carrier" generally includes all asymptomatic vibrio excretors, including those in incubation and convalescence, as well as individuals with an asymptomatic infection who excrete vibrios for only a short period. The "chronic carrier", on the other hand, continues to harbour the organism despite the appearance of circulating antibodies. When stool positivity persists for more than three weeks after infection, the existence of a chronic carrier state can be assumed.

(c) The present criteria for the identification and classification of *non-cholera vibrios* have been inadequately applied and some organisms so initially classified have subsequently been shown to belong to the genera *Pseudomonas*, *Commamonas* or *Aeromonas*. Vibrios are Gram-negative, predominantly curved rods, with a single polar flagellum, which form acid under anaerobic conditions from dextrose without producing

gas, and are oxidase- and gelatinase-positive. Most non-cholera vibrios cannot be differentiated from *V. cholerae* except in their antigenic structure and are properly considered as different serotypes. Recent studies in Japan of halophilic *V. parahaemolyticus*, the causative agent of acute gastro-enteritis, have shown it to have specific serological and biochemical characteristics. Non-cholera vibrios are often associated with diarrhoea, and can sometimes produce a dehydrating disease indistinguishable from that caused by *Vibrio cholerae*.

(d) A type of severe dehydrating diarrhoea exists, described as "non-vibrio cholera" and "non-vibrio cholera-like disease", from which no known pathogenic agent has been recovered; this condition is indistinguishable on clinical grounds from cholera during the early stage of the illness. However, purging ceases within one to two days after admission to hospital, whereas the true cholera patient may continue to purge for up to seven days. This disease occurs only among adults, whereas cholera is frequent among children; moreover, the seasonal peak may differ from that of true cholera.

2.2 Classification

The present *International Classification of Diseases* recognizes cholera as a special entity in the list of three-digit categories.¹ This allows the separate recording and compilation of statistics on cholera. However, the Committee considered that, for the better understanding of the epidemiology of cholera and its spread, it would be useful to make provision for further subdivision of cholera according to the biotypes and serotypes of the causative organism and for the reporting of clinically diagnosed, but not bacteriologically proved, cholera.

3. EPIDEMIOLOGY

3.1 Recent trends in morbidity and mortality

A review of the world-wide distribution of cholera during the past few years reveals that bacteriologically confirmed cases have been reported from most of Asia, extending from the Philippines in the east to Iran and Iraq in the west, and from Korea in the north to West Irian in the south-east. The actual morbidity cannot be assessed because of wide variations in the criteria and accuracy of reporting. The El Tor biotypes have been predominant throughout most of this area, supplanting the classical

¹ *International classification of diseases* (1957) Geneva, World Health Organization, 1955 revision.

strains even in India. However, El Tor biotypes have so far been unable to obtain a foothold in East Pakistan, and in some foci in India the classic vibrios remain the cause of the disease. In some areas, e.g., Afghanistan and Nepal, both biotypes have occurred.

This spread of cholera in pandemic-like form has involved a large number of countries that had long been free of the disease. In some countries, e.g., the Philippines, the disease has become endemic, whereas in others, e.g., Korea, Taiwan and Hong Kong, it has apparently disappeared since the initial outbreaks. Despite the infection having been introduced into Japan several times, no outbreak of cholera has occurred there.

In India, the country most highly infected with cholera, which has several important endemic areas, official records indicate no decline in the prevalence of the disease. Although there has been a decline in the mortality rate, hardly a week passes without cholera being reported from some parts of the country. Peak prevalence varies seasonally from place to place, but 65% of all cases occur between May and October. Seven states containing one-third of the population contributed over 75% of the reported "cholera" cases and 80% of the "cholera" deaths. Provisional official figures show that, in 1965, 42 684 cases and 12 743 deaths were reported from India.

Assessment of the prevalence of true cholera in infected areas is nearly impossible. The lack of adequate laboratory facilities does not allow the examination of more than a small fraction of classical cases. Moreover, the presence of non-vibrio cholera in many areas makes it impossible to estimate the prevalence of *Vibrio cholerae* from statistical data based on clinical diagnoses. Economic sanctions and social consequences which, unfortunately, may follow a report of cholera make many local health authorities reluctant to admit the presence of cholera unless an unmanageable outbreak has occurred. Cases and deaths that might be due to cholera are then attributed to diarrhoea and gastroenteritis.

3.2 Changing patterns of epidemics

The characteristics of cholera outbreaks differ in different areas. In endemic areas the disease predominates among children, whereas in newly invaded areas, where the population has no basic immunity, there is no age preference. Seasonal incidence varies in different areas: thus, the cholera epidemic in Calcutta generally precedes the annual monsoon, in Manila it occurs during the rainy season and in Dacca it follows the monsoon. Cholera can appear at any season; the outbreak in Korea occurred during the cold months.

In those areas where the techniques and materials required for effective treatment are not available, the greatest mortality occurs at the two extremes of age. Variations in the severity of the average case have been

noted, the disease generally being milder in the areas where it has been recently introduced than in the Indo-Pakistan subcontinent. A study of severe cases in Calcutta, when both the classical and El Tor biotypes were prevalent, did not disclose any significant difference in the course of the disease. Carrier rates vary with the type of community and locality rather than with the biotype.

3.3 Application of microbiological and serological techniques in epidemiology

Epidemiological studies of cholera are most effectively performed when facilities are available for bacteriological characterization of the infecting organisms isolated from patients and their environment. Such information, which will assist in the reconstruction of the actual chain of transmission, is obtainable only if there is a well-organized and properly functioning health-laboratory service. Since such services enable the causes and trends of epidemics to be studied, they constitute an essential element of public health measures for the control and prevention of cholera.

Such control and prevention will be achieved only by a laboratory service designed to seek the etiological cause of all major diarrhoeal disease, so that routine examination is made not only for vibrios but also for other enteropathogens. The central laboratory should serve as a reference laboratory and should develop techniques, supply high-quality sera and media, and advise local laboratories. These bear a fundamental responsibility, since they must be alert to recognize vibrios while handling the load of basic enteric bacteriology. Senior public health authorities must continue to show interest in laboratory findings, otherwise enthusiasm and capabilities will be lost and, when cholera does appear, it will be recognized clinically only after widespread dissemination has taken place, rather than by the detection of *V. cholerae* in the first case of overt clinical disease.

3.3.1 Laboratory services

Sample collection

The keystone of laboratory procedures is the proper collection and handling of the original sample. A definite technique must be established with specific responsibilities, delineating the type of patients from whom samples are to be collected and the methods of collection. The best material for bacteriological examination is the liquid stool itself; however, it cannot be taken from containers in which it is voided since they may, in a cholera ward, be contaminated, resulting in a false positive finding of vibrios; or the presence of disinfectant may result in a false negative report. The use of sterile rectal catheters obviates this difficulty but complicates the

procedure. The simplest satisfactory technique is the insertion into the rectum of a sterile swab, which is immediately afterwards placed in an appropriate enrichment medium, preferably after solid plates have been streaked. Arrangements must be made for the regular transportation of the collected specimens to the local examining laboratory. In addition, collectors must at all times have a supply of sterile swabs and media in screw-cap or equivalent vials (and blood-collecting devices and glassware, if serological methods are in use), so that lack of equipment does not prevent the collection of samples.

Peripheral laboratories

The collected rectal swabs are forwarded to a local laboratory. This may be a municipal or district laboratory or attached to a hospital and must be equipped to carry out basic bacteriological examinations for both enteric pathogens and vibrios. For vibrios, this includes at least plating on appropriate selective and non-selective media, picking of suspicious colonies and identification by slide agglutination. Local health authorities must be informed of positive isolates. Several isolates from each patient should be put on Kligler slants and forwarded to the reference laboratory for further study.

The peripheral laboratory should be equipped for and experienced in the use of dark-field microscopy for the rapid recognition of cholera vibrios, so that positive information can be given to health administrators without delay. If a portable microscope is available, the laboratory can, when appropriate, move to the patient's bedside to enable an immediate diagnosis to be made. Use of the dark-field technique does not eliminate the need for plating on solid media in order to recover and preserve the strains.

Reference laboratories

A *central national laboratory* should be designated that will support the local laboratories with advice, information, and necessary techniques and supplies (e.g., culture media and typing sera) and that will receive isolates for further study. This support can be furnished directly or through regional reference laboratories. The reference laboratories would carry out the standard bacteriological tests for all the markers that could serve as guides in epidemiological studies.

Of great importance in maintaining a state of preparedness in the local laboratories is the establishment by the reference laboratory of a proficiency survey technique, whereby unknown cultures are submitted to the local laboratories so that familiarity with the laboratory characteristics of cholera vibrios is not lost during inter-epidemic periods.

The central or regional laboratories (or both) should be equipped to

carry out serological studies, preferably by the vibriocidal microtechnique, on paired sera from patients suspected of having cholera. Such laboratories should also be able to conduct population surveys to determine the level of past experience and the current immunity status of a community.

Adequate laboratory supplies are essential for sustained effort in all parts of a country and to assure the satisfactory functioning of the laboratory services. Funds should be provided at the central level, where concern for cholera and diarrhoeal diseases will remain high. When the immediate danger is past, especially when cholera is absent for a long period (and when the danger of introduction of the vibrios into a non-immune population becomes greater), local concern tends to diminish or even disappear, so that the sparse funds are usually diverted to pressing current problems. Central authorities should be responsible for seeing that essential supplies are available to the laboratories and that there are adequate reserves to meet any emergency.

The identification of cholera vibrios depends on the availability of high-quality agglutinating sera. Unfortunately, many sera presently available possess agglutinins against organisms other than cholera vibrios, resulting in false positive results. In other instances, sera of inadequate potency result in false negative reports. The provision of adequate stocks of sensitive and specific vibrio-typing sera is therefore essential. Such sera may prove difficult or even impossible to obtain on a national level, and international action may be required to meet these needs. These, and possibly some other reagents, can best be obtained through international vibrio reference laboratories.

International reference laboratories for vibrios and enterobacteriaceae are needed to support the work of the national central laboratory by providing consultations and reference services, advising on new techniques, and maintaining a uniform, high level of laboratory practice. There is a need for international reference laboratories serving the various WHO Regions. An *international reference centre* is needed to co-ordinate the activities of the regional reference laboratories and to ensure the availability of typing sera of uniform potency and specificity. Such a centre would serve as a central repository for strains collected in various geographic areas. The study of strains would provide data for comparison of organisms from various areas and would assist in the eventual development of a system of global surveillance of cholera.

The Committee noted that a WHO International Phage Typing Centre had been established and is providing a valuable service. The reproduction and distribution by WHO of *Cholera Information*, giving news of recent advances in the knowledge of cholera throughout the world, has assisted in the exchange of information and views among cholera workers.

3.3.2 *Laboratory procedures*

Methods for rapid diagnosis

Although not required for the treatment of cholera, a rapid diagnostic method is helpful for isolating patients, for epidemiological and clinical investigations and for planning control measures. By means of dark-field microscopy about 80% of the cases can be correctly diagnosed within a few minutes if the patients are examined early in the course of the disease; if swabs found to be negative by this technique are incubated for 6-18 hours in an enrichment medium and re-examined by dark-field microscopy, a higher percentage of cases can be diagnosed. No special skill or equipment is required except a darkfield microscope; a vibrio density of 10^5 - 10^6 per ml is necessary for a positive result. The fluorescent antibody technique permits the diagnosis of cholera in about two hours but it requires special skill and equipment; about 90% of the cases can be diagnosed by this method.

Both dark-field microscopy and the fluorescent antibody technique are complementary to the usual method of isolating individual colonies on solid media, which permits subsequent study for markers. Bacteriological diagnosis by isolation can be performed in 4-5 hours with the help of a stereoscopic microscope; faecal matter is thinly streaked on a non-inhibitory nutrient agar plate, preferably with 0.1% Teepol, and incubated for 4-5 hours. After this time vibrio colonies can be spotted easily with the stereomicroscope and confirmed by slide agglutination with O group 1 serum. The use of oblique illumination alone is not satisfactory, since the characteristics of the colony are not fully developed.

Transportation of specimens

Whenever it is impossible to plate faecal material directly on solid media, it should be inoculated into an enrichment fluid, e.g. alkaline taurocholate-tellurite peptone enrichment medium (pH 9.2) or alkaline peptone water (pH 8.0-8.5). The simplicity and low cost of the latter fluid, together with its good performance in the field, make it a more suitable medium for general purposes; it should be distributed in screw-capped or rubber-capped containers.

The vibrios may be overgrown by commensals if kept too long in a tropical climate before plating, but this can be avoided by plating within 5-6 hours or by transferring about 0.1-0.2 ml to a fresh tube of the medium for 5-6 hours' incubation in the laboratory before plating. Cholera vibrios in this medium remain viable at room temperature for more than two weeks. If none of these media is available, strips of thick blotting-paper soaked with stool can be placed in a plastic envelope and sealed to avoid drying en route to the laboratory. The material should also be inoculated in media suitable for the isolation of other enteropathogens.

Plating and isolation

The choice of plating medium depends upon the preference of the individual worker and the facilities available. Some well-tried media (nutrient agar, pH 7.6; gelatin agar, pH 7.2; Teepol agar (nutrient agar with 0.1% Teepol), pH 7.6; and bile-salt agar, pH 8.2), are non-inhibitory or only slightly inhibitory, whereas others (Oxoid cholera medium, pH adjusted to 8.4; TCBS medium, Eiken, pH 8.6; and taurocholate-tellurite gelatin agar, pH 8.5) are highly selective. Both types of medium should be used for each specimen, since with only one type a false negative result might be obtained. The selective medium is not necessary for cases in the first or second day of illness.

Colonies of vibrios can be spotted, after overnight incubation, either with the naked eye or by a stereoscopic microscope using oblique illumination. The latter procedure makes it possible to differentiate colonies of vibrios from those of many species, including *Aeromonas*, but not always from colonies of some strains of *Pseudomonas*, *Commamonas* and non-agglutinable vibrios.

Identification and characterization of vibrios

Suspicious colonies, preferably from non-selective plates, should be tested with anticholera O group 1 serum and, if found positive, by slide agglutination with Ogawa and Inaba type-specific antisera. If the suspicious colony fails to react with the group serum, at least 5-10 colonies and, finally, a sweep from the confluent area should be similarly tested before concluding that the case is negative for agglutinable vibrios, since these may co-exist with the non-agglutinable ones.

Remnants of an agglutinable colony should be picked and put into a Kligler iron agar (KIA) slant. The growth should be serologically confirmed and then subjected to tests for Heiberg grouping, Voges-Proskauer reaction, haemagglutination of chicken or sheep blood cells, and sensitivity to 50-unit polymyxin B discs and to cholera-phage group IV at the normal test dilution. If facilities are available, some representative strains of each outbreak should be tested for sensitivity to antibiotics. Isolates from each case should be sent to the national central laboratory for further study; representative strains from each outbreak should be sent to the WHO International Phage Typing Centre for phage-typing and other studies.

Serological methods

Examination of paired sera (acute-phase serum collected within 48 hours of onset of cholera and convalescent serum collected between the 7th and 15th days) has been found very reliable for the retrospective

diagnosis of cholera. Titre increases in tests for agglutinins, using live antigen, and for vibriocin have been found to agree well with bacteriological findings. A microtechnique for both these tests can be performed on fingertip samples.

Laboratory diagnosis of carriers

Cholera patients excrete about 10^7 - 10^9 vibrios per ml of fluid with a few commensals, but asymptomatic cases and convalescent carriers excrete only about 10^2 - 10^5 vibrios per g of stool, with large numbers of commensals. This makes the recognition of vibrios more difficult in carriers than in patients.

To recognize asymptomatic cases, contacts should be examined as soon as possible after the detection of the index case. Specimens, if possible, should be collected daily for several days because more positive contacts are recognized in this way. Asymptomatic infection by *V. cholerae* in unvaccinated individuals can also be detected by observing a rise in antibody titre.

The recommended method for the recovery of vibrios is to inoculate about 3 g of fresh stool into 50-100 ml of alkaline peptone water. However, vibrios have been found to be more or less uniformly distributed on the surface, as well as within the faecal mass; rectal or stool swabs broken off into 10 ml of enrichment broth are generally used for convenience. At the laboratory, the swabs received in enrichment fluid should be incubated for 5-6 hours (including transit time in hot weather) and then plated on a selective medium. About 0.1-0.2 ml should be transferred to a second peptone-water tube for proper incubation. Plating should be done from this tube if vibrios are not isolated from the first tube; this procedure of secondary enrichment has yielded about 10% more positive isolates in a group of carriers. The recognition of colonies of vibrios on a non-inhibitory medium may at times be very difficult without the stereoscopic microscope, and the use of selective media is helpful.

For the detection of chronic carriers, serological follow-up of former cases and their contacts may prove convenient and effective. The agglutinin titre remained at a high level (640-1280) in one long-term carrier whose stools remained intermittently positive for more than four years after the spell of clinical disease. The titre generally declines to a low level within 6 to 12 weeks of recovery; thus a high antibody titre 12 weeks or more after illness in the absence of recent vaccination is an indication of the need for thorough bacteriological examination.

Culture of night-soil and water

Bacteriological examination of night-soil has been valuable in locating carriers and mild cases. . Approximately 2-3 g of well-mixed material

is placed in about 50 ml of enrichment medium, which is subcultured in 5-6 hours on to solid media.

Examination of water should include rough quantitation by spreading 0.01 ml over the surface of an inhibitory medium, as well as by adding 9 volumes of the test water to one volume of 10% peptone water, with subculture onto solid media after 5-6 hours' incubation. Examination of large quantities of water is possible by means of filters (preferably a membrane filter), either culturing the filtered material in peptone water or growing the organism on the membrane filter itself in a suitable medium; this provides a count of the number of vibrios per unit volume of filtered water.

3.4 Transmission

Two factors are involved in the transmission of cholera: (1) the transfer of the organisms and their multiplication in a new host and (2) the development of symptoms of variable severity. The requirements for the appearance of symptoms have not been defined, but are presumed to depend on a large enough challenge dose, on the physiological state of the host and on simultaneous challenge of the host with preformed toxins and vibrios, or on a combination of two or more of these factors.

3.4.1 *Infection through clinical cases*

Extensive experience has shown that hospital personnel very rarely become infected. Although such infections have been reported, they constitute the exception rather than the rule, and they may have resulted from exposure outside the ward. This experience justifies the management of cholera cases in general hospital areas, using standard isolation precautions.

It would appear that infection of the normal individual requires the ingestion of an appreciable number of vibrios. Traditionally, the cholera case is considered to be the principal source of the transmission of the disease in the community. A typical cholera patient excretes 10-20 litres of stool containing 10^8 - 10^9 vibrios per ml and is able to contaminate a wide area if he is not hospitalized. The diarrhoeal stools of the milder cases contain a similar number of vibrios per gram and may actually pose a greater hazard, since the patients are ambulant. It is particularly pertinent that mild cases are more frequent than dehydrating diarrhoea among children and that children are more likely than adults to defecate at random.

3.4.2 *Infection through carriers*

In the over-all picture of the transmission of cholera, the carrier is considered to be of great importance. Asymptomatic infections represent the base of the iceberg; they occur 5-10 times as frequently as the manifest

cholera cases. Although the formed stools of asymptomatic carriers contain only 10^2 - 10^5 vibrios per g, the relatively large number of carriers and their freedom of movement makes them a practical threat.

The frequency of asymptomatic infections is proportional to the degree of contact with the index case. In Davao (Philippines), infection was observed among 13.6% of household contacts, 8.4% of neighbourhood contacts and 0.3% of the general community. In Taiwan, 9.5% of household contacts were infected, as compared with 0.34% of neighbourhood contacts and 0.32% of the general community. The carrier rate among family contacts varies with local conditions and in different studies has ranged from 4% to 20%; rates among children have generally been found to be higher than among adults. Comparable carrier rates have been observed in different areas regardless of whether the infecting biotype was the classical or an El Tor type.

The untreated symptomatic patient passes vibrios for one to two weeks, whereas the excretion of vibrios by a person with an asymptomatic infection usually ceases at the end of one week. However, the chronic carrier with a persistent focus of infection may shed organisms intermittently for an indefinite period. The chronic infection generally seems to be in the biliary tract and can be detected by culturing duodenal fluid after the administration of a cholagogue.

Although the carrier was at one time considered unimportant in the transmission of cholera, convincing epidemiological evidence from Hong Kong, Taiwan and the Philippines indicates that the carrier often serves as the source of infection and can be of great importance in the persistence of the disease and in its transmission, within a given population or even between neighbouring countries. Furthermore, the chronic carrier constitutes a reservoir of the disease and may contribute to the perpetuation of infection from season to season. Because of the intermittent passage of organisms, the detection and control of all carriers is impossible. Although carriers might be recognizable by their high level of persisting antibodies, serological screening of large populations is not feasible.

3.4.3 *Environmental factors*

The transmission of cholera from a case or carrier to a susceptible individual depends on the ingestion of a sufficient number of vibrios under conditions that favour infection and the development of the disease. The Committee believes that cholera can occur if vibrios are introduced in any part of the world where overcrowding and poor sanitation exist. However, the establishment of endemicity requires that the sewage and waste disposal practices be sufficiently poor to favour the persistence of excreted vibrios within the environment. Poor water hygiene may lead to intensive contamination of water to serve directly as the infecting medium.

Moreover, water with a low level of faecal contamination may also carry vibrios and spread infection. The habits of the population and the conditions of their environment will ultimately determine the level of faecal-oral transmission and the likelihood that this cycle can be maintained at sufficient intensity to perpetuate the disease in the community.

Environmental conditions that provide opportunities for vibrios to multiply and later be ingested are of particular importance. Such conditions have been assessed in the laboratory. When natural conditions were simulated, with particular attention to the size and type of inoculum, temperature of incubation and other pertinent factors, laboratory studies showed that vibrios multiply readily in certain foods, e.g., milk and milk products and some varieties of boiled rice. The addition of salt to fresh fish, meat, water-melon and boiled rice makes them excellent propagating media; on the other hand, vibrios die after one or more days when placed on a wide variety of other foods and fomites.

3.4.4 *Nutritional factors*

The Committee considers that nutritional factors probably determine whether an individual will develop clinical disease when infected by cholera vibrios, but the relevant deficiency or aberration has not yet been identified, although studies on the role of thiamine, ascorbic acid, folic acid, vitamin B₁₂ and potassium have been made.

3.4.5 *Socio-economic and education factors*

Cholera is a disease of the poor and the underprivileged. This status connotes not only a restricted intake of food but also overcrowded living conditions and a home environment with very low sanitary standards. These are usually associated with little or no education, little or no knowledge of factors affecting health, and disdain for hygienic practices. Thus the environment is conducive to infection on many scores.

3.4.6 *International spread*

The factors involved in the spread of cholera across international borders are not essentially different from those involved in its spread from community to community within a country. The presence of relatively large numbers of asymptomatic infections and of people with minimal symptoms makes wide dissemination of the organism possible within one to two weeks. Chronic carriers, however, pose a greater problem because they prolong the duration of possible spread. No practical techniques are available to detect such individuals effectively, even if serological studies and duodenal drainage were performed. It is realized that quarantine measures can be applied only to controlled passenger traffic, and that

infection could still be introduced into a country through uncontrolled migration. Especially in many littoral areas, migrants live under conditions conducive to the appearance of cholera; these individuals move across borders without restraint and generally go to areas having the poorest sanitary conditions.

4. PATHOLOGY AND TREATMENT

4.1 Pathogenesis, pathophysiology and histopathology

Current studies in many research centres are expected to increase our understanding of the pathogenesis and pathophysiology of cholera. Studies of the organism have revealed the existence of separable toxic factors that can produce in laboratory models changes observed in cholera patients.

One of these causes the outpouring of fluid into the lumen of the gut in the infant rabbit and the ileal loop in the adult rabbit, and increases capillary permeability on intradermal inoculation in the guinea-pig or rabbit. Another produces a fall in the short-circuit current across the frog-skin model; this fall is considered to be a measure of the degree of inhibition of sodium transport. There is also another toxic fraction which has characteristics of the bacterial endotoxins.

The importance of acidosis in the pathophysiology of cholera is being stressed as a likely explanation of the poor outcome of treatment of the disease in children. Persistent acidosis has been observed in fully rehydrated children, and elevated pulmonary wedge pressures, correctable by raising the blood pH to normal levels, have been demonstrated by cardiac catheterization. Both these observations are supported by autopsy findings of cerebral oedema and dilatation of the right heart. The occurrence of hypoglycaemia as an important complication of cholera in the young child may be correlated with the autopsy finding of a fatty liver.

Histopathological studies have concentrated on changes in the intestinal mucous membrane, with great interest in changes in the epithelial cells and in the cells that may be associated with antibody production. Electron-microscopic studies of the experimental disease in guinea-pigs have demonstrated progressive changes in the mucosal capillary interstitial tissue, and cytoplasmic vesicles, which finally lead to the exsorption of fluid into the intestinal lumen.

4.2 Treatment

Treatment is directed towards correction of the pathophysiological changes consequent on infection by vibrios that can be eliminated by an

antimicrobial agent. The fundamental aberrations are dehydration and electrolyte loss (resulting in acidosis), which can be corrected by rehydration therapy. Cholera has become one of the most effectively treated diseases; when treatment procedures are properly applied, deaths from cholera are extremely rare.

4.2.1 *Rehydration*

Cholera patients require immediate replacement of fluid and electrolytes lost before their admission to hospital. Thereafter, the fluid balance is maintained by replacing the fluid lost during treatment.

Physiological studies have provided the means for the accurate assessment of the fluid deficit in the adult, based on plasma specific gravity (easily determined by the copper sulfate technique). Excellent results have been obtained in the adult by the administration of two units of isotonic saline followed by one of isotonic (1.39%) sodium bicarbonate solution, or by three units of isotonic saline followed by one unit of 2% sodium bicarbonate. Isotonic sodium lactate (1/6 molar) solution can be used instead of the sodium bicarbonate; it can be sterilized easily and does not readily deteriorate in storage. After the fluid initially lost has been replaced, administration of saline solution is maintained at the rate at which fluid is being lost in the stool. Thus, collection and measurement of the excreta are an essential part of the therapy. Records of fluid intake and output must be kept to ensure that the balance is maintained and that the patient does not again go into shock or become excessively over-hydrated.

The initial fluid requirement can also be satisfactorily assessed by clinical observation. Fluid is given as rapidly as possible until a full pulse returns and the general condition of the patient becomes essentially normal; filling of the neck veins is an indication that fluid replacement is adequate.

Potassium losses may be replaced orally. Green coconut water, which contains 70 mEq of potassium per litre, is a palatable drink, and a dose of 170 g for each litre of stool prevents significant potassium depletion. A 10% potassium citrate solution may be given in 15-ml doses (diluted in water) three or four times a day.

Treatment of cholera in children is more difficult. The initial fluid requirement cannot be calculated on the basis of plasma specific gravity and body-weight, so the initial fluid requirement must be judged clinically. Acidosis and potassium deficiency may be of greater importance in children. Treatment of dehydration with saline solution followed by an alkaline solution has resulted in case fatality rates of 15-20%, as compared with negligibly low rates among adults treated by the same method.

The use of a single replacement solution, with which acidosis is corrected at the same time as lost fluid is replaced, has been investigated in

several institutions. In one, a solution with a bicarbonate (or sodium lactate) content of 48 mEq/litre, approximately that of the cholera stool, was used and resulted in a case fatality rate of 0.6% in over 300 proved cholera cases in children under 10 years of age. The inclusion of potassium at a level of 13 mEq/litre obviated the need for oral replacement of this essential anion; this was provided by an isotonic solution containing (per litre) 5 g sodium chloride, 4 g sodium bicarbonate (or an equivalent amount of sodium lactate), and 1 g potassium chloride—called 5-4-1 solution. The Committee noted that studies are under way with lactated Ringer's solution (which contains 28 mEq of bicarbonate and 4 mEq of potassium per litre) and with other solutions in attempts to obtain the most effective and practical rehydrating fluid.

4.2.2 *Antimicrobial drugs*

The administration to the cholera patient of antimicrobial agents to which vibrios are sensitive shortens the duration of diarrhoea and the excretion of vibrios in the stools, and reduces the amount of fluid required for intravenous rehydration, the duration of hospitalization and the need for close supervision. Tetracycline, chloramphenicol and erythromycin have been shown to be effective; chloroiodoquine and nitrofurans derivatives have been tried with partial success. Tetracycline and chloramphenicol are equally effective whether administered intravenously or orally, causing a very rapid reduction in the number of vibrios in the stool. With three days of therapy at a dosage of 250 mg every six hours, satisfactory clinical responses have been obtained, with occasional bacteriological relapses. To ensure freedom from bacteriological relapses, it is necessary to administer 500 mg of the drug every six hours for three days. Suspensions for paediatric use are needed for the oral treatment of small children.

Antibiotic therapy can be initiated by the intravenous route and continued orally when the patients are no longer vomiting and are fully conscious. Alternatively, one may delay the initiation of antibiotic therapy for the hour or two after admission needed to correct dehydration and acidosis, after which oral therapy can be instituted.

Streptomycin-resistant vibrios appeared shortly after the massive application of this drug; the emergence of strains resistant to tetracycline and chloramphenicol is likely and surveillance should be maintained over the isolated strains to detect their appearance. It is suggested that erythromycin should not be used at present but should be held in reserve until resistance to other drugs becomes a problem. So far the emergence of tetracycline-resistant strains has not been observed in patients treated with this drug; however, some strains isolated from patients who had not been treated with antibiotic have been found (by the agar-plate diffusion

technique) to be resistant to tetracycline and chloramphenicol at a concentration of 25 µg/litre, but not at one of 50 µg/litre.

Although the administration of tetracycline or chloramphenicol for three days at a dosage of 500 mg every six hours has consistently resulted in negative stools, purging with magnesium sulfate has disclosed that some individuals continue to harbour *V. cholerae*.

In the treatment of the clinical case, when there is a rapid transit time the use of a non-absorbable drug may result in inadequate contact between the drug and the vibrios, with a poor effect. However, the condition of the intestine in the carrier state is such that the antimicrobial drug remains in contact for a much longer period, and non-absorbable drugs may prove effective. It is to be noted, however, that the existence of a chronic carrier state implies that infection is present in the biliary tract and that this has occurred despite the use of tetracycline, a drug that is absorbed by the cholera patient and excreted through the bile.

4.2.3 *Convalescence*

The Committee felt that a patient should not be discharged from control unless there have been three negative stools or three days of treatment with an effective antibiotic at a dosage of 500 mg every six hours. It must be recognized that neither procedure guarantees the absence of vibrios in the body; routine purging, which might disclose whether vibrios are present, is not a practicable procedure.

4.2.4 *Treatment in the field*

Explosive outbreaks of cholera in rural areas often exceed the capacity of local personnel to provide treatment. The management of such outbreaks calls for advance preparations, in cholera-prone areas, of mobile units with adequate personnel, supplies and equipment, trained and assembled in the inter-epidemic period.

Immediately an outbreak of cholera is reported, a mobile team should move to the site of the epidemic. The team should preferably consist of at least one doctor and two or more assistants. A suitable isolated area should be established as a treatment centre to which patients are brought. Camp cots or other locally available platforms can be used as cholera cots to permit the collection and measurement of excreta if there is a hole under the patient's buttocks; calibrated plastic buckets are convenient receptacles. An area for the sanitary disposal of the excreta must be established.

In rural areas the availability of a single cholera replacement solution is of great advantage, since the logistics of treatment are thereby simplified. Such a solution can conveniently be packed in non-toxic plastic bags or glass, together with associated sterile tubing and needles. A supply

of scalp-vein needles is very helpful for finding scalp veins or external jugular veins in children and infants. If vascular collapse occurs and peripheral veins cannot be found, the femoral veins afford a route for correcting shock, after which superficial veins can be found. The replacement solution is run in as rapidly as possible until a good pulse is restored and general clinical improvements are obtained. Thereafter, the rate of administration is reduced to match the output of the evacuations and the patient is watched closely. If a sudden and copious evacuation occurs again, the infusion rate is increased so as to replace the lost fluid as quickly as possible. Tetracycline therapy is initiated as soon as feasible and for adults a 500-mg dose is given every six hours for three days. If potassium is included in the rehydration fluid, there may be no need for its oral replacement; if the solution does not contain potassium or contains only small amounts, green coconut water (170 g per litre of stool) will replenish the loss. Fluids can be given by mouth as desired.

When cholera appears as sporadic cases of dehydrating diarrhoea, not clinically differentiable from severe diarrhoea due to other causes, treatment can be handled by local personnel. However, when it manifests itself as an explosive outbreak, overwhelming the capacity of local personnel, a mortality rate of about 50% can be expected until the arrival of the mobile team unless the local doctor or medical attendant has on hand a single replacement solution in non-toxic plastic containers or glass together with sterile tubing and needles. This solution should be in routine use for the treatment of sporadic severe or dehydrating diarrhoeas, using a "cholera cot" with proper recording of intake and output. From all these cases cultures should be taken routinely as outlined in paragraph 3.3.

The mobile team assists local personnel in disinfecting the houses of patients and superintending close contacts of cases. Team members assist in maintaining the health of the community, by arranging for the safe disposal of excreta and dead bodies, by providing a safe water supply, by carrying out vaccinations and by providing health education about the spread of cholera.

5. PREVENTION

5.1 Specific preventive measures

5.1.1 *Vaccination*

Six controlled field trials of cholera vaccines have been carried out since 1963 in India, Pakistan and the Philippines; six of thirteen vaccines given in a single dose provided statistically significant protection, with an effectiveness ranging from 40-80%. This proved that the parenteral

administration of cholera vaccine to residents of areas where cholera is endemic can afford protection against clinical disease. However, protection was generally completely lost within 3 to 6 months after vaccination. Although general and local reactions were observed among adults, the protection of adults persisted longer than that of younger individuals. Vaccines prepared with classical vibrio strains proved effective against infections with both the classical and the El Tor biotypes. Since no classical infections occurred where El Tor vaccines were tested, it was impossible to determine whether El Tor vaccine would protect against infection with classical *Vibrio cholerae*. A purified Ogawa lipopolysaccharide afforded significant protection to adults in an endemic area against infection with the Inaba serotype, but protection was demonstrated only during one cholera season (6 months) after administration, whereas immunity imparted by a whole-cell vaccine lasted through two cholera seasons.

There is no evidence that vaccination increased the number of asymptomatic infections. Although in some groups there was a reduction in secondary cases among family contacts given the vaccine, as compared with those who had received a placebo, on the whole no significant difference was noted in secondary infections between those who had received vaccine and those who had received a control preparation.

Serological studies have shown that a high percentage of the population in endemic areas, particularly in the older age-groups, has circulating antibodies; with the effective vaccines there was an increase in the antibody content in the vaccinated groups compared with the control groups.

These studies have demonstrated that the vaccine prepared from classical strains containing equal numbers of Inaba and Ogawa vibrios can afford protection in endemic areas against both the classical and the El Tor biotypes. When cholera invades new countries, it is preferable to use vaccine prepared from a classical biotype rather than one prepared from an El Tor organism until it has been demonstrated that El Tor vibrios exclusively are causing the disease. The Committee noted that the best results were obtained with a vaccine containing more than 8000 million organisms per ml, whereas the minimum requirements specified by the WHO Study Group on Requirements for Yellow Fever Vaccine and Requirements for Cholera Vaccine¹ are 4000 million organisms per ml. On the basis of controlled field trials, it is recommended that no cholera vaccine of the bacterial type should contain less than 8000 million vibrios per ml.

In the light of the present knowledge of immunization in general and cholera immunization in particular, primary immunization with vibrio antigens should be considered to confer a basic reactivity to re-stimulation that will last beyond the short period of effective protection

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1959, 179.

against the disease; a second parenteral injection (or, perhaps, oral administration of antigens, if its effectiveness is confirmed in controlled field studies) can therefore be considered effective immediately.

Undesirable reactions following vaccination have been observed principally among adults from endemic areas who have circulating antibodies and among those who have had repeated booster doses of cholera vaccine, e.g., international travellers. Those who have received several doses at six-month intervals may not need to be given booster immunizations at the same rate. Smaller intradermal doses could be considered for boosters as they are less reactogenic. When purified and less reactogenic preparations become available, it may be possible to redefine the desirable interval between booster doses on the basis of more accurate knowledge.

Two doses of cholera vaccine are assumed to be more effective for primary immunization than one dose. Controlled field trials are now under way to test the relative effectiveness of single and double doses.

Research is in progress to determine the essential requirements for antibacterial and antitoxic immunity. Pre-existing coproantibodies (intra-intestinal antibodies) may be an essential feature of antibacterial immunity. If they are important, repeated booster inoculations may be required because of the transitory nature of these antibodies. Untoward reactions to repeated inoculation might be minimized or prevented by using purified preparations given parenterally or possibly by the oral administration of the appropriate antigen. Experimental evidence concerning antitoxic immunity in cholera was discussed by the Committee, but it was concluded that its significance in man is not yet known. Studies are also under way on immunization with live avirulent vibrios.

With the presently available vaccines and knowledge, it is essential not to convey to the public and to health workers the false conviction that vaccination is a certain protection against cholera and that the administration of vaccines is an effective measure *par excellence*. Vaccination must be considered merely as an adjunct to other more important control measures.

Priorities must be established for vaccinating different population groups at an appropriate time before the anticipated appearance of the disease, since protection has often proved to be short-lived. A serological survey of the population would indicate whether all the population should be immunized or whether emphasis should first be placed on children or some other population group.

5.1.2 *Chemoprophylaxis*

Several serious hazards are involved in the administration of antimicrobial drugs to population masses in the hope of preventing emergence

of cholera cases or transmission of infection by carriers. Antibiotic agents in healthy individuals cause changes in intestinal flora that might alter their susceptibility to infection. More important is the danger of the emergence of resistant strains of vibrios and of other types of intestinal flora. There may be some justification for the administration of antimicrobial agents to direct contacts (family or household) of a known case of cholera to minimize the transmission of vibrios to the population, since there is known to be a high incidence of asymptomatic infections among this group. In this case the full dosage schedule should be used. However, large-scale administration has dangers that far outweigh the potential benefit, and should be discouraged.

5.1.3 *Vibrio phages*

For many years vibrio phages have been recommended for the treatment and prevention of cholera. Some studies have been performed, but no satisfactory evidence has yet been adduced to permit a judgment on their effectiveness.

5.1.4 *Epidemiological surveillance*

Epidemiological surveillance of the population is carried out with a view to the early detection of the presence and distribution of cholera in the community. This must be based on the surveillance of all diarrhoeal diseases diagnosed either clinically or bacteriologically (see paragraph 3.3). The availability of treatment centres for diarrhoeal disease in which a high level of treatment is maintained is of the greatest importance in achieving this goal. If effective rehydration centres existed, a large percentage of severe diarrhoeal cases would probably be admitted to them, thus permitting the early bacteriological recognition of those due to vibrios.

In addition, health officers in each area must maintain close contact with physicians in the hospitals and outpatient clinics and with private physicians to ensure, through the provision of material, the proper handling of swabs and culture media in the search for enteric pathogens as well as vibrios. Whenever it is feasible, night-soil examination is useful to obtain epidemiological information on the presence of infections.

Appropriate reporting to regional, national and international health services when sporadic cases occur should be automatic to permit advance preparations if the disease threatens to spread.

5.2 **General preventive measures**

5.2.1 *Health education*

In the inter-epidemic period, the most effective health education techniques should be used to educate the public in the prevention of enteric

disease. When cholera appears or threatens to appear, all available means and techniques of health education should be used to make the population take the necessary preventive measures.

Emphasis should be given to

- (1) food hygiene
- (2) hand washing after defecation, particularly for food handlers
- (3) the dangers of unsafe water, necessitating disinfection or boiling.

Since vaccination affords only partial protection it is not justifiable to put the sole emphasis on this aspect of prevention.

5.2.2 Sanitation

The development of techniques and facilities for proper waste disposal can control the spread of vibrios and help eliminate the threat of cholera. Emphasis should therefore be directed towards environmental sanitation and primarily towards excreta disposal, water control, fly control and food handling.

The development of properly operated water-borne sewerage facilities in urban centres and health education directed to the proper utilization of these facilities would resolve the urban sanitation problem. However, there is a great need for the development of methods of excreta disposal that are applicable in rural areas.

The provision of a safe water supply will do much to minimize the transmission of vibrios. In most of the cholera areas, existing water-supply systems flow intermittently, which is particularly dangerous because of the possibility of backflow. However, most villages are still without a centralized water supply system and many rely on individual water points that are often grossly contaminated.

In accordance with the accepted principles of community water supplies,¹ every effort should be made to provide conveniently distributed safe water in ample quantities to meet all personal and household needs essential for sanitation and cleanliness.

In some areas, the sanitary disposal of the dead is of great importance in epidemic periods, when the facilities may be overtaxed, resulting in improper handling and disposal of bodies.

5.3 Prevention of international spread

The Committee reviewed the methods available to prevent infection spreading across national borders.

Even the administration of the most effective vaccine now available does not rule out the possibility that an individual may excrete *V. cholerae*.

¹ *Off. Rec. Wld Hlth Org.*, 1959, 95, 42 (Resolution WHA 12.48).

If an effective vaccine has been given, at best it will only moderately reduce the likelihood of an individual's developing the disease or becoming a carrier. At present a quarantine officer has no means of detecting with certainty whether an individual traveller is infected or not. Even the use of rectal swabs would not detect all carriers, since vibrios are frequently excreted intermittently. Existing quarantine measures, as defined by the *International Sanitary Regulations*,¹ as well as excessive measures that have been practised by some countries, have not been able to prevent the spread of cholera from one country to another.

The Committee reviewed the consequences of the imposition of severe and excessive restrictions on countries that had reported cholera. At times the presence of cholera has not been reported by infected countries for fear that severe travel and trade restrictions would be taken against them by cholera-free countries. Excessive measures in fact induce cholera-infected countries not to disclose the presence of disease, which in turn deprives the health authorities of cholera-free but receptive countries of the advance warning that would enable them to make preparations to prevent invasion by cholera. Under these circumstances, an international system of surveillance loses its effectiveness. Without honest and prompt reporting, the introduction of infection in new areas becomes easier and often results in wide dissemination of disease before it is detected. This, in turn, greatly increases both the mortality and the difficulties of encompassing the disease and preventing its further spread. The Committee felt that the present excessive restrictions practised by some countries, besides being ineffective in preventing the introduction of cholera, are making international surveillance and co-operation in the control of cholera practically impossible.

The Committee considers that countries should refrain from imposing excessive measures, especially in relation to trade in safe food and other products. Instead, in a spirit of international co-operation, they should fulfil their obligations concerning the notification of cholera and the adoption of preventive and control measures based on current knowledge.

6. RESEARCH NEEDS

The need for further research in cholera is evident since, at present, preventive measures are rather ineffective and cannot achieve the desired control and eventual eradication of this disease. The Committee considers that basic research in the pathogenesis of cholera may lead to effective

¹ *International Sanitary Regulations* (1966) Geneva, World Health Organization, third annotated edition.

cholera control. However, carriers and their role in the transmission of the disease and the improvement of vaccines are subjects that deserve priority.

6.1 Carriers

Carriers, especially long-term carriers (who represent a reservoir of infection), are of particular concern. Research is needed to develop : (a) more effective and rapid methods of detecting carriers, (b) improved methods of treating carriers and (c) a better understanding of the pathological and immunoserological background of the carrier state. The study of detection methods should be directed not only towards the examination of stools but also towards the improvement of methods for detecting vibrios in the environment, particularly in sewage, night-soil and water. The study of markers of *V. cholerae* to facilitate tracing and study of the carrier state deserves attention.

6.2 Vaccine studies

In view of the relatively low effectiveness of current vaccines, further studies based on modern immunological and biochemical techniques are needed for :

- (a) improving antibacterial vaccines, including the development of purified antigens
- (b) evaluating antitoxic immunity
- (c) evaluating oral killed vaccines
- (d) developing and evaluating oral live vaccines
- (e) evaluating animal models in the study of immunological agents
- (f) investigating the routes of immunization and appropriate dosages, dose schedules and intervals between doses.

6.3 Treatment of cholera

The present treatment of cholera is effective, but it is symptomatic; further biochemical studies, especially of conditions in children, could make it more rational. The search for a new specific treatment of cholera and the adaptation of treatment procedures to field conditions deserve further attention. The development of simple techniques for the preparation of rehydration fluid in the field is desirable.

6.4 Prevention of cholera

The development of simple and practical devices for the disinfection of water, food and wastes under field conditions deserves further exploration and study.

7. CONCLUSIONS

At present the world is witnessing a new pandemic of cholera which, so far, has involved large areas of Asia. National endeavour and international co-operation should not be spared to limit its spread, save human lives and prevent economic loss.

Although further research is needed to improve preventive measures and achieve effective control of cholera and, eventually, to eradicate it, present knowledge permits the application of (1) highly effective methods of treatment that should practically prevent loss of life, (2) other measures of limited effectiveness, such as vaccination, and (3) long-term measures, such as general and health education, environmental sanitation, water and food control and sewage disposal, which are very effective but which cannot be applied immediately on a large scale owing to financial limitations. More intensive international assistance is needed for the countries where cholera is endemic so that they may rid themselves and the world of the threat of cholera. Extensive control programmes would require resources, determination and time.

The existence of short-term and long-term carriers, the abundance of cases with mild clinical manifestations and the limited effectiveness of preventive measures, in particular vaccination, do not allow the institution of quarantine measures that would completely prevent the international spread of cholera. If, instead of taking excessive, ineffective and outdated measures, countries were to fight cholera in a spirit of international co-operation and in the light of modern scientific achievements, many lives and resources could be saved.

Knowledge of the treatment of cholera should be widely disseminated to the medical community in countries affected, and facilities for the application of therapeutic methods should be provided wherever there is need.

Surveillance of cholera and other diarrhoeal diseases and enteric infections is an essential prerequisite for timely and well-planned public health action. This action, however, can be taken only when health services have developed diagnostic laboratories, rehydration centres, field teams, sanitation, food and water control, and health education activities. Such services are widely needed, especially in developing countries, where

cholera and other enteric infections are claiming many lives, particularly among children.

Further research, both basic and applied, is needed with the immediate goals of developing more effective vaccines, elucidating the role of carriers in the transmission of the disease, and improving the methods for their detection and treatment. International co-operation could contribute much to the speedier development of cholera research, and through it, ultimately, to the control and possible eradication of cholera.

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Second Report

CORRIGENDUM

Page 12, line 2

delete vibriocin
insert vibriocidin

Page 18, paragraph 1, line 6

delete anion
insert cation

Page 19, line 2

delete 25 µg/litre, but not at one of 50 µg/litre
insert 25 µg/ml, but not at one of 50 µg/ml