Chapter 1
The Public Health Role of Clinical Laboratories

A. Epidemic Diarrhea

The two most common types of epidemic diarrhea in developing countries are watery diarrhea caused by *Vibrio cholerae* serogroup O1 and bloody diarrhea caused by *Shigella dysenteriae* serotype 1 (Sd1). This chapter presents an overview of these and other organisms that cause epidemic dysentery and cholera. Knowing the epidemiology and clinical presentation of these organisms will aid in understanding the procedures presented in the following chapters.

1. Epidemic cholera

Cholera is a secretory diarrheal disease caused by enterotoxin-producing strains of *V. cholerae*. Although over 150 serogroups of *V. cholerae* have been identified, for decades toxigenic *V. cholerae* serogroup O1 was the only known cause of epidemic cholera. After a large epidemic in Asia in 1992 and 1993, it became clear that toxigenic *V. cholerae* serogroup O139 also could cause epidemics very similar to those caused by *V. cholerae* O1. According to World Health Organization (WHO) guidelines, both *V. cholerae* O1 and O139 are now recognized causes of cholera and should be reported the same way. Isolates of non-O1 and non-O139 *V. cholerae* can cause illness, but they do not pose the public health threat of the O1 and O139 serogroups.

Additional details on the epidemiology, historical background, clinical manifestations and treatment of cholera are presented in Chapter 5.

2. Epidemic dysentery

Dysentery, defined as diarrhea with visible blood, can be caused by many different organisms, including *Shigella* spp., enterohemorrhagic *Escherichia coli* serotype O157:H7, *Campylobacter jejuni*, enteroinvasive *E. coli*, *Salmonella* spp. and, infrequently, *Entamoeba histolytica*. Of these organisms, the only ones known to cause large epidemics are *Shigella dysenteriae* serotype 1 (Sd1), and much less frequently, *E. coli* O157:H7. Additional details on the epidemiology, historical background, clinical manifestations and treatment of Sd1 infection are presented in Chapter 3.

Although uncommon, a species of parasitic ameba, *E. histolytica,* deserves mention. This organism is an occasional cause of dysentery, especially in young adults, but does not cause epidemic disease. Asymptomatic infection with *E. histolytica*, however, is frequent in developing countries, being present in up to 10% of healthy persons. Examination of specimens should be done by a trained microscopist since the organism must be differentiated from nonpathogenic amebae and from white blood cells, which are often mistaken for amebic

trophozoites. In some epidemics of dysentery due to Sd1, *E. histolytica* was also identified and initially thought to be the cause. Because of this incorrect diagnosis, persons with dysentery were treated with anti-amebic drugs, resulting in continued transmission of Sd1 and excess preventable mortality. Finding *E. histolytica* in a bloody stool during an epidemic of dysentery does not indicate that it is the cause of the epidemic, or even that it is the cause of dysentery in an individual patient.

E. coli O157:H7 has caused at least one large outbreak of dysentery in southern Africa. It is suspected to have caused additional outbreaks, but these were not confirmed by microbiologic culture. *E. coli* O157:H7 is included in this manual so that laboratory workers will be familiar with the organism and will be able to identify it if necessary. It may return in the future to cause additional epidemics; laboratories must be prepared to identify it.

Additional details on the epidemiology, historical background, clinical manifestations and treatment of *E. coli* O157:H7 are presented in Chapter 7.

B. Public Health Role of the Laboratory

Clinical laboratories play an especially crucial public health role during epidemics. A laboratory may be the only one in a country that can quickly provide the information needed to develop appropriate treatment policy during an epidemic. In countries with scarce resources, the role of the laboratory is to use those resources to provide the best information for developing treatment policy, rather than to focus on the diagnosis of individual patients. During an epidemic of cholera or dysentery, the laboratory has four primary roles:

- Initial identification of the organism causing the epidemic
- Initial determination of the antimicrobial susceptibility patterns
- Monitoring for changes in antimicrobial susceptibility patterns
- Defining the duration and geographic extent of the epidemic

The World Health Organization (WHO) recommends that countries at risk for epidemics establish an epidemic control committee. Since the laboratory plays an important role in the identification and control of epidemics, a microbiologist should be a part of the epidemic control committee.

1. Initial identification of the organism causing the epidemic

Preparation/laboratory network

In countries at risk for epidemics of dysentery or cholera, the laboratory's first role is to be prepared for an epidemic. This means having the supplies (or ready access to supplies) necessary to identify *V. cholerae* O1/O139 and *Shigella*. Annexes A and B in this manual list laboratory supplies required for isolation, identification, and antimicrobial susceptibility testing. A country-wide public health laboratory network should be established (see Annex C). All countries should have at least one national or central laboratory capable of

identifying *V. cholerae* O1/O139 and *Shigella*, determining antimicrobial susceptibility, and sending isolates to an international reference laboratory (Annex D).

To maintain a laboratory's capability to determine the antimicrobial susceptibility patterns of bacterial pathogens accurately and reproducibly, investments must be made in the infrastructure of the laboratory. These investments include a steady supply of the material resources needed to perform appropriate testing; a trained staff with expertise to conduct the laboratory tests and sufficient time, materials, and supplies to maintain this expertise; and quality control of the staff, supplies, and reagents. Because antimicrobial susceptibility testing is so resource intensive, WHO recommends that this testing be carried out at only one or two laboratories in the country. Peripheral laboratories may perform initial isolation of *Vibrio* spp. or *Shigella* spp., and then refer isolates to the central or national reference laboratory for final confirmation and determination of antimicrobial susceptibility. Peripheral laboratories may also be the sites of focused studies to determine etiologic agents causing an outbreak. First-level laboratories should be supplied with transport medium and the means of sending the specimens to the next level laboratory or to the central laboratory.

Diagnosing epidemics

During a suspected epidemic, the laboratory will determine the organism causing the epidemic and its antimicrobial susceptibilities. An epidemic may be suspected on clinical grounds: for instance, a surveillance system based on clinical diagnosis may note an increase in the number of cases of diarrhea. The laboratory should become involved as soon as possible to identify the causative agent. This underscores the need for good communication between the laboratory, the epidemiologists, and clinicians and other health care workers.

At times, the laboratory may be the first to suspect an epidemic. Laboratory workers may note an increase in the number of stool specimens submitted, an increase in the proportion of stool specimens with blood, or the appearance of a new organism. When a laboratory worker suspects an outbreak or epidemic, he or she should contact the appropriate clinicians and public health authorities as soon as possible.

Once the organism causing the epidemic is identified, it is not necessary to examine a large number of stool specimens. Patients can be treated on the basis of their syndrome.

Diagnosing dysentery epidemics

If an epidemic of dysentery is suspected, the most common cause in most parts of the world is Sd1. During an outbreak or epidemic, Sd1 is likely to be isolated much more frequently than the other organisms that cause dysentery. Therefore, a laboratory should conserve its resources and, according to WHO guidelines, once Sd1 has been confirmed as the cause of an epidemic, patients presenting with dysentery should initially be treated as if they are infected with Sd1. There is no

need for the laboratory to examine the stools of all patients. Rather, it is better to take specimens from a small number of patients during an outbreak or to conduct periodic surveillance for organisms causing dysentery (see below).

If Sd1 is not isolated during a suspected outbreak, the laboratory should test for *E. coli* O157:H7. If neither of these organisms is isolated, arrangements should be made to send specimens to a reference laboratory.

Besides Sd1 and *E. coli* O157:H7, a number of organisms contribute in various proportions to the burden of dysentery in a country. The predominant causes of dysentery will vary by geographic location and time of year. Seasonal peaks occur and may reflect changes in the proportions of the various causative organisms. Laboratories should conduct periodic surveys of the organisms causing dysentery in order to monitor antimicrobial susceptibility patterns and to help clinicians and public health authorities develop rational guidelines for empiric treatment. Procedures for conducting such surveys are described in Annex E.

Diagnosing cholera epidemics

If an epidemic of cholera is suspected, the most common cause is *V. cholerae* O1. If *V. cholerae* O1 is not isolated, the laboratory should test for *V. cholerae* O139. If neither of these organisms is isolated, arrangements should be made to send stool specimens to a reference laboratory.

Infection with *V. cholerae* O139 should be handled and reported in the same manner as that caused by *V. cholerae* O1. The associated diarrheal illness should be called cholera and should be reported as a case of cholera to the appropriate public health authorities.

2. Determining antimicrobial susceptibility patterns of epidemic organisms

Antimicrobial susceptibilities should be determined for the first 30 to 50 isolates identified by the laboratory at the beginning of an epidemic. That number will provide sufficient information to develop antimicrobial treatment policy for the organism. After that, the laboratory should conduct periodic surveys to detect any changes in antimicrobial susceptibility patterns (see Annex E).

The laboratory should not routinely test antimicrobial agents that are not available in the country or antimicrobial agents that are not recommended by WHO as efficacious in the treatment of cholera or dysentery (see Chapters 3 and 5). In addition, if all isolates are resistant to a particular antimicrobial agent during the first round of testing (for example, Sd1 resistance to ampicillin or trimethoprim-sulfamethoxazole), it is probably not useful to test against those agents during future surveys.

Once the organisms are isolated and the antimicrobial susceptibility patterns determined, these results should be transmitted as quickly as possible to the national epidemiologist and to other public health officials. They can then be used to make rational choices for antimicrobial treatment policy.

It is useful to send 10 to 20 of the initial isolates to an international reference laboratory for confirmation of the identification and antimicrobial susceptibility pattern (Annex D).

3. Monitoring for changes in antimicrobial susceptibility

As the epidemic progresses, periodic surveys of 30 to 50 isolates of the epidemic organism should be carried out to detect any changes in the antimicrobial susceptibility pattern of the organism causing the epidemic. These should be conducted every 2 to 6 months, depending on conditions and resources. Any changes should be reported to the national epidemiologist and to other public health officials to modify the antimicrobial treatment policy. If any major changes are noted, it is useful to send isolates to an international reference laboratory for confirmation (Annex D).

4. Defining the duration of the epidemic

The laboratory can help define the end of the epidemic, especially with cholera epidemics. In the course of an epidemic, the number of cases may decrease for several reasons: seasonal variation, transition to an endemic state, or disappearance of cholera from an area. Cholera may nearly disappear in cool seasons, only to reappear in the summer months. The laboratory can assist in determining if the epidemic has actually ended by periodically analyzing stool specimens from patients with acute watery diarrhea. In order for an area to be declared cholera-free by WHO, twice the incubation period (a total of 10 days) must pass without evidence of *V. cholerae* O1/O139. However, because of seasonal variation, surveillance should be maintained for at least 12 months.

Similarly, seasonal variation is seen with epidemic dysentery. The laboratory can periodically analyze stool specimens from patients with dysentery to see if Sd1 is still present in a particular area.

5. Other duties of the laboratory during an epidemic

In addition to the major duties outlined above, the laboratory can support other activities related to the epidemic.

Epidemiologic studies

At times, the laboratory may be asked to provide laboratory support to an epidemiologic study. By combining epidemiologic and laboratory data, studies that examine modes of transmission or risk factors for illness can be more specific and provide better information for the control of the epidemic.

Defining the magnitude of the epidemic and improving surveillance data

Cultures taken from a series of patients that meet the clinical case definition used during an epidemic can determine the predictive value of the definition. Such studies will confirm the accuracy of the case definition used for surveillance purposes and can provide a more accurate picture of the magnitude of the epidemic.

In addition, the laboratory may be called upon to support other activities such as environmental monitoring for *V. cholerae* O1/O139. These requests place additional demands on the resources of the laboratory. Therefore, the microbiologist must be part of the decision-making process to determine whether the laboratory has the capacity to support the particular request and whether it is an appropriate use of the laboratory resources.

References

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