



FIGURE 193-1 World distribution of cholera in 2010–2012. WHO, World Health Organization. (Courtesy of Drs. M. and R. Piarroux, Université de la Méditerranée, France; with permission.)

before becoming a persistent endemic problem. Currently, >90% of cholera cases reported annually to the World Health Organization (WHO) are from Africa (Fig. 193-1), but the true burden in Africa as well as in Asia is unknown because diagnosis is often syndromic and because many countries with endemic cholera do not report cholera to the WHO. It is possible that >3 million cases of cholera occur yearly (of which only ~200,000 are reported to the WHO), resulting in >100,000 deaths annually (of which <5000 are reported to the WHO).

After a century without cholera in Latin America, the current cholera pandemic reached Central and South America in 1991. Following an initial explosive spread that affected millions, the burden of disease has markedly decreased in Latin America. In 2010, a severe cholera outbreak began in Haiti, a country with no recorded history of this disease. Several lines of evidence indicate that cholera was likely introduced into Haiti by United Nations security forces from Asia, raising the possibility that asymptomatic carriers of *V. cholerae* play an important role in transmitting cholera over long distances. To date, the outbreak has involved more than 700,000 individuals, resulting in thousands of deaths. The recent history of cholera has been punctuated by such severe outbreaks, especially among impoverished or displaced persons. These outbreaks are often precipitated by war or other circumstances that lead to the breakdown of public health measures. Such was the case in the camps for Rwandan refugees set up in 1994 around Goma, Zaire, and in 2008–2009 in Zimbabwe.

Sporadic endemic infections due to *V. cholerae* O1 strains related to the seventh-pandemic strain have been recognized along the U.S. Gulf Coast of Louisiana and Texas. These infections are typically associated with the consumption of contaminated, locally harvested shellfish. Occasionally, cases in U.S. locations remote from the Gulf Coast have been linked to shipped-in Gulf Coast seafood.

In October 1992, a large-scale outbreak of clinical cholera caused by a new serogroup, O139, occurred in southeastern India. The organism appears to be a derivative of El Tor O1 but has a distinct LPS and an immunologically related O-antigen polysaccharide capsule. (O1 organisms are not encapsulated.) After an initial spread across 11 Asian countries, *V. cholerae* O139 has once again been almost entirely

replaced by O1 strains. The clinical manifestations of disease caused by *V. cholerae* O139 are indistinguishable from those of O1 cholera. Immunity to one, however, is not protective against the other.

PATHOGENESIS

In the final analysis, cholera is a toxin-mediated disease. The watery diarrhea characteristic of cholera is due to the action of cholera toxin, a potent protein enterotoxin elaborated by the organism in the small intestine. The toxin-coregulated pilus (TCP), so named because its synthesis is regulated in parallel with that of cholera toxin, is essential for *V. cholerae* to survive and multiply in (colonize) the small intestine. Cholera toxin, TCP, and several other virulence factors are coordinately regulated by ToxR. This protein modulates the expression of genes coding for virulence factors in response to environmental signals via a cascade of regulatory proteins. Additional regulatory processes, including bacterial responses to the density of the bacterial population (in a phenomenon known as *quorum sensing*), modulate the virulence of *V. cholerae*.

Once established in the human small bowel, the organism produces cholera toxin, which consists of a monomeric enzymatic moiety (the A subunit) and a pentameric binding moiety (the B subunit). The B pentamer binds to GM₁ ganglioside, a glycolipid on the surface of epithelial cells that serves as the toxin receptor and makes possible the delivery of the A subunit to its cytosolic target. The activated A subunit (A₁) irreversibly transfers ADP-ribose from nicotinamide adenine dinucleotide to its specific target protein, the GTP-binding regulatory component of adenylate cyclase. The ADP-ribosylated G protein upregulates the activity of adenylate cyclase; the result is the intracellular accumulation of high levels of cyclic AMP. In intestinal epithelial cells, cyclic AMP inhibits the absorptive sodium transport system in villus cells and activates the secretory chloride transport system in crypt cells, and these events lead to the accumulation of sodium chloride in the intestinal lumen. Because water moves passively to maintain osmolality, isotonic fluid accumulates in the lumen. When the volume of that fluid exceeds the capacity of the rest of the gut to resorb it, watery diarrhea results. Unless the wasted fluid and electrolytes are adequately replaced, shock (due to