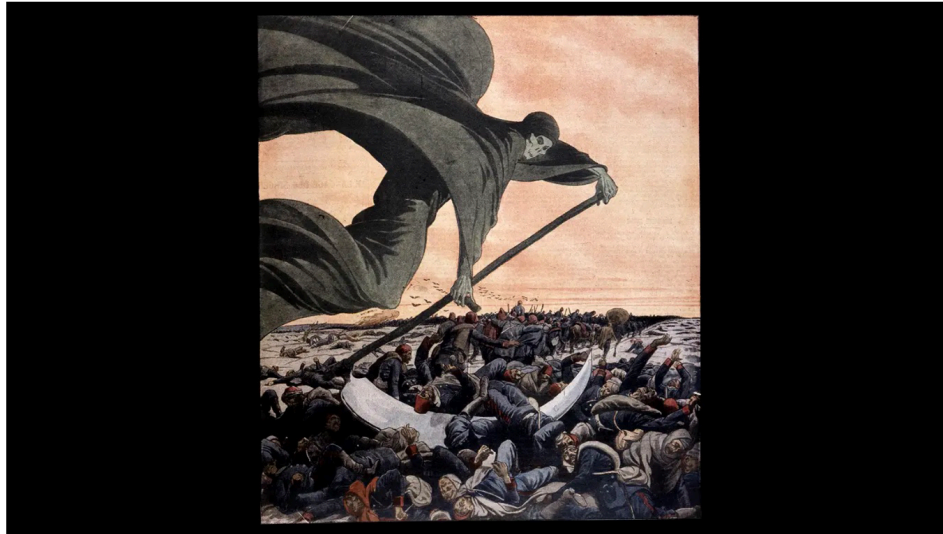


Cholera Returns With a Vengeance

— Climate change, conflicts, and depleted stocks of vaccine compound mounting concerns

by Claire Panosian Dunavan, MD December 22, 2022



"Le Choléra" first appeared in 1912 in an illustrated supplement of France's *Le Petit Journal*.

It has been a bad year for cholera, the fecally transmitted scourge once depicted as a supernatural reaper wielding a giant scythe. When the artwork above, "Le Choléra," first appeared in 1912, cholera's pathophysiology was still a mystery, but its clinical wrath wasn't. By then, it was public knowledge that cholera could sometimes transform a previously healthy human into a withered, gray corpse in a matter of hours.

Then came further scientific insights about cholera's comma-shaped, toxin-bearing bacillus that forms "micro-colonies" in human intestinal crypts, where *Vibrio cholerae* ultimately delivers its two-fisted punch: one set of subunit toxins attaching to GM1 gangliosides on the epithelial surface of small bowel cells, which, in turn, enables a second subunit toxin to reprogram those cells to secrete sodium and water.

This molecular assault unleashes cholera's sometimes-massive flux that far outweighs the loss of fluid and electrolytes triggered by any other gastrointestinal pathogen. One silver lining? The ability to resuscitate cholera sufferers with oral rehydration salts mixed in clean water or, in more severe cases, with IV infusions. And, starting in 2013, the World Health Organization's (WHO) stockpile of oral cholera vaccine (OCV) has been one more boon for the global poor who might otherwise suffer cholera. Yet, in 2022, cholera has resurged to such a degree that it is now striking fear, given that there are woefully scant tools and infrastructure to contain it in many of its traditional strongholds.

Cholera's Modern Burden

Today, experts believe, cholera still threatens more than a billion people in 69 countries opens in a new tab or window, annually infecting 1.3 to 4 million and killing up to 143,000. But because distinguishing one form of watery diarrhea from another isn't easy in its largely impoverished

haunts, its true burden is hard to prove. Nonetheless, newly erupting or protracted outbreaks stand out because of cholera's "equal-opportunity" toll on children and adults.

In 2022, such outbreaks occurred in 29 countries as compared to 23 in 2021 or the previous average of 20 country outbreaks per annum over the last 5 years. In addition, according to the WHO, 2022's global case-fatality rate climbed to 1.9% (2.9% in Africa). Root causes and contributing factors include a lack of investment in water and sanitation combined with conflict and complex humanitarian crises; climate change (cyclones in Mozambique and Malawi, for example, or flooding in Pakistan and drought in the Horn of Africa); fragile health systems and personnel stretched thin by other diseases; and a looming shortage of OCV.

This brings us to Haiti, where after a 3.5-year disease-free interval, cholera resurfaced at the end of September 2022. Haiti's story, in particular, holds significant lessons.

Cholera in Haiti: Past and Present

Louise Ivers, MD, is an infectious diseases specialist who is now the faculty director of Harvard's Global Health Institute and the executive director of Massachusetts General Hospital's Center for Global Health. Before assuming these posts, Ivers worked for many years for Partners in Health, a non-profit founded by the late Paul Farmer, MD, PhD. Her initial mandate was to expand community-based healthcare in Haiti for people with HIV and tuberculosis and malnourished children.

Then, January 2010 brought a catastrophic earthquake to Haiti followed 9 months later by the country's first-ever cases of cholera, which were eventually linked to an ill-fated leak of sewage from a Nepalese U.N. peacekeepers' camp. A local flurry of cases quickly rippled into a country-wide epidemic that sickened 820,000 people and caused close to 10,000 deaths. Ivers oversaw Partners in Health's on-the-ground operations and later partnered with the Haitian non-profit GHESKIO in a pioneering roll-out of OCV. It was clearly an unforgettable time.

"The first days and weeks we were just so busy trying to take care of thousands of people in our clinics, setting up treatment facilities, distributing water products, getting community health workers trained ..." Ivers recalled in a 2017 interview. "The stories I heard were humbling. There was so much suffering and so much fear. People lost whole families to cholera in a wave of illness that they (and we) had never before experienced."

This year, in contrast, when Haiti's latest outbreak erupted and rapidly spread (by mid-December, cholera had already caused suspected infections in nearly 15,000 people and 291 registered deaths, everyone from officials in the Ministry of Health to Haiti's poorest residents were far better prepared to fight it. At the same time, however, they were hampered by global donors' failure to deliver on earlier promises to improve local water.

In Haiti, 35% of residents currently lack access to safe water and up to 65% have inadequate sanitation or none at all; places to wash one's hands with soap and clean water are available to less than a quarter of the population.

"People know they should wash their hands and treat their water, but they don't have the resources to do it ... some literally have to choose between food and school and soap," Ivers recently said.

Haiti is also facing "the worst socio-political situation I've observed in my 20 years in the country," she added. "The gang violence and political stranglehold have had a huge humanitarian impact." Recent shortages of fuel have also hindered outreach and travel by healthcare workers and the pumping of potable water.

The next challenge? Local authorities must now decide who will receive rationed doses of OCV.

An Uncomfortable Question

Well before December 12, 2022, when Ivers and I spoke on the phone and Haiti was due to receive 1.6 million OCV doses, WHO was nervous about its rapidly depleting stockpile of OCV, having already dispensed two-thirds of this year's 36 million doses.

Adding to WHO's worry is the coming drop-out in 2023 of one of only two providers of low-cost OCV for use in humanitarian emergencies. The decision by Shantha Biotechnics, a fully owned subsidiary of Sanofi, was announced in 2020. Right now, that leaves South Korea's EuBiologics, maker of Euvichol, as the sole OCV manufacturer.

So, here's a question to ponder: Now that cholera has returned with a vengeance in 2022, what company or consortium will step up in light of the limited return on investment of producing vaccines exclusively meant for desperately poor countries?

What argument around investing in vaccines to fight cholera might resonate with Americans? I asked Ivers. She didn't mince words. "To me, it's always the moral argument. With very rare exceptions, cholera kills poor people who don't have access to the most basic human needs of safe water, sanitation, and food to eat. In 2022, it's just incomprehensible that we could be willing to let people die of dehydration and diarrhea because they don't have clean water plus other preventive tools."

In those words, I heard an echo of the impassioned vision of Ivers' long-time mentor Farmer, who never stopped believing in the right to health of the poorest of the poor. Perhaps it's a fitting end-of-the-year message for us all.

Claire Panosian Dunavan, MD, is a professor of medicine and infectious diseases at the David Geffen School of Medicine at UCLA and a past-president of the American Society of Tropical Medicine and Hygiene. You can read more of her writing in the "Of Parasites and Plagues" column.