EXPLORING CHOLERA PREDICTION BY ANALYZING ENVIRONMENTAL RISK FACTORS AND TRANSMISSION PATHWAYS

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Abstract: *Climate affects aquatic Vibrio cholerae. Socioeconomic variables and other factors affect cholera outbreaks. Since 1960, millions have contracted cholera. Hence, cholera remains a health risk, particularly when hydrological and environmental changes affect human vulnerability. Cholera outbreaks can either epidemic or endemic. Traditional compartmental susceptible-exposed-infected-recovered (SEIR) models predict human cholera transmission through the fecal–oral route. These models ignore additional infection routes like pathogen mobility and illness transmission heterogeneity. Trigger-only models have predicted real-time outbreaks but not cholera transmission. Since cholera outbreaks may become endemic, a full transmission model is needed to predict quantitative environmental risk. Given V. cholerae's autochthonous aquatic nature and illness prediction, we examine epidemic and endemic trigger module development.*

Keywords: *Vibrio cholerae; trigger; transmission; prediction; cholera; environmental parameters*

Introduction

Vibrio cholerae-contaminated water has caused cholera for eons. During the 1960s, the seventh cholera pandemic has killed millions [1–3]. An estimated one million cases are reported yearly in Latin America, sub-Saharan Africa, and Southern Asia [4,5]. The WHO expects four million worldwide cholera cases each year [4]. Many cholera cases, especially in developing areas, go unreported.

Recent coastal cholera outbreaks [7,8]. In aquatic habitats with hydrological and environmental changes, V. cholerae flourishes. Disasters can cause massive cholera outbreaks. One of 2016's worst cholera outbreaks followed Hurricane Matthew's rains on Haiti's southern coast [9]. Broken water, sanitation, and hygiene (WASH) infrastructure, high temperatures, and above-average rainfall exposed the population to filthy water. Cholera followed.

In conflict, infectious infections have killed more individuals than combat casualties [10]. Since March 2015, Yemen has experienced major civil unrest. The first sporadic cholera outbreak occurred in Yemen in October 2016. After the initial reports, cholera infections fell for a few months until the WASH infrastructure failed, triggering a massive increase. Public health suffered by the disease's recurrence and environmental exposure. Yemen suffered the largest cholera outbreak in history by 2017 [11], accounting for an estimated 80% of global cholera cases during 2015 [12]. The Yemen cholera outbreak indicates that manufactured disasters may have similar or worse health effects.

Epidemic cholera occurs intermittently or in huge outbreaks, whereas endemic cholera occurs annually, often with

seasonal peaks. Epidemiological surveillance implies the Yemen cholera outbreak began epidemically [13]. High air temperatures and heavy rains in WASH-deficient regions cause epidemic cholera. Hence, cholera will spread more [14,15]. In contrast, endemic cholera has been reported in locations where V. cholerae is persistent, even at low abundance, and circulates in aquatic habitats (e.g., rivers, estuaries, and coastal aquatic ecosystems providing circumstances suitable for the bacterium) (e.g., rivers, estuaries, and coastal aquatic ecosystems providing conditions favorable for the bacterium). Environmental factors may induce endemic cholera to recur seasonally [16,17]. Cholera outbreaks may become endemic, increasing exposure to and transmission of V. cholerae [18]. From our past investigations [2,19–23], V. cholerae ecology must be examined in the context of its natural watery environment and a changing climate that may re-emerge cholera.

Cholera is triggered and transmitted. The trigger module helps V. cholerae multiply, persist, and disseminate (TM). V. cholerae will interact more with people when TM displays high bacterial abundance and poor WASH infrastructure. Following a TM, the transmission component (TrM) entails intricate human-contaminated water interactions and cholera epidemics. TrM's main theory is that intestinal colonization and cholera germ shedding may contaminate drinking water [18]. Under proper conditions, feces–environment–oral transmission spreads the bacterium. We study the TM and TrM of epidemic and endemic cholera in the context of V. cholerae as a bacterium autochthonous to the aquatic environment and prediction of human cholera.

Vibrio cholerae and Its Natural Habitat

Gram-negative aquatic bacterium Vibrio cholerae causes cholera. V. cholerae was clinically diagnosed during outbreaks [24]. Culture-based approaches discovered environmental V. cholerae before epifluorescent microscopy [25,26] and molecular markers. Those studies underestimated environmental populations because V. cholerae may become VBNC. The VBNC state lets bacteria stay metabolically dormant between outbreaks under unfavorable conditions. Environmental conditions increase VBNC cell cultivability and virulence. V. cholerae attaches to zooplankton via converting to biofilm. Zooplankton—copepods—eat phytoplankton. Copepods affect phytoplankton blooms. V. cholerae thrives in nutrient-rich coastal waters. As a copepod may contain 104 V. cholerae cells, consuming untreated water with a few copepods increases the chance of infection. Copepods transmit diseases. V. cholerae is abundant in sediment and aquatic animals (e.g., crustaceans, arthropods, fishes, waterfowl, and aquatic plants). V. cholerae, phages, and protozoa may form hostile relationships that reduce microbial populations and change evolution.

V. cholerae has many genotypic and phenotypic features with Enterobacteriaceae, and toxigenic strains may produce cholera toxin, a major virulence factor, by horizontal gene transfer mediated by a lysogenic bacteriophage. The presence and broad distribution of its virulence genes in the environment are well documented, and genes that contribute to V. cholerae's

pathogenicity for humans may also have environmental relevance (e.g., allowing metabolic processes, establishing symbiosis, and/or modulating predator/prey relationships in the natural aquatic environment). New evolutionary lineages with mutations may enable V. cholerae adapt to aquatic settings. Chitin and nutritional limitation may influence horizontal gene transfer. It is important to determine the total number of V. cholerae in samples because many environmental isolates encode various virulence factors and genetic mutations, some of which can alter virulence factor production, horizontally acquire additional pathogenicity genes, and even undergo serogroup conversion.

Seasonal aquatic environment changes cause cholera outbreaks in endemic locations. The Bengal Delta region's hydroclimatic environment creates bi-modal peaks in cholera cases during outbreaks. Cholera cases surge in warmer months in South America and Africa. Heatwaves and growing sea temperatures (up to 1.5 °C over the previous half-century) have been associated to long-term increases in pathogenic Vibrio spp., such as V. cholerae, V. parahaemolyticus, and V. vulnificus, throughout Northern Europe and the Atlantic coast of the US [21]. While certain Vibrio spp., such as Vibrio splendidus, express virulence factors at low temperatures, increases in Vibrio abundance in Northern Europe and the US were connected with an unusual incidence of environmentally acquired Vibrio infections in humans [21]. Increasing water temperature could lengthen V. cholerae's seasonal abundance, harming public health.

V. cholerae is aquatic and essential to nitrogen cycle. As a re-emerging infectious disease and in risk prediction models, V. cholerae ecology must be understood in terms of environmental variables that drive cholera. Early warning systems will also safeguard public health in locations prone to natural disasters like hurricanes and earthquakes or active conflict like social instability or civil war, which destroy clean water and sanitation infrastructure.

Trigger and Transmission Components for Prediction of Cholera

Travel spreads cholera [24]. Hydroclimatic processes impact aquatic V. cholerae distribution, growth, and incidence [2]. Hence, global travel, climate change, and population exposure to new disease outbreaks spread cholera. Environmental prediction modeling may improve epidemiological cholera control. In 1996, Colwell [2] proposed remote sensing for cholera epidemic prediction models. Several studies have related V. cholerae to environmental variables such sea surface temperature, height, chlorophyll, precipitation, water storage, and salinity and advocated utilizing them to anticipate cholera risk. Hence, cholera trigger and transmission environmental factors are automated. While both TM and TrM are important in understanding the global persistence of cholera, epidemic sites have higher mortality rates (>3%) than endemic areas (<1%) [15]. Intervention efforts have focused on TM of predictive cholera modeling systems.

In 2013, Jutla et al. [15] suggested an epidemic cholera trigger risk prediction method based on anomalously high temperatures and precipitation during a four-week period in a location with damaged or impaired WASH

infrastructure. This environment exposed people to polluted water. If any prerequisite is missing, this theory predicts a lower pandemic likelihood. South Sudan, Cameroon, Zimbabwe, Haiti, Mozambique, Rwanda, Central African Republic, Nepal, and Bangladesh validated the idea geographically and temporally. Forecasting natural or anthropogenic cholera epidemics was included. Natural and anthropogenic disasters that damaged WASH facilities were generally followed by heavy precipitation, creating an environment conducive for V. cholerae growth and increased human contact with polluted water sources. Hence, predictive environmental TMs may help policymakers and health specialists control and eliminate cholera. After an outbreak, the TM and TrM should follow cholera. The transmission component, which focuses on human disease dynamics, is better for cholera forecasting and public health decision-making than the TM. A region's actual case count and the model's prediction have been reduced by several modeling efforts (i.e., the forecasted number of cases). Most TrMs adopt the compartmental model because of its simplicity. Compartmental models classify people as Susceptible (S), Exposed/Infected (E/I), or Recovered (R) (R). Epidemiology study employs the four-chamber SEIR transmission model [18]. Population transition rates assess disease patterns (i.e., S, E, I, and R). Figure 1 depicts a basic SIR model expanded to S-E-I-R to account for the pathway between susceptible and exposed populations that may become infected.

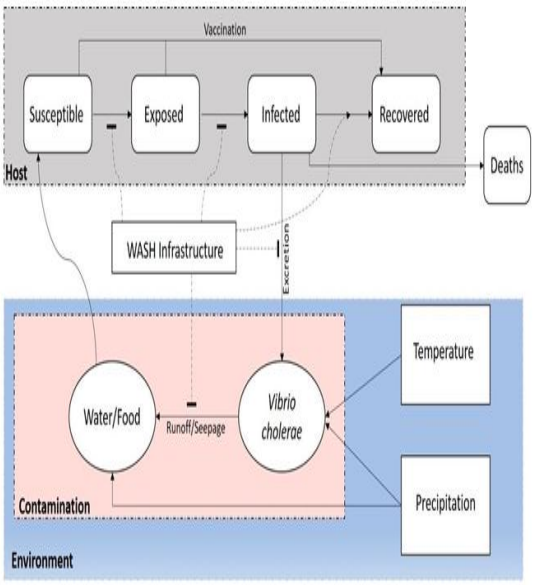

Figure 1. Fundamental cholera susceptible-exposed-infected-recovered (SEIR) transmission model.

Four entities—S, E, I, and R—cause cholera epidemics in the SEIR model. Hence, a population needs V. cholerae and susceptible individuals. A random epidemic cannot become pandemic without all four elements. Human-pathogen cycles drive cholera. SEIR-based TrM resilience depends on interaction capture. Hence, several studies have improved the SEIR model utilizing mathematical and biological concepts to represent complex cholera outbreaks. Table 1 shows SEIR model cholera pandemic research.

Different population structure, socio-economic characteristics, and other factors impacting cholera transmission dynamics have been proposed for more complex SEIR modeling models. Mathematical complexity in an SEIR model addresses cholera transmission stochasticity.

Yet, rigorous mathematical complexity may impair intervention assessment and behavioral change. Simplifying assumptions reduces predictive power and uncertainty. V. cholerae, the pandemic

serogroup, induces vibriocidal antibodies that prevent reinfection. Modeling cholera vaccines implies vaccinated vulnerable individuals are "resistant" since they have the same protection rate as naturally sick people. While models assume a stable population age, cholera is more frequent in children under 5 and the elderly. SEIR implies rational sickness response. This assumption requires the vulnerable population to be educated about the severity of the cholera epidemic, boil or filter water, clean food preparation spaces, correctly prepare food (particularly seafood), and practice adequate sanitation, including excreta disposal. SEIR models presume rationality, but measuring human behavior realistically is challenging. This assumption simplifies the model but fails to incorporate cholera transmission heterogeneity, increasing model prediction error. Cholera modeling assumes homogenous mixing of susceptible and infected persons, complicating human factor explanation. Socioeconomic status profoundly affects individuals. To prevent the issue of homogenous mixing, sensitive populations have been split into low- and high-risk groups or age, neighborhood, and behavioral risk categories. Education prevents cholera in at-risk populations most cost-effectively.

These methods predict cholera transmission in well-mixed populations, but they do not account for indirect infection processes such pathogen translocation or disease transmission heterogeneities. Human-environment interaction predicts cholera. Traditional SEIR models predict highly infectious human disease propagation by direct human-to-human contact (e.g., influenza and COVID-19 viruses) better than cholera, which requires indirect transmission. Indirect transmission pathways need water quality, seasonality, and climate-driven SEIR models. Seasonality is studied in Bangladesh and Yemen, where monsoons generate bimodal cholera peaks [13,17]. SEIR models benefit from environmental influences. V. cholerae in aquatic environments is multifaceted, therefore one environmental variable cannot reflect indirect cholera transmission. Cholera epidemic dynamics must be modeled using direct and indirect transmission pathways. In real-time cholera prediction, environmental parameter models outperformed SEIR models, suggesting indirect transmission channels should be investigated. Sensitivity study shows parameter uncertainty in SEIR models, demonstrating that slight inaccuracies in model parameters like infection rate may cause substantial performance changes. Due to parameter uncertainty and inability to capture indirect transmission channels, SEIR models have had less success forecasting cholera than other infectious diseases.

Table 1. Cholera prediction using variants of susceptible-infectious-recovered models.

Author(s)	Study Descriptions/Methodology	Important Findings and Outcomes
Codeço 2001 [18]	Proposed mathematical model to explain the dynamics of epidemic and endemic cholera. This study is one of the first applications of the SIR model for cholera transmission.	• Cholera epidemiology depends on social and environmental factors. • Complex interaction between host and pathogen is difficult to model.
Wang et al., 2015 [83]	Separated ordinary differential equation (ODE) and reaction-convection-diffusion partial differential equation (PDE) models to examine the homogeneous and heterogeneous environments associated with cholera transmission.	• Basic reproduction number (R_0) remains a sharp threshold for disease dynamics even when human behavior is considered. • Proposed mathematical justification of several consequences associated with human behavior.
Ieszaros et al., 2020 [84]	Proposed a mathematical model for cholera incorporating transmission within and between households.	• Vaccine interventions appeared more effective than water treatment or antibiotic administration to control household cholera.
Abrams et al., 2013 [85]	Developed three cholera surveillance models to forecast the expected number of cases in Haiti during the 2010–2011 cholera epidemic.	• Models increased in complexity as more information became available: first projection estimated 105,000 cholera cases the first year; subsequent projections using different methods estimated up to 652,000 cases. • Timely and realistic projections are crucial in areas with limited resources: real-time projections allowed public health officials to plan and implement response measures better.
Torres et al., 2018 [82]	Proposed and analyzed a SITRV (susceptible-infectious-treated-recovered-vaccinated) type model for cholera.	• The SITRV type model fits well for the cholera outbreak in Yemen April 2017–2018. • The model provides important conclusions concerning vaccination campaigns during a cholera outbreak.
Che et al., 2020 [86]	Used a "fitted" demographic equation (i.e., disease-free equation) to capture total population and a fitted low-high risk structured cholera differential equation model to study reported cholera cases in Cameroon 1987–2004.	• Dual strategies of either vaccination and treatment or vaccination and improved sanitation or combined strategy of vaccination, treatment, and improved sanitation reduce the basic reproductive number of cholera cases. • Rates of scaled contact and the vaccination of susceptible populations are important parameters for cholera prediction.
Dangbé et al., 2018 [87]	Proposed a model considering climatic factors and human behavior on the spread of cholera	• The transmission and spread of cholera can be affected by climatic factors, the proportion of malnourished individuals, and the number of individuals practicing proper hygiene. • Disease-free equilibrium stability depends on the basic reproduction number (R_0).
Baracchini et al., 2017 [56]	Proposed a stochastic, rainfall–temperature driven model to examine the seasonality of cholera in Bangladesh.	• Rainfall buffers disease transmission in wet regions while enhancing cholera resurgence in dry regions. • Local variation of temperature and rainfall can be used to explain seasonal patterns.
Koepke et al., 2016 [97]	Proposed a predictive 'susceptible-infected-recovered-susceptible' (SIRS) type model in the form of continuous-time hidden Markov states to estimate the contribution of water depth and water temperature on the spread of cholera.	• Hidden states can be used to predict an increase in infected individuals weeks before the observed number of cholera cases increases, thereby providing early notification of the epidemic. • Added support to the hypothesis that environmental forces influence the trigger of a cholera outbreak.
Perez-Saez et al., 2017 [58]	Proposed a probabilistic spatial model to investigate the role human mobility plays in cholera transmission.	• With respect to cholera risk, highly populated urban centers are more sensitive to El Niño/Southern Oscillation than rural periphery. • Cholera risk is largely transmitted from a climate-sensitive core to the periphery. • Included human mobility as a model parameter to improve outbreak prediction performance.

1. Discussion

Marine animal, plant, and prokaryote communities—essential to life on Earth—have suffered from climate change. Precipitation and temperature changes have caused global infectious diseases to originate and re-emerge throughout the last 50 years. The IPCC's Fourth Assessment Report forecast long-term increases in precipitation, temperature, and catastrophic events including droughts, floods, hurricanes, and tornadoes. Complicated environmental interactions impact disease agents' ecological niches. V. cholerae has expanded globally. Pandemic cholera only included V. cholerae serogroup O1. Non-O1 V. cholerae may produce moderate to fatal diseases. V. cholerae non-O1 infections, a prominent climate change-related disease, are growing.

Climatic fluctuation may affect infectious disease genesis, dissemination, and prevalence locally and globally, endangering public health. Haiti's cholera pandemic [9]. Yemen's 2016 civil war caused cholera. Cholera is spreading there. Haiti and Yemen had high temperatures and precipitation with cholera, validating the trigger theory. Despite advancements, a compartmental cholera predictive modeling system that tracks disease transmission is still lacking. Cholera in Haiti and Yemen requires quantitative environmental risk models. Global models must use real-time data and comparison data baselines to improve output and prediction.

Water contains V. cholerae.

Cholera is manageable but not eradicated. Public health needs cholera risk assessment predicting algorithms. Transmission components and predictive modeling are common. Trigger components are needed to study cholera dynamics and development. Triggers improve quantitative risk modeling and disease intervention. Most cholera

mechanistic studies employ the susceptible-exposed-infectious-recovered compartmental model. Mechanism-driven compartmental models cannot assess cholera spread uncertainty. Transmission modeling for quantitative risk prediction improves outcomes. Satellite remote sensing will soon finish cholera prediction transmission.

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