January 2023

Developing And Using Cholera Models In Northwest Syria

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Master of Public Health Thesis
April 2023

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Abstract

Researchers have utilized transmission dynamic modeling to determine interactions between hosts and pathogens in many humanitarian settings. However, modeling for the cholera outbreak in Northwest Syria (NWS) has yet to be completed. This thesis presents a path towards cholera model building in NWS by investigating the current cholera outbreak, outlining how to create a compartmental model in this region given its complexities, and determining ways potential cholera models could be utilized in NWS. Intricacies involving the region's ongoing civil war, significant internally displaced persons (IDP) population, and the February 2023 earthquake add complexities to modeling in this region. For the modeling process to begin, an equitable, trusting relationship with humanitarian actors and other stakeholders must be built. Modeling cholera in NWS also involves tackling the challenges of data availability and sensitivity from it being a conflict zone. The parameter research and estimation process will need to be context specific to account for the complexities of NWS being a conflict zone. Field epidemiology is one way to collect information surrounding the parameters of the pathogen and the host, but doing so in a humanitarian conflict has been challenging. Demography parameters are difficult to estimate in NWS due to insufficient infrastructure, security issues, the large percentage of IDPs in the population, and the lack of Civil Registration and Vital Statistics (CRVS). Models can be utilized to incorporate interventions and cost-effectiveness. Modeling the transmission dynamics of the cholera outbreak in NWS will allow health organizations and NGOs to maximize preparedness and correctly allocate resources.

Acknowledgments

First, I am deeply grateful to my advisor, Dr. Kaveh Khoshnood, for his support and mentorship throughout the thesis process. His expertise in humanitarian health has been invaluable to me and played a critical role in the success of this thesis.

Similarly, I would like to thank my secondary advisor, Dr. Danielle Poole, for her continued support and input. Her expertise in population health in the humanitarian field contributed substantially to this thesis.

I would also like to thank those at the Assistance Coordination Unit’s Early Warning and Response Network in Turkey, especially Dr. Naser Almhawish, for their continuous support and for always answering my inquiries.

Finally, I would like to acknowledge those affected by the earthquake on February 6, 2023, in Turkey and Syria. My thoughts are with all those affected and their families.

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Introduction

Transmission dynamic modeling has been used in multiple humanitarian settings, including conflict zones and other high-risk settings, to determine interactions between hosts and pathogens under the impact of scarce medical resources. For example, infectious disease modeling regarding COVID-19 has been performed to provide helpful insights for refugee camps in Bangladesh[1], Syrian refugees in Lebanon[2], and the Moria displacement camp in Lesbos, Greece.[3]

Researchers have specifically modeled cholera in Yemen[4], Haiti[1,5], and multiple African countries[6] to determine epidemic trajectories, discover impactful interventions, and learn about influential conditions (e.g., environmental and socio-economic) that affect cholera transmission. However, transmission dynamic modeling specific to the cholera outbreak in Northwest Syria (NWS) has not yet been completed. Modeling the transmission dynamics of the cholera outbreak in NWS will allow health organizations and non-governmental organizations (NGOs) to be more prepared regarding the kit volume needed and determine hospital readiness (e.g., healthcare workers and bed allocation). In addition, evaluating the potential impact of interventions will give decision-makers in these organizations more knowledge about where to appropriate funding.

Modeling the transmission dynamics of the cholera outbreak in NWS will give decision-makers a lens into what the epidemic trajectory of cholera will look like in the future. This thesis describes cholera in NWS as it relates to the current outbreak, outlines how to develop a compartmental model in this region given complexities, identifies the challenges with modeling in this region, determines ways potential cholera models could be utilized in NWS, and provides recommendations and insights into the future directions of modeling in this region. Additionally, this thesis serves as a foundation for modelers who aim to model the cholera epidemic in NWS by identifying relevant and useful data sources that could be utilized during their research process.

Background

Cholera

Cholera is an acute diarrheal infection caused by consuming food or water contaminated by the bacterium, *Vibrio cholerae*.[7] About 10 percent of people who get cholera will experience severe symptoms. These symptoms include the following in the early stages: watery diarrhea (sometimes called "rice-water stools"), cramps in the legs, thirst, restlessness or irritability, and vomiting.[7] It generally takes anywhere from 12 hours to 5 days post-ingestion for an individual to develop symptoms; however, most individuals infected with *V. cholerae* do not exhibit any symptoms. These asymptomatic individuals can still potentially infect other people because bacteria can remain in an infected person's feces for up to ten days before being shed back into the environment.[8]

It is critical to have quick access to treatment during a cholera outbreak. With prompt and appropriate treatment, the case fatality rate should remain below one percent. Oral rehydration solution (ORS) can be quickly administered to treat most patients successfully.[8] Patients who are severely dehydrated risk going into shock, so they must receive intravenous fluids immediately. Antibiotics are also provided to these severely dehydrated patients to shorten the duration of their diarrhea, reduce the amount of *V. cholerae* excretion in their stool, and reduce the number of fluids they need to rehydrate.[8] The mass distribution of antibiotics is not recommended as it can add to antimicrobial resistance. Additionally, antibiotics have not been shown to stop the spread of cholera.[8]

There are currently three World Health Organization (WHO) pre-qualified oral cholera vaccines (OCV): Dukoral®, Shanchol™, and Euvichol®. Each of these vaccines requires two doses for complete protection. Shanchol™ and Euvichol® can be given to individuals over the age of one year, and Dukoral can be administered to those over the age of two years.[9] Euvichol® and Shanchol™ are practically the same vaccines, just produced by separate manufacturers. Two doses of Euvichol® and Shanchol™ protect against cholera for three years, and a single dose provides short-term protection. These two OCVs are currently available for mass vaccination campaigns through the Global OCV Stockpile, which the Global Alliance for Vaccine and Immunization (GAVI) supports. Dukoral® is generally given to those traveling.[9]

The global cholera trend is moving towards more widespread and intense outbreaks. From January to October 2022, 29 countries across the globe reported cholera cases — a drastic increase compared to previous years.[10] As a result, the global supply of cholera vaccines has been severely strained. To combat this, the International Coordinating Group (ICG), which handles emergency supplies of cholera vaccines, temporarily suspended the routine two-dose OCV regimen for the cholera outbreak response campaign and switched to a single-dose approach instead.[10] Switching to a single dose will allow more people to get at least short-term protection.

Cholera in Humanitarian Settings

Cholera is a severe threat in humanitarian settings. Often, these settings lack infrastructure and do not meet the minimum safe water requirements. Therefore, the introduction or presence of *V. cholerae* in the environment can result in large cholera outbreaks that quickly develop with devastating outcomes.[11] *V. cholerae* in an area often points to inequity and a deficiency of social development.[8] The foundation of cholera control and management is water that is both safe and accessible, adequate sanitation in the region, and economic development. Therefore, measures that target implementing sustainable water, sanitation, and hygiene (WASH) solutions to ensure safe water use, fundamental sanitation, and proper hygiene practices in areas that may be at an increased risk for cholera outbreaks are essential.[8]

The health risks associated with displacement, overcrowding, and inadequate initial water and sanitation treatment among those entering the camp population make refugee camps specifically more susceptible to cholera outbreaks.[12] Between 2009 and 2016, 26 of the roughly 500 refugee camps and sites that were mandated to report to UNHCR documented confirmed cases of cholera. This likelihood of cholera spreading can be significantly reduced by timely and proper camp planning, preparedness, coordination with local Ministries of Health, and commitment to minimum WASH norms.[12]

Conflict in Northwest Syria

The violent government crackdown on public demonstrations in support of a group of teenagers arrested for anti-government graffiti in Daraa in March 2011 marked the beginning of the conflict in Syria. These arrests, in turn, inspired more demonstrations which were also violently suppressed by the Syrian government. As a result, the conflict quickly grew, the nation became embroiled in a civil war, and millions of Syrian families were forced to leave their homes.[13] By June 2021, the Civil War in Syria was the greatest humanitarian crisis associated with war. More than 606,000 people had died, and roughly 13 million Syrians had experienced displacement.[14]

A region that this conflict has heavily impacted is NWS which is an opposition-controlled area composed of parts of the Idleb and Aleppo Governorates. It is home to approximately 4.4 million people, 2.8 million of whom are categorized as internally displaced persons (IDPs).[15] NWS became a shared location that Syrians escaped to during Syrian regime advances post-2015 when Russia entered the conflict. Most health care in NWS is provided by NGOs.[16]

A variety of factors impact healthcare delivery in this region, including funding and assistance often being weaponized or politicized. In addition, there is a lack of a centralized body to coordinate actions, healthcare facilities lack the staff and resources needed to operate sufficiently, and healthcare facilities often are the target of deliberate attacks despite being protected from attack under International Humanitarian Law (IHL).[16]

The Outbreak of Cholera in Northwest Syria: 2022

At the end of August 2022, a cholera outbreak in Syria began, mainly in the Aleppo Governorate. A rapid assessment performed by health affiliates found the outbreak's source was likely connected to individuals drinking unsafe water from the Euphrates River and individuals using this contaminated water for crop irrigation.[17]

On September 19, 2022, the first cholera case in NWS was confirmed, and by October 22, 2022, 159 lab-confirmed cholera cases, along with two deaths, had been documented in NWS.[18] It is estimated that over 2.1 million people currently reside in the areas of NWS that are most at risk for experiencing a cholera outbreak.[19] As of February 18, 2023, there were 48,586 suspected cases of cholera and 21 confirmed resulting deaths reported in NWS since the start of the outbreak. Of these cases, nearly half were children under five.[20] Per the WHO guidelines, an individual is considered a suspected cholera case in regions with a confirmed cholera outbreak if they are presenting with or dying from acute watery diarrhea. A confirmed case of cholera requires diagnostic laboratory testing.[21] However, diagnostic testing of every case is not feasible in a resource-limited setting, such as NWS. Relying on symptoms can be insightful and less resource intensive.

Teams in NWS are currently implementing different actions to mitigate cholera in the region. The Assistance Coordination Unit (ACU) is a national, non-political, non-governmental, and non-profit organization that was established in 2013. They are physically located in Gaziantep, Turkey, but conduct much of their work in NWS.[22] The WASH team for the ACU centers its attention on investigating WASH services in areas deemed cholera hotspots.[21] This examination includes obtaining samples of drinking water, analyzing sewage networks and other sanitation facilities, describing hygienic practices, and evaluating agricultural markets in terms of their water sources and products. Additionally, the ACU teams administer awareness sessions about cholera, including prevention and control strategies. These sessions are for local authorities and affected individuals identified during the investigation.[20]

On January 19, 2023, UNICEF and GAVI delivered the first allotment of just over 1.7 million OCVs to NWS via the Bab al-Hawa crossing.[23] Crucial to this delivery was the resolution passed on January 9, 2023, by the UN Security Council to extend cross-border aid access to NWS for an additional six months. The WHO and UNICEF led the launch of a cholera vaccination campaign starting on March 7, 2023. The Sarmada, Maaret Tamsrin, Dana, and Atmeh districts in Idleb and the A'zaz district in Aleppo were deemed the areas most at risk for cholera. The campaign aims to reach a total of 1.7 million people over the age of one in these at-risk areas. As of March 15, 2023, nearly 1.4 million people had been vaccinated against cholera.[24] Additionally, a lack of funding is viewed as a primary obstacle to consistent and coordinated healthcare response in NWS. As a result, there have been concerns over whether or not a lack of funds will compromise the ability of healthcare providers in the region to carry out a vaccination campaign.[23] Local humanitarian organizations, including the Free Idlib Health Directorate and Syria Response Coordinators, have emphasized the problematic slow delivery of medical aid and OCVs to NWS and have increased pressure on the international community to provide additional support for cholera treatment and isolation centers.[23] Crucial funding is also needed to sustain Cholera Treatment Units (CTUs) and strengthen other healthcare needs.[25] As of late 2022, the WHO supported six cholera treatment centers in NWS.[26]

2023 Turkey–Syria Earthquake

On February 26, 2023, an earthquake with a magnitude of 7.7 on the Richter scale hit southern Turkey and northern Syria. As of February 28, 2023, there have been over 4,500 deaths and 8,700 injuries reported in NWS alone, along with more than 10,000 buildings completely or partially destroyed.[27]A total of 137 cities and towns in NWS were affected, seven of which were heavily affected. Those residing in these areas may not have shelter for a long time. Additionally, water and sanitation systems in these areas have also been destroyed, making partially destroyed housing uninhabitable. The population of these heavily affected cities is 374,514.[27]

The post-earthquake period has seen a lot of population movement. As of February 26, 2023, nearly 30,000 Syrian refugees from Turkey had crossed the border into Syria via the Bab Al-Hawa, Bab al-Salameh, and Jarablus border crossings.[27] The migration came after the border crossings between Syria and Turkey announced that they would begin accepting Syrians residing in Turkey who were receiving temporary protection granted by Turkey. These Syrians will not be permitted to return to Turkey for three months but are not allowed to stay in Syria for longer than six months. Reported reasons for fleeing Turkey for Syria were the deterioration of living conditions, the high cost of housing, and the interruption of livelihoods during the earthquake.[27]

The earthquake has also had significant effects on healthcare and cholera in NWS. UN OCHA reported that as of February 26, 2023, at least 55 health facilities in NWS had sustained damage and 15 health facilities were shut down.[28] The ACU reported there was a significant decrease in the number of cholera cases reported and samples collected after the earthquake. They attributed this to the fact that health facilities were shut down and individuals were helping earthquake victims.[20]

The WASH team at the ACU is working to assess water stations in order to estimate the impact of the earthquake in the NWS region regarding water quality. They assessed a total of 642 stations.[20] As of February 28, 2023, they determined that approximately 29 stations were suspended due to the earthquake and 50 stations experienced damage to the ground tank. Additionally, they reported that some water resources experienced an increase in turbidity for two days following the earthquake.[20] These findings are important as inadequate water treatment can lead to the spread of cholera.

Developing Cholera Models for the 2022 Outbreak in Northwest Syria

Research as it Relates to a Humanitarian Setting

Research in the humanitarian response context is difficult, but much needed, as there is currently very limited research to help governments and organizations to respond to humanitarian crises.[29] Robust methodologies are exceptionally scarce in the context of refugee populations and IDPs. Additionally, there are increasing concerns about equity in the research process.[30] Many key stakeholders and partners are involved when wanting to conduct a research study, such as modeling, in a humanitarian setting. However, involving multiple stakeholders in a collaborative research project in humanitarian settings is complex and challenging.

Often, academics are a stakeholder that can serve as the key driver for a research endeavor. However, research methods developed and conducted by academics in the global north frequently have themselves performing the central role of study design, analysis, and funding. In contrast, other stakeholders perform tasks that involve community engagement, data collection, and primary analyses.[30] This unbalanced dynamic creates multiple problems. First, there is a risk that the academics in the global north do not entirely understand how the research question applies to field operations. Therefore, when other stakeholders cannot contribute significantly to the research question, data analysis, and interpretation, the results may not apply to the context of the situation. Additionally, this may cause less buy-in with implementers, with them not incorporating the results into eventual programs.[30]

Leresche et al. conducted a study that found academics, humanitarian actors, and health authorities utilize their respective complementarities to construct a more comprehensive strategy when working together.[30] Additionally, they found that providing space to define research questions, creating a longer-term collaboration, allowing for relative financial independence, and specifying organizational responsibilities were all essential to collaborative research.

An equitable approach to modeling in NWS would start with building a trusting relationship with other stakeholders, including humanitarian actors and health authorities, and keeping everyone involved and informed throughout the process, including formulating the research question, model design, and implementation. This approach would create an open and longer-term collaboration. Additionally, this approach would ensure complexities that influence cholera in this setting are accounted for and that power dynamics are not at play to ensure a smoother implementation of results.

Data Availability and Sensitivity

Data that is accurate and timely is critical for understanding the level of disease transmission occurring in current humanitarian crises and predicting subsequent outcomes. However, data availability limitations are often seen in humanitarian settings for various reasons, including disruption in surveillance activities, data sensitivity, and overall lack of reporting.

However, the humanitarian data ecosystem is improving as more organizations move from manual to automated data sharing.[31] With humanitarian organizations interacting with and sharing considerable amounts of data, awareness of the importance of responsibly collecting and sharing data has increased. Data in humanitarian settings can contain sensitive information about populations, allowing specific individuals or groups to be identified. As a result, disclosing sensitive data in humanitarian settings can cause vulnerable populations to be further hurt or exploited.[32]

In the 2022 version of, *The State of Open Humanitarian Data*[33], the Centre for Humanitarian Data team for UN OCHA reported continued improvement in bridging the gaps in most humanitarian settings. This is due to global advocacy, investment, field-level data sharing, and outreach. They determined enhancing access to forecast, observational, and impact data should be a focus for 2022, as it would be critical in developing preparedness frameworks in humanitarian settings. To accelerate these efforts, a new category will be devoted to this in the Humanitarian Data Exchange (HDX) Data Grids.[33]

The authors spoke of predictive modeling in the 2021 version of *The State of Open Humanitarian Data.*[31] They walked through detailed data inputs used for the OCHA-Bucky COVID-19 model. This model predicts the number of COVID-19 cases, hospitalizations, and deaths and gives decision-makers in humanitarian settings the ability to better plan and manage resources. At the time of publishing, it was being used by UN OCHA field offices in six countries.[31] Challenges related to data were recurring when trying to build the model. First, they experienced difficulties regarding the timelessness of data as many national-level datasets were not revised regularly. They also experienced issues with data quality and missing data. Because of these data constraints, they had to adjust their model to specific datasets and make assumptions regarding time. Additionally, they used similar or neighboring countries when there was a gap in a country's data.[31]As NWS also experiences gaps in data availability, utilizing similar assumptions to combat the lack of data will become a useful tool in modeling the current cholera outbreak.

The HDX, managed by UN OCHA's Centre for Humanitarian Data, is one source of data in humanitarian settings.[34] This effort was launched in July 2014 to make humanitarian data easier to locate and use for research. To share data via HDX, you must create an account and become an editor of a registered organization or create a new one. Furthermore, the HDX team manually inspects all uploaded datasets to the platform to ensure data validity and support responsible data exchange.[35] The HDX platform does not currently contain information on the cholera outbreak in NWS but has other datasets that could be important depending on one's research question. For example, HDX has datasets that include the location of the health sites in Syria[36] and another dataset that includes the needs of NWS camps in the winter of 2022.[37]

One group actively involved in surveillance and improving public health through data collection in NWS is the ACU. The ACU's Early Warning Alert and Response Network (EWARN), specifically, is regarded as the primary accredited source for information surrounding UNICEF and WHO public health indicators.[38] A few of their goals include strengthening the capacity for surveillance, bettering data utilization when responding to suspected outbreaks, monitoring the effects of interventions, and facilitating data and plan-based approaches in public health.[38]

EWARN is currently providing updates on the cholera outbreak in NWS and monitoring suspected and positive cases, cases who have recovered, and deaths.[39] Daily and weekly reports on the cholera outbreak are available for download on their website and provide detailed information on suspected cases, confirmed cases, and cholera deaths. Epidemiological data is also available in these reports, such as age and sex distribution, location information, case fatality rates, attack rate, and signs and symptoms of cases.[39] The data from the reports can be used more readily as it is publicly available and easy to access.

Building a Compartmental Model

The *Introduction to Infectious Disease Modeling* defines a transmission dynamic model as a model that incorporates contact and transmission between individuals.[40] This model can be further classified as compartmental, meaning individuals in the population are divided into broad subclasses deemed "compartments." The model follows the course of infection for these individuals as a whole.[40] Researchers have modeled cholera using compartmental structures; however, many models have differed drastically from others. This is because model structure depends on multiple components. First, a transmission model's structure should mirror the natural history of the disease. Therefore, meaningful disease classifications and transitions need to be described in addition to essential categories in the actual population. Secondly, how accurate the model predictions need to be is a component that determines model structure.

Finally, the research question *enormously* determines the model structure.[40] Researchers structure their model with the end goal of simulating multiple scenarios in regard to treatments, vaccination, and other interventions. One example includes a modeling study performed by A.

Mwasaa and J.M. Tchuenche, who aimed to study the impact of educational campaigns, vaccination, and ORS treatment as cholera control strategies.[41] To account for this study's aim, the researchers had to include separate compartments for vaccinated individuals, individuals who had received the educational campaign, and treated individuals.

Models can also account for age or another social group dependency if relevant to the research question. This could be useful if modeling an intervention specific to an age group or social group (e.g., vaccinating just young children or those at the highest risk).[40]

When building a cholera model for NWS, it is imperative to consider the natural history of cholera, the need for accuracy, and the research question one is trying to answer. Involving key stakeholders and partners is imperative in this step as they will help shape research questions based on context-specific complexities, which will drive model structure.

Gathering and Estimating Model Parameters

Pathogen Parameters

To demonstrate the transmission dynamics between cholera and humans, a model must include parameters specific to cholera. This can consist of parameters specific to the *V. cholerae* and how the vibrios and humans interact. The parameters that are important to include will rely heavily on the research question and the structure of the model. Some parameters specific to the bacteria include the rate of human water contamination, cholera life span in the water reservoir, and per capita recovery rate.[42]

Some of these parameters are more known than others. One example of a parameter that experiences a high level of certainty and has more available data is the per capita recovery rate which is approximately equal to the reciprocal of the duration of infection. On the other hand, the rate of water contamination by infectious people depends on multiple factors which are largely unknown in most contexts.[42]

There are potential avenues to collect data via field epidemiology for each parameter, but data collection in a humanitarian conflict setting has been challenging. Therefore, relying on assumptions from historical data from studies conducted in nearby or similar settings while getting insight from partners in NWS is a feasible option when gathering and estimating these parameters.

Demography Parameters

To demonstrate the long-term transmission of an infection, a model may need to include critical elements of the demography (births, deaths, and migration) of the population being modeled.[40] However, problems arise with gathering and estimating these parameters in NWS for various reasons.

Being a complex emergency setting, estimating population size in NWS is difficult due to the lack of CRVS and security matters. Additionally, over 50% of the population of NWS is categorized as IDPs making mobility a factor that adds complexity to estimating population size.[15] Similarly, death registration is particularly lacking in humanitarian settings due to civil and medical infrastructure frequently suffering from insufficiencies and disruptions. Political advocacy, monitoring, analyzing, and documenting trends and effects in population health status, and mortality estimation must be a fundamental element of any humanitarian health relief procedure because accurate mortality data is critical for strategic planning.[43]

There are a few possible ways to address this lack of demography data when modeling cholera in NWS. It is imperative to remember, though, that an essential part of demography estimation includes first gaining insight from partners in NWS as they will understand these parameters best and how to proceed when gathering and estimating them. One way to estimate demography data is by using assumptions to fill critical data gaps. For example, similar to the OCHA-Bucky COVID-19 model[31], assumptions can be made that NWS is similar to the Syrian Arab Republic as it is a neighboring area that experiences similar complexities associated with conflict. This would allow the modeler to utilize demography data from the Syrian Arab Republic in the model, which is much more widely available. The World Bank publishes data annually in the Syrian Arab Republic, including infant mortality rate, under-five mortality rate, sex-specific mortality rates, crude birth rate, crude death rate, and life expectancy at birth.[44]

Additionally, new technologies, including tracking populations through cell phone data, have been used in modeling studies to analyze population movements. While data like this does not produce information on mortality and births, it does give an idea of population movements and overall population estimates in an area, both of which play key roles in modeling studies. An example of this was displayed when Bengtsson et al.[45] utilized mobile phone data to predict the spatial spread of the 2010 Haiti cholera epidemic. The movements of nearly three million anonymous mobile phone SIM cards were used to generate a national mobility network. This mobile phone-based model outperformed two retrospectively optimized gravity models. The researchers concluded that mobile operator data can benefit preparedness and response efforts during cholera outbreaks.[45]

Force of Infection

Another essential parameter when modeling cholera is the force of infection, often denoted as λ_t. The force of infection is the risk that a susceptible individual becomes infected from time t to t+1.[40] This force of infection for a pathogen generally relies on the number of infectious people in a population and how often they come into contact with others, assuming individuals mix randomly.[40] The force of infection is often given by the following equation in models experiencing density dependency (where β indicates the rate of effective contact per unit time, t indicates a unit of time, and I indicates the number of infectious individuals at time t):

$$\lambda_t = \beta * I_t$$

In one basic model of cholera transmission dynamics, the force of infection depends on three parameters: the contact rate between the susceptible individuals with water contaminated with *V. cholerae* (β), *V. cholerae* concentration in the water supply (B), and the concentration of *V. cholerae* at which the infection rate is 50% of the maximum infection rate (κ).[42] Some researchers have expanded their models to adapt to certain research questions, which has, in turn, affected the parameters that influence the force of infection. For example, some researchers believe that hyperinfectious bacteria are crucial to understanding cholera transmission dynamics.[5] Therefore, their models include separate compartments for hyperinfectious *V. cholerae* and low-infectious *V. cholerae* reservoirs. The hyperinfectious *V. cholerae* reservoirs experience very high infectiousness. However, other researchers have argued that these extra compartments are only important when research questions are specific to the hyperinfectious state.[42]

Calculating the force of infection for cholera comes with many complexities. Many factors influence the rate at which susceptible individuals contract cholera, most of which are difficult to measure. For example, the "contact rate" and the *V. cholerae* concentration are frequently unknown in most settings.[42] Additionally, an easy procedure does not exist that can convert the outcomes of experimental studies into the "contact rate" between susceptible people and contaminated water or the concentration of *V. cholerae* in the water that will cause susceptible individuals to become infectious. Since β can seldom be estimated directly from experimental studies, it is generally calculated by fitting models to time series data.

The complexities of calculating the force of infection for cholera multiply when changing the model to be specific to NWS. First, one complication of calculating the force of infection is that it relies on the assumption that individuals mix randomly in a population, meaning the probability that two individuals have contact with one another is the same regardless of a characteristic.[40] This assumption allows for rough estimates of the dynamics of how compartment numbers change over time. If, however, mixing is not at random, as we expect with most populations, including NWS where there are large numbers of IDPs and people living in refugee camps, estimates based on models assuming homogeneous mixing may not be reliable. This is one limitation of these models.

Additionally, model fitting from time series data is usually how β is calculated. However, as data availability in this region is limited, finding the exact time series data for the model may prove difficult. Nevertheless, as mentioned before, organizations like the ACU's EWARN is currently providing updates on the cholera outbreak in NWS.[39] Reports on the cholera outbreak are available for download on their website and provide detailed information on case numbers and other epidemiological data.

It is imperative to note that forming a trusting relationship with the affected community and key stakeholders and keeping everyone involved and informed throughout the process is essential when utilizing data from a humanitarian organization. Additionally, obtaining essential approvals and agreements when using time series data is often necessary as this data often includes patient health information. Examples of these could include Institutional Review Board Approvals and Data User Agreements.

Table 1 is a summary of potential data sources that can be used to gather key parameters that may be utilized when modeling cholera in NWS. As mentioned previously, relying on assumptions from historical data from studies conducted in nearby or similar settings while getting insight from partners in NWS is a feasible option when gathering and estimating these parameters.

Table 1. Examples of potential data sources that can be used to gather key parameters.

Parameter	**Example Value(s)**	**Source**
V. cholerae infectious dose in Humans	10^3 - 10^8 cells	46
Death rate of V. Cholerae in the environment	$(30\ \text{days})^{-1}$	5
Birth rate, crude - Syrian Arab Republic (2020)	20 births per 1,000 people	47
Mortality rate, infant - Syrian Arab Republic (2021)	18 infant deaths per 1,000 live births	48
Mortality rate, under-5 - Syrian Arab Republic (2021)	22 deaths per 1,000 live births	49
Life expectancy at birth, total - Syrian Arab Republic (2020)	72 years	50
Recovery rate, cholera	$(5\ \text{days})^{-1}$	5
Proportion of cases asymptomatic	0.79	5
Rate of excretion of V. cholera, symptomatic patient	$1.3\text{x}10^{11}$ cells per day	5
Rate of excretion of V. cholera, asymptomatic patient	$1.3\text{x}10^{8}$ cells per day	5
Rate of the waning of natural immunity	$(0.8\ \text{years})^{-1}$	5
Total Population of Northwest Syria	4,500,000	51
Contact rate between the susceptible individuals with water contaminated with V. cholerae (β)	Value obtained by fitting to time series case data (e.g., case counts from EWARN reports)	39

Proposed Utilizations for Cholera Models in Northwest Syria

There are several different ways compartmental transmission dynamic models of cholera could be used in NWS. General forecasting can allow for the prediction of disease dynamics and case estimation for maximum preparation. Researchers can also narrow their models to be more specific to research questions pertaining to intervention strategies. Models incorporating these strategies can give researchers a lens into what the epidemic trajectory of cholera will look like when certain intervention measures are applied and allow them to make informed decisions surrounding intervention policies.

Oral Cholera Vaccines

OCVs are an efficient, short-term way of controlling and preventing cholera outbreaks. In addition, besides the direct protection they provide to vaccinated recipients, they provide significant herd immunity to non-vaccinated individuals.[52] As OCVs are a major tool for controlling cholera outbreaks, incorporating them into cholera modeling has become common and would benefit NWS. Vaccination modeling is important for a multitude of purposes, including determining dosing, timing, and the most effective vaccine target group.

Leung, Eaton, and Matra[53] completed one example of cholera vaccine modeling that aimed to determine the optimal vaccine dose strategy for different age groups to minimize cholera infections and deaths. They discovered that with a restricted vaccine supply in the short term, the best vaccine strategy prioritizes a single dose for those over five years of age. They also discovered that, compared to the standard two-dose approach, the single-dose strategy could prevent anywhere from 1.2 to 1.8 times as many cases and deaths. However, they found it is best to administer a second dose for long-term protection, assuming more vaccines become available.

Because the global supply of cholera vaccines is being severely strained[10], conducting a modeling study like this in NWS would be extremely beneficial. The outputs of this model would inform decision makers what vaccine strategy is most effective in terms of averting the most cases and deaths.

Water, Sanitation, and Hygiene (WASH) Interventions

Accessible and safe water, adequate sanitation, and economic development are the cornerstones of cholera control and management. WASH solutions in areas at risk for cholera outbreaks become crucial to guarantee safe water consumption, basic sanitation, and proper hygiene practices.[8] Therefore, modeling WASH strategies in areas at risk for cholera is extremely important.

One example of modeling WASH measures is through a study performed by Andrews and Basu.[5] They simulated the effects of clean water provisions on the cholera outbreak in Haiti in 2011. They modeled these provisions specifically as a weekly 1% reduction in the proportion of the population consuming contaminated water. They projected that this clean water intervention would prevent 105,000 cholera cases (95% CI: 88,000–116,000) and 1,500 deaths (95% CI: 1,100–2,300) in Haiti from March through November 2011. More cases and deaths were averted via this WASH provision than their prediction of vaccinating 10% of the population.

Modeling WASH as it relates to cholera in humanitarian settings, such as NWS, is imperative as water and sanitation systems are frequently susceptible to attack during conflict, and WASH services must prepare to support those in times of crises. Those already suffering from malnutrition and weakened immune systems become even more susceptible to water-borne diseases when there is neither potable water nor adequate sanitation and hygiene facilities. A modeling study like the one performed by Andrews and Basu[5] can be done in NWS. This would be extremely beneficial as it would quantify the effects of certain WASH policies on cholera incidence, which may make them more likely to be implemented, and point to where the efficient allocation of financial resources lies.

Age-Based Interventions

The cholera outbreak in NWS has disproportionally affected children in terms of incidence. As of February 2023, nearly half of cholera cases in NWS were children under five.[20] Therefore, creating age-structured models to show age-based interventions in areas at risk for cholera is extremely important.

Modeling OCVs with an age structure element can be done to determine what age group is most effective (e.g., avert the most deaths or cases or is the most cost-effective) to vaccinate. This was done by Khan et al. in Dhaka, Bangladesh.[54] The authors used cholera incidence data from Dhaka, estimates of vaccination coverage rates gathered from literature, and a transmission dynamic model of cholera transmission, to estimate the number of cholera cases and deaths averted for three different groups: 1 to 4-year-olds, 1 to 14-year-olds, and all persons over 1-year-old. They assumed the use of a two-dose killed whole-cell oral cholera vaccine. They determined that a program that targets all children aged 1 to 14 years old in mass cholera vaccination campaigns every three years and children aged 12 to 15 months annually as part of the routine immunization program would prevent 14,400 cases. They concluded this would be the most cost-effective and efficient program option.[54]

Because the global supply of cholera vaccines is being severely strained[10] and the disproportion incidence of cholera in children under 5[20], conducting a modeling study like this in

NWS would be extremely beneficial. This model's outputs would help decision-makers determine the most effective age-population to target when implementing a vaccine program.

Infants (i.e., children under one year old) are also susceptible to cholera. In the 1974 cholera outbreak in Bahrain, the highest attack-rate of cholera occurred in the 6 to 11-month age group; however, it is worth noting that this distribution does not occur frequently with cholera outbreaks.[55] Also, it is critical to consider that children under one year of age are not eligible to be vaccinated for cholera[9] making alternative interventions necessary for this age group. The publicly- available EWARN reports do not currently contain information on the percentage of cases that are infants. If this information were to become available, potential models could explore different interventions related to this age group. For example, a case control study conducted in Bahrain found that, during the week prior to illness, significantly more cases than controls were primarily bottle-fed (more than 50% milk intake via bottle) rather than breast-fed.[55] One could predict the number of cholera cases and deaths an educational campaign centered around informing parents of safe bottle feeding and formula practices would avert via modeling.

Cost-Effectiveness Analysis

Conducting a cost-effectiveness analysis would be extremely beneficial when modeling in this region. A cost-effectiveness analysis aids in the identification of interventions that are relatively inexpensive but have the potential to reduce the burden of disease significantly. Analyzing an intervention's cost-effectiveness enables the identification of means by which resources can be redirected to accomplish more and demonstrates the value of shifting resources from less cost-effective to more cost-effective interventions.[56] This sort of analysis would be imperative as funding for healthcare, treatments, and OCVs, especially post-earthquake, has been a critical obstacle in NWS.[23]

Conclusion

Researchers have utilized transmission dynamic modeling to determine interactions between hosts and pathogens in the face of limited medical resources, including that between cholera and humans. However, transmission dynamic modeling for the cholera outbreak in NWS has not yet been completed.

There are many critical steps when developing a cholera model in this region. Building a trusting relationship with stakeholders, such as humanitarian actors and health authorities, and keeping everyone involved and informed throughout the process, including formulating the research question, model design, and implementation would be the first steps in an equitable approach to modeling in NWS. Modeling cholera in NWS also involves tackling the challenges of data availability and sensitivity from it being a conflict zone. Utilizing assumptions in the model and building partnerships with stakeholders conducting surveillance in this region is pivotal. When constructing the model, it is essential to consider the natural history of cholera, the need for accuracy, and the research question. During this step, it is essential to involve key partners because they will assist in shaping research questions based on context-specific complexities, which will drive the model structure.

The parameter research and estimation process will need to be context specific to account for the complexities of NWS being a conflict zone. Field epidemiology has the potential to collect data on pathogen/host parameters, but it has been challenging to do so in a humanitarian conflict setting. As a result, when gathering and estimating these parameters, a viable option is to rely on assumptions derived from historical data from studies conducted nearby or in similar settings while gaining insight from partners in NWS. Demography parameters are difficult to estimate in NWS due to insufficient infrastructure, security issues, the large percentage of IDPs in the population, and the lack of CRVS. Complexities of calculating the force of infection for cholera multiply when changing the model to be specific to NWS as non-random mixing could occur and data availability in this region is limited. Additionally, finding the exact time series data for the model may prove difficult; however, suspected and confirmed weekly case counts are published by EWARN.

In NWS, compartmental transmission dynamic models of cholera could be utilized in various ways. Case estimation and disease dynamics can be predicted using general forecasting for optimal preparation. Additionally, researchers can narrow their models to be more specific to intervention strategy-related research questions. Modeling OCVs in NWS would be beneficial given the severe shortage of cholera vaccines worldwide. Modeling WASH as it relates to cholera in NWS would also be valuable, as water and sanitation systems are frequently susceptible to attack. Modeling age-specific interventions would also be beneficial as children under five make up nearly half of the suspected cases and children under one cannot be vaccinated. Cost-effectiveness analyses would allow for the identification of means by which resources can be redirected to accomplish more and enable stakeholders to identify the most cost-effective allocation of funds.

Recommendations and Future Directions

The 2023 earthquake in Turkey/Northern Syria has created a further need for modeling cholera in NWS. Future research includes producing the models and conducting modeling studies on cholera in this region. Transmission dynamic modeling for the cholera outbreak in NWS has not yet been completed.

The modelers should consider the conclusions made in this thesis. The limited resources, including financial constraints and damaged infrastructure, hinder the modeling process and points to the immense need for investments to be made toward building healthcare capacities from the international community. Increasing data availability while balancing data sensitivity will be essential for accurate future modeling in this region. This will involve strengthening surveillance capacity, investing in the organizations that provide surveillance data, such as the ACU, and increasing the reliability and accuracy of mortality data by expanding the use of practices such as verbal autopsies.[57]

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