Review

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Mechanisms of cholera transmission via environment in India and Bangladesh: state of the science review

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Abstract

Objectives: Cholera has a long history in India and Bangladesh, the region where six out of the past seven global pandemics have been seeded. The changing climate and growing population have led to global cholera cases remaining high despite a consistent improvement in the access to clean water and sanitation. We aim to provide a holistic overview of variables influencing environmental cholera transmission within the context of India and Bangladesh, with a focus on the mechanisms by which they act.

Content: We identified 56 relevant texts (Bangladesh n = 40, India n = 7, Other n = 5). The results of the review found that cholera transmission is associated with several socio-economic and environmental factors, each associated variable is suggested to have at least one mediating mechanism. Increases in ambient temperature and coastal sea surface temperature support cholera transmission via increases in plankton and a preference of *Vibrio cholerae* for warmer waters. Increased rainfall can potentially support or reduce transmission via several mechanisms.

Summary and outlook: Common issues in the literature are co-variance of seasonal factors, limited access to high quality cholera data, high research bias towards research in Dhaka and Matlab (Bangladesh). A specific and detailed understanding of the relationship between SST and cholera incidence remains unclear.

Keywords: Bangladesh; cholera; climate; India; mechanisms.

Introduction

Cholera remains a significant public health issue in many parts of the world as the seventh global pandemic continues to persist since 1961 [1]. The disease is caused by ingestion of pathogenic strains of the bacteria *Vibrio cholerae*, most commonly through contaminated water, although to a lesser extent through improperly cooked contaminated seafood [2]. The dynamic nature of cholera burden is highlighted by the dramatic variation in number of cholera cases per country reported to the WHO over the past 46 years (Figure 1). Indeed, cholera epidemics were common in Europe in the 19th century but cases are almost non-existent in high income countries in recent years (with the exception of a few imported cases), mainly due to improved water, sanitation, and hygiene (WASH) facilities [3]. However, despite a slow but significant improvement in global access to effective sanitation and clean drinking water, the global burden of cholera remains high [4]. This is widely anticipated to be aggravated by climate change [5, 6] and it is likely that the Indian subcontinent, and in particular Bangladesh and parts of India, will be particularly vulnerable due to its long coastline, tendency for significant floods, high population density and sustained poverty [7].

The Indian subcontinent has a long history of cholera [8]. The region has been the origin of six out of the past seven global pandemics [9] and experiences an estimated 820,000 cases annually, primarily in India and Bangladesh [4]. The effects of cholera endemicity in the subcontinent extend further than just the region itself as endemic regions often provide the source of epidemics in other parts of the world. Cholera in 19th century Europe derived from colonial incursions, particularly of the Indian subcontinent [10], with

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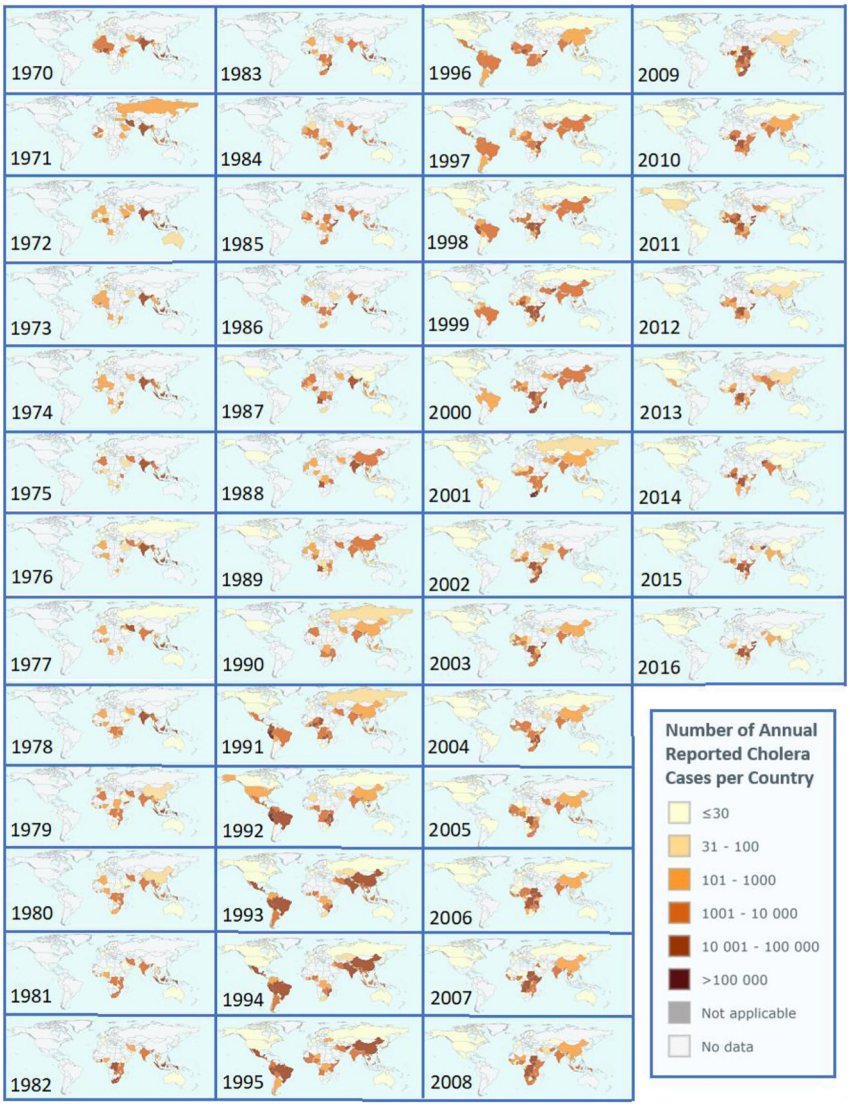

Figure 1: Annual cholera cases worldwide reported to WHO for the period 1970–2016. Data available from https://gamapserver.who.int/gho/interactive_charts/cholera/atlas.html.

transmission occurring through infected people and possibly in the bilge water of ships [11–13]. In more recent history, the strain of *V. cholerae* which seeded the 2010 outbreak of cholera in Haiti resulting in half a million cases and 7,000 deaths has been attributed to infected United Nations peace-keeping troops from Nepal [14]. Finally, the largest outbreak in recorded history, the ongoing 2016 outbreak in Yemen [15], has been traced to outbreaks in East Africa, which in turn originated in South Asia [16]. Therefore, cholera in South Asia is at the root of cholera globally, and reducing cholera in this region could have wide-reaching effects.

A comprehensive understanding of the mechanisms which drive cholera transmission via the environment is essential for both effective prediction and mitigation through interruption of these mechanisms. However, due to the complex relationships between several factors thought to drive global outbreaks, a complete understanding is still lacking. This review aims to establish the primary factors associated with increased cholera transmission via the environment, and to identify the specific mechanisms which mediate these associations. An overview of these primary factors associated mechanisms is provided in Table 1.

Environmental transmission of cholera

The seasonal nature of cholera has been long recognised since the late 19th century. Globally, cholera epidemics demonstrate strong seasonal patterns in most endemic regions, with exceptions mostly located close to the equator where seasonal variation is limited [53]. Within the Indian subcontinent, two distinct patterns emerge. The first is a single peak during the rainy season (May-August) with often zero reported cases outside of seasonal outbreaks [17, 30]. This pattern is present in the drier parts of India including Delhi [54], Hyderabad [55], and Chandigarh [56]. The second pattern appears to be unique

Table 1: Summary of factors associated with increased environmental transmission of cholera in India and Bangladesh.

Factor associated with increased cholera transmission via environment	Proposed mechanisms
Reduced rainfall	Increased *V. cholerae* concentration [17–20]
	Increase in Vibrio-phages concentration [21, 22]
	Increased salinity [23–27]
Increased rainfall	Flooding [18, 28]
	Contamination of water sources through rainfall run-off [29]
Increased ambient temperature	Preference of *V. cholerae* for warmer waters [23, 24, 30, 31]
Increased ocean sea surface temperature	Changes in rainfall patterns [28, 32–36]
Increased coastal sea surface temperature	Preference of *V. cholerae* for warmer waters [23, 24, 30, 31]
	Increased phytoplankton [37, 38]
	Increased zooplankton [39–41]
Increased sea surface height	Coastal water intrusion [42, 43]
Deceased socioeconomic status	Sanitation [44–46]
	Household water treatment [47, 48]
	Education levels [49, 50] population density [49, 51]
	Malnutrition [52]

to the area surrounding the Bay of Bengal, namely West Bengal and Bangladesh. This is characterized by an annual dual-peak cycle; the first occurring in the spring (pre-monsoon) and the second in the Autumn (post-monsoon) with a marked lull in cases during the main monsoon [18, 57–61]. These two patterns suggest that cholera transmission is associated more with the environmental conditions of some seasons compared with others. Further, a 2011 study comparing spatial and social clustering of cholera in Matlab, Bangladesh found that while cholera always clustered spatially, clusters rarely occurred within social networks implying transmission was via environment rather than through person-to-person contact [62].

The evidence supporting a temporary environmental reservoir of pathogenic *V. cholerae* (strains within O1 and O139 serogroups) is strong. It has been frequently isolated during cholera outbreaks in a variety of fresh and brackish water sources across the Indian subcontinent [31, 63–67]. However, the onset of epidemics via primary transmission from an environmental reservoir requires persistence of pathogenic *V. cholerae* during inter-epidemic periods, a somewhat disputed topic in the literature [39]. In coastal regions surrounding the Bay of Bengal, the evidence is strong; both strains are considered autochthonous to the Gangetic Delta [66, 68, 69] and have been successfully isolated in coastal regions of Bangladesh between seasonal outbreaks [70] suggesting that *V. cholerae* are capable of surviving and even reproducing without human transmission. The permanent environmental reservoir theory explains the onset of seasonal epidemics by suggesting that *V. cholerae* concentrations increase in response to favourable conditions such as elevated water temperature [71], reduced salinity [23], and increased presence of phyto- and zooplankton which act as nutrient rich mini-reservoirs [66, 72].

However, other studies have shown that pathogenic *V. cholerae* require the presence of Na^+ ions for survival [23, 24], with the O1 serogroup unable to survive beyond 24 h in salinity levels outside the Goldilocks range of 0.25–3.0% [73]. These findings are consistent with the proliferation of the bacteria in the brackish waters surrounding coastal regions, yet does not explain the persistent endemicity in many inland parts of the Indian subcontinent where the local aquatic environment contains almost zero salinity [31].

Miller et al. [74] proposed two potential explanations: (1) seasonal movements of people or availability of contaminated seafood; and (2) environmental reservoirs of pathogenic *V. cholerae* are in fact viable in freshwater environments e.g. through protection by aquatic biota such as zooplankton. More recent evidence supports the latter hypothesis, for example, a well-documented characteristic of cholera cases in Bangladesh is the simultaneous appearance of epidemics. This has been witnessed across both coastal and inland regions of Bangladesh [25, 75], as well as the simultaneous onset of mini-epidemic clusters within Matlab Demographic Surveillance Site in Bangladesh [19]. If the bacteria were spread only via movement of humans or food, a delay would be expected between outbreaks. The existence of simultaneous outbreaks therefore supports a strong role of primary transmission via the environment even in inland regions. However, Faruque et al. [76] suggest that while a delay between outbreaks may be present in the data, this is likely to be caused by a bias in reporting. They suggest that most outbreaks are caused by a single bacterial clone implying a single source, therefore arguing that the first few cases of a cholera epidemic go unnoticed in countries with limited health information infrastructure. If this is the case, separate outbreaks could indeed be spread from a

single source, which would provide support for the first of Miller's hypotheses.

With regard to the viability of inter-epidemic survival of *V. cholerae* in freshwater environments, Jubair et al. [77] propose the existence of 'persister' cells. The authors found that certain O1 *V. cholerae* bacteria were able to remain culturable for over 700 days in fresh lake water microcosms by switching to a 'rugose' phenotype. This switch causes the bacteria to produce Vibrio polysaccharide which confers protection against a variety of environmental stresses including osmotic and oxidative stress. However, the importance of these 'persister' phenotypes remains unclear as few published reports are available on the occurrence of rugose *V. cholerae* in the natural environment [78]. An alternative explanation is the capability of *V. cholerae* to enter a dormant low-metabolic state known as viable but non-culturable (VBNC) [79]. The bacteria enter this state in response to physiochemical stress (e.g. lower temperatures or nutrient availability), in which they do not respond to conventional culture methods of bacteria detection. Importantly, while it appears that *V. cholerae* are less infectious while in VBNC state [80], they are able to revert back to a culturable state upon animal passage [81] or the presence of more favourable growth conditions [82]. There is also evidence to support Miller and colleagues' theory of protection from aquatic biota. Using fluorescent antibody techniques capable of detecting bacteria in VBNC state [83], found *V. cholerae* O1 survived for over 15 months *in vitro* in low salinity conditions (0.05%) within the mucilaginous sheath of the aquatic alga, *Anabaena variabilis*. The presence of VBNC *V. cholerae* O1 has been observed *in situ* outside of cholera outbreaks in freshwater samples from North India [67, 84], albeit in small concentrations. However, in a later study the authors sampled *A. variabilis* taken from pond water in Dhaka and were unable to isolate the bacteria during the inter-epidemic periods Jan/Feb and June/July [85]. This suggests that the persistence of pathogenic strains of *V. cholerae* during inter-epidemic periods in freshwater environments, while possible, is to be likely rare.

The precise mechanisms by which pathogenic *V. cholerae* is continually reintroduced into the environment, particularly in inland regions lacking brackish water, remains uncertain. It is nonetheless clear from the literature that secondary transmission in the region, which defines the growth, spread, and persistence of an outbreak occurs largely via the environment. This is made evident by the strong seasonal signature and frequent isolation of pathogenic bacteria in the aquatic environment during epidemics. As a result, in considering the factors that influence environmental transmission of cholera, this review will focus on secondary transmission.

Methods

To prepare this state-of-the-science review we performed a literature search according to PRISMA guidelines of original research describing factors influencing cholera transmission via the environment in India and Bangladesh. The key inclusion criteria were: (i) a clearly defined and individually considered environmental or socio-economic influencing factor; (ii) an epidemiological cholera health outcome OR evidence of changes to *V. cholerae* O1 or O139 in the local environment; and (iii) located within the region of India and/or Bangladesh. We considered experimental, observational and qualitative studies published in peer-reviewed journals for inclusion, previous reviews and letters to editors were excluded. Furthermore we excluded any intervention study which simultaneously changed multiple factors such as combined water treatment and handwashing programmes as the individual effects could not be deduced.

In order to provide a holistic summary of the topic, we took a broad view and considered all literature returned on PubMed from the search terms ("*cholera*" OR "*V. cholerae*") AND ("*transmission*" OR "*Epidemiology*") AND ("*India*" OR "*Bangladesh*"). The temporal scope of search spanned from 1st January 1970 until the most recent search date 10th November 2021. The initial search produced 1,178 texts which were screened according to a two-stage process: first article titles and abstracts were assessed based on potential relevance, second the remaining texts were read in full. Finally we supplemented the selected texts with further relevant studies found through previous literature reviews and examination of bibliographies. Figure 2 summarizes the search methodology using a PRISMA based flow diagram.

Results

The initial literature search resulted in 1,178 publications, of which 6 were duplicate. 1,057 were excluded in the abstract screening process, and a further 72 were excluded during full-text screening, leaving 43 texts for inclusion. These publications were supplemented by a further 26 texts identified from previous literature reviews and reference lists of the selected texts, including four *In vitro* studies as they were considered highly relevant to the research question. This resulted in 56 texts for inclusion in the final review. The majority of texts (n=40) focussed on Bangladesh as a study area, which mainly consisted of the rural region Matlab, and the urban capital Dhaka (n=17, n=15 respectively). Three considered other regions of Bangladesh and a further seven either considered Bangladesh as a whole or did not specify the region. Nine studies used India as a case study, and selected regions were much more varied although three were focussed on Kolkata. The literature identified six broad variables which were suggested to influence environmental transmission of cholera: rainfall, ambient temperature, ocean sea surface temperature, coastal sea surface temperature, sea surface height, and economic and social development. Within each influential factor, several mediating

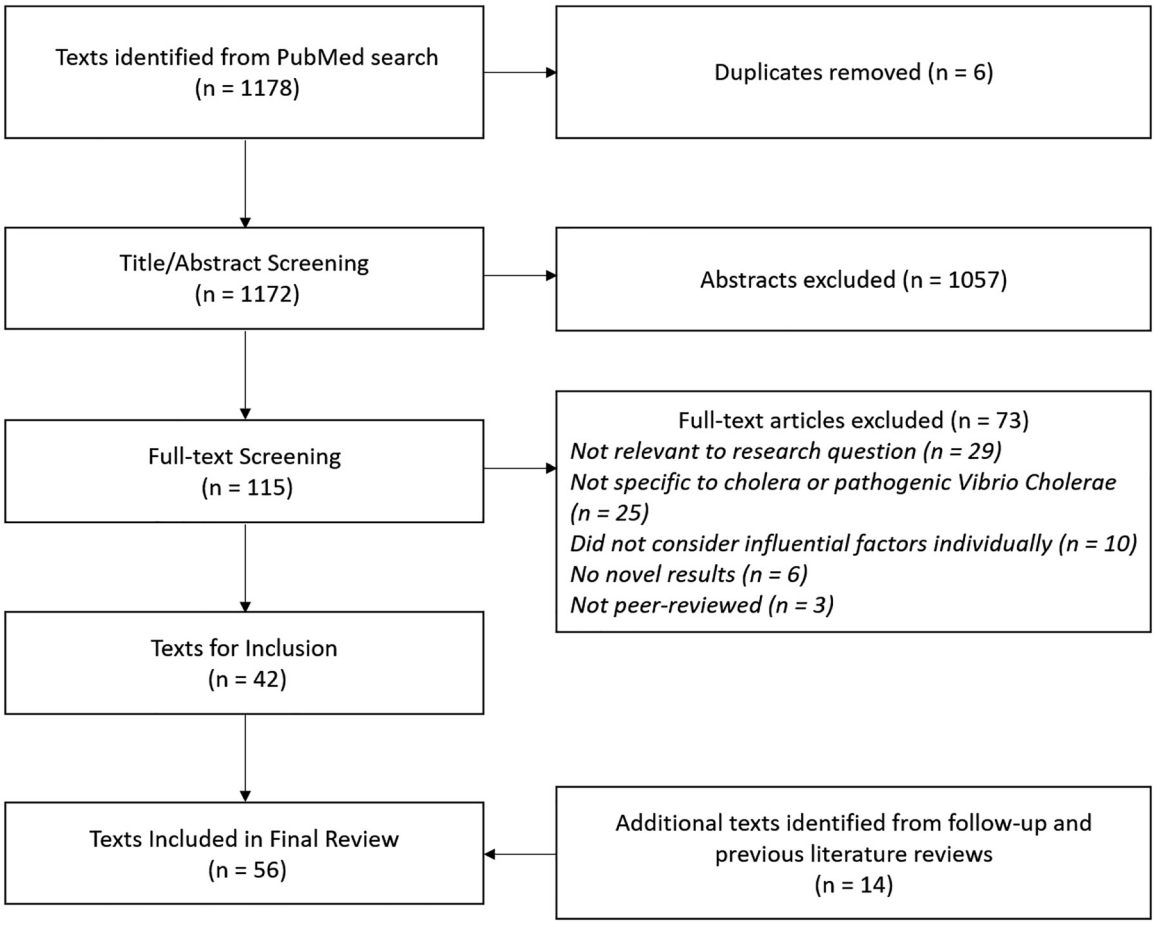

Figure 2: PRISMA flow diagram summarizing search methodology.

mechanisms were suggested. These are given below followed by a discussion of the results.

Rainfall

The literature presented a complex relationship between cholera incidence and rainfall in India and Bangladesh. As mentioned in the introduction, the northern and inland endemic regions of India generally present a single peak in cases during the summer monsoon; several studies have demonstrated a positive correlation between the size of this peak and rainfall levels [30, 86]. Conversely, coastal regions surrounding the Bay of Bengal, namely Bangladesh and West Bengal, exhibit unique dual-peak behaviour with a lull in case numbers during the monsoon and peaks either side of the main rainy season. The second, and generally larger, of these peaks occurs post-monsoon and holds a similar positive association with rainfall [18, 57, 60]. Interestingly however, the first annual peak occurs in the pre-monsoon when the region is typically experiencing drought conditions. Further, during this period, cases are usually negatively correlated with rainfall, with drier years leading to stronger pre-monsoon peaks [18, 20]. In this section we provide the mechanisms presented in the literature to explain the both the positive and negative associations between rainfall and cholera incidence.

Low levels of rainfall

Mechanisms presented in the literature to explain the negative relationship between rainfall and cholera cases during the Bay of Bengal spring peak generally describe a corresponding reduction in the water levels of local aquatic reservoirs such as rivers and ponds. This is consistent with associations between low river levels and cholera cases witnessed in northern India [87, 88], and Bangladesh [6].

Increased concentration of *V. cholerae* due to reduced water volume

A commonly cited explanation for this phenomenon hinges on the dose-dependent nature of cholera infection, meaning

that a high number of bacteria must be consumed to cause infection. The concentration of pathogenic *V. cholerae* in a water source and the volume consumed are thus both highly relevant. It is thought that lower water levels in the spring result in higher concentrations of the bacteria. Also, as surface water becomes scarcer more people begin to share bathing/washing/drinking water [89]. This not only increases likelihood of contamination of the water source, but also increases the population at risk due to more people using the water source. This hypothesis may also explain the sudden drop in cases during the mid-monsoon lull in Bangladesh by suggesting that the sudden influx of water through surface runoff into the Ganges-Brahmaputra-Meghna (GBM) river system causes a dilution effect and 'washes out' the pathogenic bacteria [17, 19].

V. cholerae predation by vibriophages

Faruque et al. [21] argued that the peak and decline of a cholera epidemic cannot be sufficiently explained by envoking immunity or the environment, citing the fact that often epidemics decline in the absence of any significant change in weather. They suggest vibriophages, a phage known to infect *V. cholerae*, may control levels of pathogenic *V. cholerae* bacteria in water reservoirs. They hypothesized that the seasonal nature of cholera epidemics in endemic regions is, in part, due to amplification of O1- and O139-specific phages in response to increases in levels of these bacteria [21]. This curtails the proliferation of pathogenic bacteria in a manner similar to that described by the Lotka-Volterra equations allowing outbreaks to become self-limiting in both freshwater and estuarine environments. The phage hypothesis further claims to predict the onset of the post-monsoon peak in Bangladesh by suggesting that the monsoon rain and associated increase in river flow 'washes out' the vibriophages, thereby reducing 'predation' pressure on *V. cholerae* and allowing a second epidemic to take hold [76].

Support for this hypothesis exists in water samples taken from Dhaka which demonstrate an inverse correlation between the presence of vibriophages capable of lysing a given serogroup of *V. cholerae* and the presence of a strain of that same serogroup [76]. However, Ruiz-Moreno et al. [17] pointed out that the phage hypothesis would imply a phage cycle with lags slightly behind the cholera cycle, which was not observed in the data. They also found that inclusion of this hypothesis into a mathematical model did not improve its ability to explain historic cholera mortality data in Bengal.

Increase in salinity

A strong negative correlation has been well documented in the Bengal Delta between winter rainfall and spring cholera with a lag of around 8 weeks [26, 57] suggesting that low winter river levels caused by low winter rainfall could contribute to an increased spring cholera peak. These studies have proposed that this lag allows time for pathogenic *V. cholerae* to multiply in newly saline estuaries, eventually reaching a concentration high enough to produce cholera in humans. This is supported by the strong drought-associated spring peaks witnessed in some coastal regions such as Mathbaria in Bangladesh where saltwater intrusion is more pronounced [25], but is contrasted by inland regions such as Chhatak which only experience a single flood-associated autumn peak [57]. Further, a study from Huq et al. [26] found a significant association between water conductivity (implying higher salinity) in the coastal region Bakerganj and cholera cases, but not in any of the other three sites studied (all further inland).

High levels of rainfall

There is a relationship between high levels of rainfall and cholera outbreaks during the monsoon in inland India, and post-monsoon outbreaks in the regions surrounding the Bay of Bengal. The proposed mechanisms involve flooding, and wastewater runoff.

Increase in flooding

Akanda et al. [18] indicated an association between flooding and cholera in Bangladesh with their finding that the probability of a large autumn cholera outbreak was distinctively higher for high flood years. It is suggested that this flooding causes mixing between sewers, exposed drains, reservoirs and rivers leading to significant contamination of water sources with *V. cholerae* [18, 28]. Further, particularly in urban areas, flooding may lead to increased contact between individuals and contaminated flood water [90].

In Dhaka, a flood protection zone appeared to be highly effective at reducing cholera incidence, with residents outside of the zone experiencing 38% more cases [49]. However, Carrel et al. [91] conducted a regression analysis considering households both within and outside a similar flood prevention effort conducted in Matlab, a rural region of Bangladesh that experiences significant annual monsoon flooding of the Dhonagoda River. They found households within flood-protected areas reported more cholera cases than those in areas which were not protected. The authors proposed two potential explanations for these findings. First they suggest that an influx of uncontaminated water upstream may flush out local bacteria. Flood-protected areas lack the 'flushing' effect of monsoon rains resulting in greater continued exposure to cholera bacteria in the environment. Secondly, they conjecture the difference could be explained through behavioural changes. 'Protected' communities may have a false sense of security regarding water supplies, and therefore have a more relaxed attitude towards potentially contaminated

surface water. These results are in agreement with a previous study in Matlab which found living in a flood-protected area increased likelihood of cholera by 2.47 times [51].

Contamination of water sources via rainfall runoff

An alternative, though related, mechanism to explain the positive rainfall-cholera relationship and contamination of water sources is that of surface run-off. This theorises that surface runoff feeds uphill organic sediment such as faecal waste from the land into water sources, thereby causing contamination [29]. Islam et al. [92] found significant faecal contamination including the isolation of O1 and O139 *V. cholerae* in municipal drinking water sources in Dhaka following the 2004 floods. The level of faecal contamination was still present, but significantly reduced after the floods receded. Further, a significant relationship was found in Kolkata between cholera cases and localized rainfall anomalies, though interestingly not large scale rainfall (affecting upstream catchments, and therefore river levels), suggesting a greater role of surface-run off contamination rather than flooding [68]. It is also possible that *V. cholerae* survival rates are enhanced during periods of intense rainfall due to insoluble iron washed into water courses which aids the multiplication of *V. cholerae* [93].

Ambient temperature

Laboratory microcosm studies have indicated a preference of *V. cholerae* for warmer waters, resulting in increased proliferation of the bacteria [23, 24]. This suggests an increase in ambient temperatures may result in a corresponding greater concentration of pathogenic *V. cholerae* and consequently greater probability that inhabitants will ingest an infectious dose. As a result, temperature has been invoked as a partial explanation for the Bangladesh spring peak as the rise in cholera cases coincides with elevated temperatures occurring between March and May [17].

The appearance of cholera cases in North India have been demonstrated to generally follow an increase in *V. cholerae* in the aquatic environment in the previous month, which is in turn preceded by a rise in temperature a further month before this [30]. Another study considering inland regions in Northern India/Pakistan found the odds of a cholera outbreak occurring were significantly higher when the temperature was above the climatological average over the previous 2 months [87].

Other studies have found less significant relationships between cholera incidence and ambient temperature. An autoregression study in Vellore [86] found no association, however lag times were not explicitly considered. A study in Bangladesh found a significant positive association between risk of cholera and heatwave after a 2-day lag, but only on wet days; on dry days there was no association [5]. They also found that the heatwave was effectively mitigated in households with a large percentage of medium-dense tree cover canopy around, potentially due to the cooling effects of shade and evapotranspiration. This suggests that rural areas may be less susceptible to heatwaves than urban areas with limited vegetation. Islam et al. [94] conducted a classification analysis on the relationship between climate variables and cholera cases in Matlab, Bangladesh. They found that increases in both temperature and sunshine hours positivity affect the variability of monthly cholera occurrence (i.e. high sunshine hours can compensate for low temperature). Summer in Bangladesh is associated both with higher temperature and fewer sunshine hours compared other seasons, and could therefore partially explain the summer lull in Bangladesh cholera despite the higher temperatures.

Ocean sea surface temperature (SST)

Ocean temperatures are unlikely to directly affect proliferation of *V. cholerae* as the bacteria do not live further from land than estuaries due to adverse conditions. However, due to coupled atmosphere-ocean processes such as the El Niño Southern Oscillation (ENSO) and the more localised Indian Ocean Dipole (IOD), ocean temperatures may influence cholera on land indirectly via changes in monsoon rainfall [95] and ambient temperatures [32] in India and Bangladesh.

A strong association between these climate processes and cholera have been extensively demonstrated in the literature in the context of the Bengal [28, 32–36], and was found to account for over 70% cholera variance in Dhaka during the period 1980–2001 [34]. However, studies describing the influence in inland India are more sparse. As with most influential factors, the strength of the association is dependent on context. Perez-Saez et al. [96] found spatial heterogeneity regarding its influence with a stronger ENSO sensitivity in the core of the city compared with the periphery. This matched similar results from Reiner et al. [97] who suggest the differences are likely to be caused by differences in population density and socio-economic conditions with the core of the city representing the highest levels of population density and poverty.

Coastal sea surface temperature (SST)

A related, though distinct, relationship appears to exists between coastal SST and outbreaks in Bangladesh. In 2000 Lobitz et al. [71] first found a statistically significant peak in cholera cases around a month following a peak in coastal SST for two out of the three years considered. The phenomenon

Table 2: Summary of findings relating coastal SST to cholera outbreaks.

Cholera dataset	Relationship	Hypothesized mechanism
Bengal (1891–1940) [61]	Spring SST has significant positive correlation with spring cholera. No association found between SST and winter/autumn cholera.	Increase in ocean plankton
Dhaka, Bangladesh (1992–1995) [71]	Positive correlation with lag (undefined).	Increase in ocean plankton
Dhaka, Matlab (1996–2002) [35]	0.1 °C increase in SST associated with cholera incidence increase of 4.8% in Dhaka, and 9.0% in Matlab.	None
Dhaka, Bangladesh 1980–2007 [57]	Strong negative correlation between winter SST and spring cholera. Weak positive correlation between spring SST and spring cholera. Strong positive correlation between summer SST and autumn cholera.	Cooler winter SST causes higher plankton abundance
Kolkata, India; Matlab, Bangladesh (1997–2006) [68]	SST was found to be an insignificant variable in a prediction model for cholera incidences in both areas.	Collinearity with chlorophyll *a* concentration or precipitation
Matlab, Bangladesh (1983–2003); Nha Trang (1985–2003) + Hue (1985–1995), Vietnam [6]	SST is not associated with magnitude of cholera outbreaks in Matlab or probability of outbreak in Nha Trang. However, positive correlation exists between SST and probability of outbreak in Hue.	None
Matlab, Bangladesh (2003–2007) [42]	No significant association found between SST and cholera incidence.	None
Matlab, Bangladesh (1988–2001) [3]	Significant negative correlation at 2-month lag. Weak positive correlation at 0- and 1-month lag.	None

has since been extensively studied, particularly among the coastal regions of the Bay of Bengal (BoB) however, findings have been inconclusive, as shown in Table 2. Some studies have concluded strong correlation between the two variables in line with the original findings from Lobitz et al. For example, a time-series regression by Hashizume et al. [35] found that each 0.1% increase in monthly SST in the preceding 0–3 months was associated with a 9.0% increase in cholera hospitalisations in Matlab and a 4.8% increase in Dhaka after accounting for sea surface height. Similarly, in Matlab, Ali et al. [3] found a 25% increase in cholera incidence associated with a one degree Celsius increase in SST in the current month, and 18% in the preceding month. When the spring and autumn peaks of the BoB were considered separately, Akanda et al. [57] found a strong positive correlation between summer SST and autumn cholera cases, and a strong negative correlation between winter SST and the spring cholera peak in Dhaka. Similarly Bouma and Pascual found a significant positive correlation with spring cholera in a Bengal dataset from 1891 to 1940, though found no association with winter/autumn cholera. Finally, others have found no significant correlation at all. Emch et al. [6] found no association when using an ordered probit model despite analysing a very similar dataset to Ali et al. a result repeated two years later by the same lead author [42]. De Magny et al. [68] developed predictive models to identify environmental signatures associated with cholera epidemics in both Kolkata and Matlab and found that SST was not a helpful predictor of cholera in either region. The authors suggested this was due to collinearity between variables.

The most obvious explanation for the positive correlation is the preference of *V. cholerae* for warmer water [3], as demonstrated in the previous section describing the positive association between ambient temperature and warmer waters. However, the inconsistency of this relationship suggests multiple mechanisms could be involved. The reviewed literature proposed two alternative theories as listed below.

Increase in phytoplankton

Numerous studies have found a significant positive correlation between plankton abundance and *V. cholerae* in the Bay of Bengal [66], and freshwater sources in India [30] and Bangladesh [26, 98]. Further, when Escobar et al. [99] developed a statistical model to identify variables associated with *V. cholerae* presence in global marine environments, they found 'mean chlorophyll-a' (often used as a proxy for phytoplankton as it can be easily measured using remote sensing) to be the most informative variable, accounting for 49% of variance in *V. cholerae* presence.

Two main mechanisms have been proposed to explain why increased phytoplankton concentration might directly result in increased in *V. cholerae* abundance. First, algal blooms alter the dissolved oxygen and carbon dioxide content, and thus raise the pH of water [30, 35]. *V. cholerae* are better able to survive and reproduce in more alkaline water [24, 100, 101], thereby leading to an increase in their concentration. Second, certain phytoplankton such as cyanobacteria can act as reservoirs for *V. cholerae* [66, 102] which provides them with essential nutrients, especially during inter-epidemic periods.

A study in Matlab, Bangladesh found a significant positive correlation between ocean chlorophyll and high cholera outbreaks following a 2-month lag [6]. The 2-month lag is important as it allows time for the *V. cholerae* numbers to

increase before reaching the critical concentration necessary for an outbreak.

The Spring cholera peak appears to be most pronounced in coastal regions, compared with inland regions [25]. Further, a later study by the same authors considered the two annual peaks individually and found the relationship between SST and cholera was only significant during the spring peak [42]. Another Bangladesh study found that spring cholera outbreaks were strongly correlated with winter ocean chlorophyll concentrations in the previous year [57]. These findings appear to suggest a strong role of coastal intrusion in Spring cholera in coastal regions, indicating a coastal reservoir of bacteria in Southern Bangladesh, aided by previous year fall and winter plankton abundance.

Increase in zooplankton

An alternative explanation proposed in the literature for the relationship between temperature and cholera involves an extra degree of separation: copepods, a family of chitinous zooplankton. Similar to the relationship with phytoplankton, *V. cholerae* are known to hold a commensal relationship with copepods by binding to the exoskeletons where they metabolize the chitin as a nutrient source [103]. A rise in the copepod population is thought to assist outbreaks in three ways:

a) The bacteria are capable of metabolizing the chitin from the exoskeleton of copepods as a nutrient source [93], thereby facilitating growth.
b) *V. cholerae* can form large multicellular structures known as biofilms on the surface of copepods which improves the bacteria's resilience to changes in salinity and pH as well as resistance to certain lytic vibriophages when compared to its free-living state [81, 104].
c) Growing on a biofilm promotes entry of *V. cholerae* into a hyperinfectious state, likely due to increased protection from stomach acid [105].

Despite the seemingly convoluted nature of this relationship, there is much evidence to support it. An intervention study conducted in Matlab, Bangladesh found that surface water filtered through sari (6 yard fabric worn by women) cloth reduced cholera incidence by 48% compared with a control group where participants did not use any filter [40]. Sari cloth is far too coarse to filter bacteria but can effectively filter copepods, suggesting a significant proportion of individuals may have been infected via *V. cholerae* living on copepods rather than free-living bacteria [41].

Huq et al. [26] found no independent association between phytoplankton and number of cholera cases, but did find strong correlation between zooplankton and cholera with a lag of 8 weeks. They suggest the environmental factors influencing phytoplankton production, primarily sea surface temperature, also have a significant effect on copepod concentration. Further, adsorption of vibrios to zooplankton was found to improve at higher pH levels caused by increased phytoplankton [106], and also increased temperature [30] thereby strengthening this link. An alternative and complementary theory is an increase in adherence of *V. cholerae* to copepods in warmer waters, as demonstrated in laboratory microcosm experiments [24].

Interestingly, the degree to which bacteria attach to zooplankton appears to be largely dependent on the strain. Rawlings et al. [107] found that *V. cholerae* O1 consistently achieved higher abundances than *V. cholerae* O139 in colonizing adults of each copepod species. Before the appearance of the O139 strain in 1992, cholera outbreaks were exclusively caused by *V. cholerae* O1. Later epidemics however, have been caused by a combination of both O1 and O139 strains [108]. The findings from Rawlings et al. could therefore potentially provide an explanation for the seemingly contradictory findings in the association between coastal SST and cholera outbreaks in Bangladesh in datasets from 1891 to 1940 [61] and 1980 to 2007 [57]. The former found a strong correlation between spring SST and concurrent cholera prevalence and no correlation during the second peak, whereas the latter describes a weak correlation with SST during the spring and a strong positive correlation during the autumn peak. Given the increased role of coastal waters during the spring peak [18], it would therefore make sense that earlier outbreaks involving solely O1 strains would be more affected by zooplankton concentration and therefore SST.

Sea surface height

The reviewed literature contained two studies which directly considered the association between sea surface height (SSH) and cholera incidence. An early (2000) study from Lobitz et al. [71] found that cholera outbreaks in Bangladesh during the considered period were often preceded by an increase in SSH. However, only three years of data were considered and therefore statistical conclusions were unable to be drawn. A later statistical model which considered the influence of SSH on cholera hospitalizations in Matlab over a 24 year period found a significant negative correlation between SSH and cholera during the spring peak, but no association during the autumn peak [42].

Economic and social development

Unsurprisingly, the literature indicated a strong relationship between cholera incidence and socio-economic status. In a statistical analysis of cholera cases across India from 2010 to 2015, Ali et al. [109] found that % mobile phone ownership

(used as a proxy for poverty) was a significant risk indicator for cholera, as were literacy rates. Further, Hamner et al. [110] found an increased likelihood of contracting cholera of 6.94 among families with monthly incomes under 3,000 rupees ($40) in Varanasi, India. The two studies which considered the relationship between socioeconomic status and hospitalisations in Bangladesh both focussed on the Matlab region and both found a significant association [42, 50].

Access and use of household water treatment systems are a potential mediator for this relationship. Point-of-use chlorine tablets have been shown effective at inactivating *V. cholerae* present in household water supplies in Dhaka [47]. Initial studies into the effectiveness of HWT systems on cholera incidence seem highly promising. An early intervention study in the urban slums of Calcutta, India found a 58% reduction in cholera prevalence when chlorinating water when compared to a control group [48].

An alternative mediating factor is population density which has been linked to cholera incidence in Matlab, Bangladesh [49]. This is likely to be due to increased contact between individuals, as well as the decreased sanitation conditions often found in dense urban areas. Within the rural area of Matlab, Study participants who shared latrines with other households had a 2.8 times great chance of being hospitalized with cholera [51].

Further socio-economic factors may include malnutrition which has been linked to prolonged shedding of *V. cholerae* [52]. Finally Education levels have been linked to both cholera incidence [50] and morbidity [49]. The precise mechanism by which education may affect cholera risk is not fully understood, but is considered to be related to personal hygiene [50].

Discussion

The results of our literature review indicate that environmental transmission of cholera is influenced by numerous factors. We suggest that there are essentially two variables that affect the rate at which cholera is transmitted: the concentration of pathogenic *V. cholerae* in water bodies, and the level of contact between humans and potentially infected water bodies. An increase in either of these two variables will increase likelihood of an outbreak. These two variables are in turn likely defined by three socioeconomic factors (HWT usage, sanitation availability, population density) and seven environmental factors (water level, salinity, phage concentration, rainwater run-off, pH, phytoplankton concentration, and zooplankton concentration) in addition to others. While the socioeconomic factors are mainly driven by income, environmental factors are interconnected and are in turn influenced by rainfall, sea surface temperature, and ambient temperature. A diagrammatic representation of these variables and their interconnections is provided in Figure 3.

A common issue we observed in the literature was that of 'untangling' the roles of different climatic drivers due to covariance. The recent wealth of remotely sensed environmental data provided by the rise in satellites has led to many researchers conducting correlational analyses. Given that all environmental factors considered vary seasonally, it can be assumed that any seasonal factor will show at least a weak correlation with cholera incidence, thus making it difficult to differentiate between causative and merely correlational relationships. Covariance is also a problem at an interannual scale. Cholera outbreaks are known to be associated with El Nino events which provide both positive rainfall anomalies and an increase in SST [20].

Low levels of rain

The reviewed literature suggested three potential mechanisms for explaining the association between reduced rainfall and cholera incidence: reduced water volume, predation by vibriophages, and increased salinity. King et al. [111] have argued that this association is, in part, an illusion. They suggested that the monsoon lull is not due to environmental mechanisms but rather the inherently self-limiting nature of cholera outbreaks and high levels of asymptomatic cases that provide temporary immunity and deplete the susceptible population. During monsoon, the susceptible pool then replenishes, and is ready for another outbreak at the end of the season. However, Pascual et al. [112] question the validity of this theory by pointing out that seasonal outbreaks in Bangladesh tend to curtail prior to significant depletion of susceptibles. Further the depletion of susceptibles hypothesis cannot explain why drier years tend to result in stronger pre-monsoon peaks, and we therefore suggest that environmental mechanism(s) contribute to the associations between reduced rainfall and cholera incidence.

While the results of the review found evidence to suggest that each of the three proposed mechanisms was a plausible explanation of the drought-cholera association, none of the studies were able to demonstrate direct causal evidence making it difficult to differentiate between the relative importance of each. The comparative lack of reported drought-associated peaks within inland areas and the demonstrated association with conductivity in coastal regions perhaps points to an increased importance of the increased salinity hypothesis. However, this evidence merely suggests an association between coastal intrusion and cholera transmission could be caused by other coastal processes such as plankton abundance.

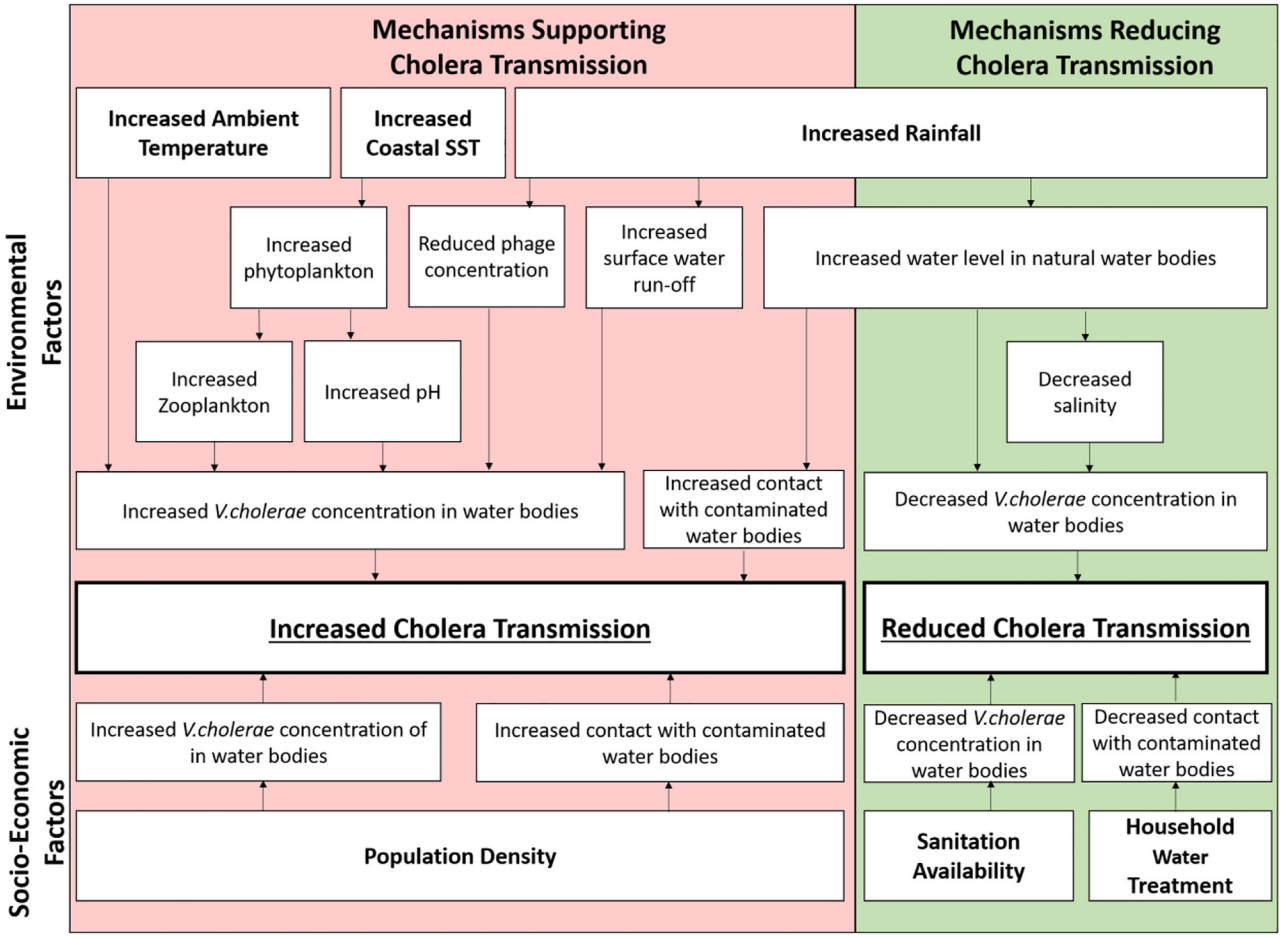

Figure 3: Diagrammatic representation of mechanisms of cholera transmission via the environment in India and Bangladesh. Mechanisms in the red zone display a positive relationship with cholera transmission; factors in the green zone imply a negative. Variables in both zones display both negative and positive relationships with cholera transmission.

Finally, it is possible that the drought-cholera association can be explained by non-environmental processes. For example, stored household water is a significant source of *V. cholerae* contamination [48, 113], and therefore an increase in stored water may contribute to cholera outbreaks particularly during periods of drought. A study in Northwest Bangladesh found that households tend to store more water during the dry season due to uncertainties in supply [114]. Low availability of drinking water is also common during the dry season in coastal regions due to depletion and salinization of tube wells [115]. To our knowledge, no specific investigations have been conducted to test the hypothesis that increases in storage water act a mediating factor in the relationship between drought and cholera increase.

High levels of rainfall

The reviewed literature suggested two potential mechanisms for the association between increased rainfall and cholera incidence in inland India as well as the post-monsoon outbreak in the regions surrounding the Bay of Bengal: increased flooding, and contamination of water sources via wastewater runoff. Post-monsoon floods can be significant, particularly in Bangladesh where an average of 18% of land-surface is inundated and can even exceed 60% during high flood years [116].

In the literature we found conflicting results regarding the effectiveness of flood protection zones. An intervention in Dhaka suggested these zones conferred significant protection against cholera, however two studies considering the effects of a similar flood protection zone in Matlab suggested residents within the zone were at greater risk of cholera. This discrepancy could potentially highlight the difference in driving mechanisms between urban and rural areas. For example the flushing effect described by Carrel et al. could hold greater importance in rural areas and outweigh increased risks of cross-contamination. Whereas in urban areas, where population density is much higher, the risks of cross-contamination may be greater than that in urban

areas. Further, risk of exposure to contaminated flood water may be greater due to lack spacing forcing households onto high risk areas. These studies may warn against the dangers of oversimplification when examining cholera transmission, as well as the importance of specific contexts.

Ambient temperature

The reviewed literature suggests that an association between ambient temperature and cholera incidence exists when considered at a lag time of around two months. Within the context of Northern India, Taneja et al. [30] note that elevated air temperature alone can only assist an already present reservoir of *V. cholerae,* and would not be sufficient to bring about an epidemic in regions with low or non-existence bacterial presence during inter-epidemic periods. In northern regions this would require the accompaniment of an appropriate transmission mechanism such as cross-contamination of surface water and sewage via increased rainfall. However, in more coastal regions where pathogenic *V. cholerae* are present year-round, elevated temperature may increase concentrations of pre-existing *V. cholerae* communities to sufficient level to cause infection.

Coastal sea surface temperature

The review found highly mixed results regarding the relationship between coastal SST and cholera outbreaks with different studies finding any of positive, negative or neutral relationships. Part of this complex relationship may be a result of the complexity of the relationship between phytoplankton and SST. Globally, it is generally the case that higher SSTs lead to reduced phytoplankton biomass due firstly to enhanced vertical stratification (resulting in reduced nutrient flux to the upper oceans where phytoplankton reside), and secondly an increase in the metabolic rate of primary consumers such as zooplankton [117, 118]. However, the negative effect of increased SST on phytoplankton productions appears to be strongest at higher latitudes. Gregg et al. [37] found that despite a global decline in ocean primary production in line with an increase in SST, production in the North Indian Ocean has increased by 13.6% between 1980 and 2002 – the most significant increase of all regions studied. This is supported by Chaturvedi [38] who found a year-round positive relationship between SST and chlorophyll in Northeast (coastal) Bay of Bengal. However, they found no relationship along the West coast of India. The implication of this is that while the association between SST and phytoplankton may be important to cholera prevalence in coastal Bangladesh, it is likely to be less relevant to outbreaks in India. Further, it is possible that the relationship between SST and phytoplankton may vary over time due to changes in global ocean processes. This may partially explain differences in associations with cholera when using colonial datasets compared with current, and may also suggest that extrapolating the results of this review when considering the effects of future climate on cholera incidence should be treated with caution.

A further complication in the relationship between SST and cholera incidence which may explain the inconsistent results is the presence of feedback loops within the proposed mechanisms influencing cholera incidence. Zooplankton rely on phytoplankton as a nutrient source, and thus their numbers are strongly linked in a predator-prey relationship [119]. Increased river runoff during the monsoon has been shown to dramatically increase phytoplankton biomass in the BoB [120]. Lewandowska et al. [118] have suggested that increased SST leads to the higher levels of chlorophyll in the BoB, but only when accompanied by major freshwater discharge. This fits with the findings from Coastal BoB, when seasonal river discharge is high, the correlation between SST and chlorophyll is positive. Coastal SST can affect rainfall over the subcontinent, and thereby influence cholera via rainfall mechanisms. A significant positive correlation exists between coastal SST in the Bay of Bengal and Bangladesh rainfall during the month of June [121]. This could potentially explain the strong positive correlation between summer SST and cholera prevalence in Dhaka during the autumn found by Akanda et al. [57] Our findings suggest the mechanisms mediating the association between coastal SST and cholera incidence are multiple and interlinked. Due to this complexity, the specific relationship between the two variables remains largely unclear, but is likely to be strongest in coastal regions during the spring peak.

Sea surface height

The results of the review produced limited evidence regarding the association between SSH and cholera incidence, although the available research suggests a neutral or potentially negative relationship. This is contrary to expectation as it could be anticipated that a positive relationship would be found due to coastal water intrusion or increased flooding. It has been argued that correlations found between SSH and cholera may be confounded by the third variable of increasing SST which mediates an increase in SSH through expansion of sea water [122]. Hashizume et al. [35] also found that an association between SSH and cholera was eliminated when adjusting for SST. Further, it

should be noted that long-term indirect associations between SSH and cholera may become more apparent as gradual sea level rise caused by ice melt due to global warming leads to large scale population displacement and therefore increased population density [123], and saltwater contamination of crops and groundwater sources [124]. Further the GBM delta, which accounts for most of Bangladesh and the Indian state of West Bengal, is subsiding at a mean rate of 5.6 mm/year due to a variety of natural and anthropogenic causes [125]. This will further increase the apparent sea level rise and associated land loss in the region.

Economic and social development

While it is well established that poverty and cholera are strongly linked [126], the relative importance of each individual factor remains difficult to define. This is due to inherent and inevitable collinearity between poverty related variables. For example, despite it's likely importance, sanitation conditions were not retained in a regression model to predict cholera incidence in Dhaka due to collinearity with population density [49]. Root et al. [50] found that some poverty related risk factors such as household assets and sanitation access were so highly correlated that separating the variables was a futile exercise. Nevertheless, given the faecal-oral nature of cholera transmission, certain factors such as access to adequate sanitation are widely accepted to be a fundamental cholera prevention strategy [127, 128].

Further we identified a significant lack of good quality studies assessing the effectiveness of specific HWT systems on cholera prevalence [129], particularly with other low cost treatments such as boiling which is highly effective at killing *V. cholerae* in laboratory environments [130]. The use of household water treatment (HWT) systems is limited within India and Bangladesh. According the 2012 India Human Development Survey, only 17.8% of those surveyed used any form of HWT such as boiling or filtration [131], while usage is even lower in Bangladesh, representing a mere 10.5% of the population in 2019 [7]. We therefore consider that there is significant potential for interventions in this area. Further research into the relative effectiveness of specific systems may allow increased efficiency of such interventions.

Limitations

This review has several limitations. Firstly the search was performed on only one platform and texts were selected for inclusion by only one researcher. Second, due to language limitations of the authors and an effort to limit the scope of the search, only texts published in English after 01/01/1970 were included in the search. This means that it is likely that some key texts may have been missed in the search process. Finally this review aimed to take a broad view at all evidence of factors which may influence environmental transmission of cholera across the relatively broad context of India and Bangladesh. For example, a systematic review focussed on the relationship between SST and cholera may help to disentangle the associated mechanisms and explain discrepancies between existing analyses.

Further work

We four areas in which the current understanding is unclear and could therefore benefit from further research:

a) What are the main sources of infection for index cholera cases in freshwater regions?
b) Does the presence of vibriophages affect the course of cholera epidemics?
c) Which household water treatment systems are most effective in preventing cholera transmission?
d) Could increases in stored water act as a mediating mechanism to explain the association between drought and cholera incidence?

Further, it is recognized that the Indian subcontinent is a large region with diverse environment, weather, and people. This made clear by the differences in the seasonal patterns as described in the seasonality section. A significant proportion of cholera research in the area, and indeed the world, has been conducted in Bangladesh, and specifically the regions of Dhaka and Matlab. This is due to a comparative wealth of high-quality longitudinal cholera data from hospitals in these two areas. While efforts have been made to provide a balanced summary of factors affecting cholera incidence across the subcontinent, a bias towards Bangladesh has been inevitable. Finger et al. [132] stress the importance of modelling approaches in a case-dependent basis due to huge variation in dominant infection mechanisms in different geographical and social contexts. Further, the lack of varied epidemiological data limits comparisons between regions which could help in disentangling of driving mechanisms. Consequently, we consider increased reliable and consistent cholera surveillance, with anonymized data made accessible to researchers, to be of maximum importance in developing an accurate and comprehensive understanding of endemic cholera.

Conclusions

In this paper, we review the evidence supporting the mechanisms of environmental cholera transmission within India and Bangladesh. Non-environmental transmission appears to play a limited role in the proliferation of cholera outbreaks on the Indian subcontinent. Evidence in support of the key role environmental transmission in this region remains compelling. We deduce that this transmission is most likely influenced by both climatic (namely rainfall, ambient temperature, and sea surface temperature) and socio-economic factors (namely HWT usage, sanitation availability and population density). These variables influence transmission via multiple mechanisms, and are expected to hold complex relationships with cholera case numbers.

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