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Mapping cholera outbreaks and antibiotic resistant *Vibrio cholerae* in India: An assessment of existing data and a scoping review of the literature

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ABSTRACT

Although fluid and electrolyte replenishment remains the mainstay of clinical management of cholera, antibiotics are an important component of the strategy for clinical management of moderate to severe cases of cholera. The emergence of antibiotic resistance (ABR) in *Vibrio cholerae* has led to difficulties in case management. The past decade has also seen the development of cheap and effective oral cholera vaccines (OCVs). In addition to the two-dose strategy for widespread immunization, OCVs have also been shown to be effective in containing outbreaks using a single-dose schedule. In this scoping review we map the states and union territories (SUTs) of India which are prone to cholera outbreaks followed by a scoping review of peer-reviewed publications about ABR outbreaks of cholera employing the Arksey and O'Malley framework. Using the data reported by the Integrated Disease Surveillance Program (IDSP), we identified 559 outbreaks of cholera between 2009 and 2017, affecting 27 SUTs. We defined SUTs which had reported outbreaks in at least three out of the last five years (2012–2016) or had experienced two or more outbreaks in the same year in at least two of the last five years to be outbreak-prone. The scoping review identified 62 ABR outbreaks, with four SUTs accounting for two-thirds of them: West Bengal (14), Maharashtra (10), Odisha (10) and Delhi (7). Overall, this scoping review suggests that there is an increasing trend of ABR in *Vibrio cholerae* isolated from outbreaks in India. This opens up avenues for exploring the role of antibiotic stewardship in the clinical management of diarrhea, the institution of vaccination as an infection prevention intervention to reduce selection pressure, and the deployment of high quality surveillance systems which report accurate, real-time data allowing appropriate and timely public health responses. It is crucial to counter the issue of ABR in cholera before it assumes a menacing magnitude.

1. Introduction

Cholera has been subject to intense academic scrutiny over the past decades, but has continued to be a public health menace in many parts of the world [1,2]. With changing geopolitical scenarios, political and civil unrest, and the breakdown of public health infrastructure, pockets of areas with extreme vulnerability to infectious diseases have emerged [3,4]. Cholera represents a particularly difficult problem in these contexts, especially in relation to displaced populations, refugees, and migrants. In addition to these

Abbreviations: ABR, Antibiotic Resistance; AMR, Antimicrobial Resistance; CBHI, Central Bureau of Health Intelligence; CENTRAL, Cochrane Central Register of Controlled Trials; COMBACTE-MAGNET, Combatting bacterial resistance in Europe - molecules against Gram-negative infections; CT, Cholera Toxin; DGHS, Directorate General of Health Services; EPI-Net, Pan European Epidemiological Network of COMBACTE-MAGNET; GTFCC, Global Task Force on Cholera Control; ICDDR,B, International Centre for Diarrhoeal Disease Research, Bangladesh; ICMR, Indian Council of Medical Research; IDH, Infectious Diseases Hospital, Kolkata; IDSA, Infectious Diseases Society of America; IDSP, Integrated Disease Surveillance Program; LMIC, Low- and Middle-Income Country; MeSH, Medical Subject Headings; NHP, National Health Profile; NICED, National Institute of Cholera and Enteric Diseases; OCV, Oral cholera vaccine; ORS, Oral Rehydration Solutions; OTC, Over-the-Counter; SUT, States and Union Territories; TCP, Toxin Coagulated Pilus; UNGA, United Nations General Assembly; WHO, World Health Organization.

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especially vulnerable areas, cholera remains endemic in many parts of the world, prominent amongst them being the Gangetic plains of India, which is believed to be the epicenter for six of the seven cholera pandemics [44].

Cholera is caused by toxigenic strains of *Vibrio cholerae* serogroups O1 and O139. *V. cholerae* O1 and O139 serogroups express Toxin Co-regulated Pilus (TCP) and produce Cholera Toxin (CT), a critical virulence factor, and may cause secretory diarrhea and intestinal colonization. Other than O1 and O139, there are other vibrios that are designated as *V. cholerae* non-O1, non-O139 or non-agglutinating vibrios.

Given the massive fluid loss experienced by cholera patients, it remains a rapid cause of dehydration and death. Official estimates state that the mortality from cholera remains low, to the tune of 1%, but recent evidence points to massive under-reporting of both cases and deaths due to cholera [5,6]. Antibiotics have been established as part of the strategy for optimal management of cholera to reduce the disease morbidity and mortality [7,8]. The emergence of antibiotic resistance (ABR) has, however, intensified the threat of cholera [9–11]. The emergence of ABR as a major public health challenge was identified when the United Nations General Assembly (UNGA) brought the global leadership together to declare its commitment to combat the emergence of ABR [12,13].

With these issues in mind, we have used two approaches – analysis of existing data (Integrated Disease Surveillance Program and facility based surveillance for diarrheal disease etiology and antimicrobial resistance profiles of causative bacterial agents) and a scoping review of the published literature – to identify vulnerable, outbreak-prone states and union territories (SUTs) of India. We expect that this review will help to identify potential policy directions to address the emergence of ABR in *Vibrio cholerae*. This review would enable us to not only identify the vulnerable SUTs based on existing data, but also would help us understand whether the emergent crisis of AMR is a major issue in cholera control. With the Global Task Force on Cholera Control (GTFCC) calling for an end to cholera by 2030, these findings are likely to help the policymakers identify which areas to first target in order to reduce the burden of cholera in the nation, whilst also emphasizing the need to undertake systematic cholera surveillance, unbiased by reporting sensitivities and outbreak-only reporting, to estimate the true burden of the disease in the country.

2. Methods

We obtained data from two sources to fulfill the objectives. First, we analyzed the data from the IDSP to identify the SUTs that are particularly vulnerable to outbreaks of cholera; second, we conducted a scoping review of peer-reviewed publications to assess the extent of ABR in cholera outbreaks reported from India.

2.1. IDSP data

The IDSP was initiated with the primary objective of strengthening and maintaining decentralized laboratory-based IT enabled disease surveillance system for epidemic prone diseases, to monitor disease trends and to detect and respond to outbreaks in early rising phase through trained Rapid Response Teams (RRTs). Further details of the mechanisms, platform and quality assurance are available on the IDSP website [14–16]. IDSP data is focused on reported outbreaks, thus, may not reflect the endemic cases, some of which may be captured through the scoping review.

For IDSP data, we included only outbreaks which were attributed to *Vibrio cholerae* (irrespective of O1 or O139), based on laboratory confirmation; data was extracted from 25th week of 2009 (ending on 21 June 2009) till the 41st week of 2017 (ending on 15 October 2017). There were several outbreaks of acute watery diarrhea, which could not be attributed to a specific causative agent, which were not included in the current analysis.

2.2. Scoping literature review

For the scoping review, we followed the Arksey and O'Malley framework, which consists of six stages, as described here [17–19]. We chose the scoping literature review approach after extensive consultation with experts and internal discussion because the initial, structured search strategies revealed few high-quality peer-reviewed, quality assured publications. Using the scoping review approach would allow us the freedom to choose from a wider complement of studies, and particularly focus on mapping the gaps in the areas of the current research questions. The extreme diversity – clinical, methodological, and statistical – was also a challenge for risk of bias assessments for systematic reviews; for a scoping review, this step was deemed optional. As higher quality evidence becomes more plentiful, we can build on the findings of the current study to conduct a systematic review [20]. In the subsequent section we describe the six stages of the Arksey and O'Malley framework for scoping reviews, and outline the methodological details as they pertain to the current study.

Stage 1: Identifying the research question

We posited that the emergence of ABR in *Vibrio cholerae* would spell a potential public health disaster, especially keeping in mind the emergence of pockets where cholera is entrenched. With this context to build on, we designed the following research questions:

- By examining the IDSP data, we tried to address the following: Which SUTs are especially vulnerable to outbreaks of cholera in India?
- Through the scoping review approach, we tried to address the following: What is the extent of the problem of ABR in cholera outbreaks reported from India in peer-reviewed journals?

Stage 2: Identifying relevant studies

The second source of data was the scoping review. Search strategies were developed for three databases: PubMed, MedInd/IndMed and Web of Science. We developed a structured search strategy keeping the following terms in mind: "outbreaks", "cholera", "ABR" (or "AMR") and "India".

For PubMed, we used Medical Subject Headings (MeSH) for cholera, cholera vaccines, outbreaks, and drug resistance. The terms were appropriately combined with the Boolean Operators AND and OR. We limited our search to India by incorporating an "India"[all fields] limit. The detailed search strategies for all three databases have been provided in Appendix A.

Stage 3: Study selection

The list of studies identified by the search strategy was managed using an online reference management software (Covidence). The removal of duplicate references was automatically done by this software, followed by independent screening of the publications by two of the authors (PC and SK). On the first pass, the studies were screened based on their titles and abstracts (if available). Conflicts in the decision to include a study were resolved through mutual discussion; when there was uncertainty about the decision, the authors preferred to include them for the next step of full-text review. On the second pass, we screened the full texts of articles for inclusion in the review. The screening process was guided by a set of inclusion and exclusion criteria. We included studies which ana-

lyzed part or all samples obtained from an outbreak, in India, which was obtained through clinical surveillance (rather than archived samples), and where *Vibrio cholerae* (irrespective of O1 or O139) was one of the several pathogens studied as an etiology for the outbreak.

After the list of articles to be included in the review was curated, one author (PC) scanned the bibliographies of the included studies to identify additional publications that may have been missed by the structured search strategies. The process is summarized in Fig. 1, and the inclusion and exclusion criteria are provided in Appendix B.

Stage 4: Charting the data

We developed two databases which guided the analysis of this review. The first database comprised the outbreak data from the IDSP and outlined reported details about the location of outbreaks. For the purposes of this review, we concentrated on the state from which the outbreak was reported. IDSP data was available from the 25th week of 2009 (ending on 21 June 2009). We extracted data till the 41st week of 2017 (ending on 15 October 2017), which was the most recent weekly update reported at the time of the preparation of this manuscript.

From the studies selected in the previous step, we extracted data on the proportion of samples reported to be resistant to a given set of antibiotics. We avoided a meta-analysis because the study designs, tested antibiotics, and methods of ascertaining resistance status were too heterogeneous across studies.

Stage 5: Collating, summarizing and reporting the data

We summarized outbreaks in different states by year to identify the states that reported a high frequency of outbreaks. We identified states that reported outbreaks of cholera in three out of the

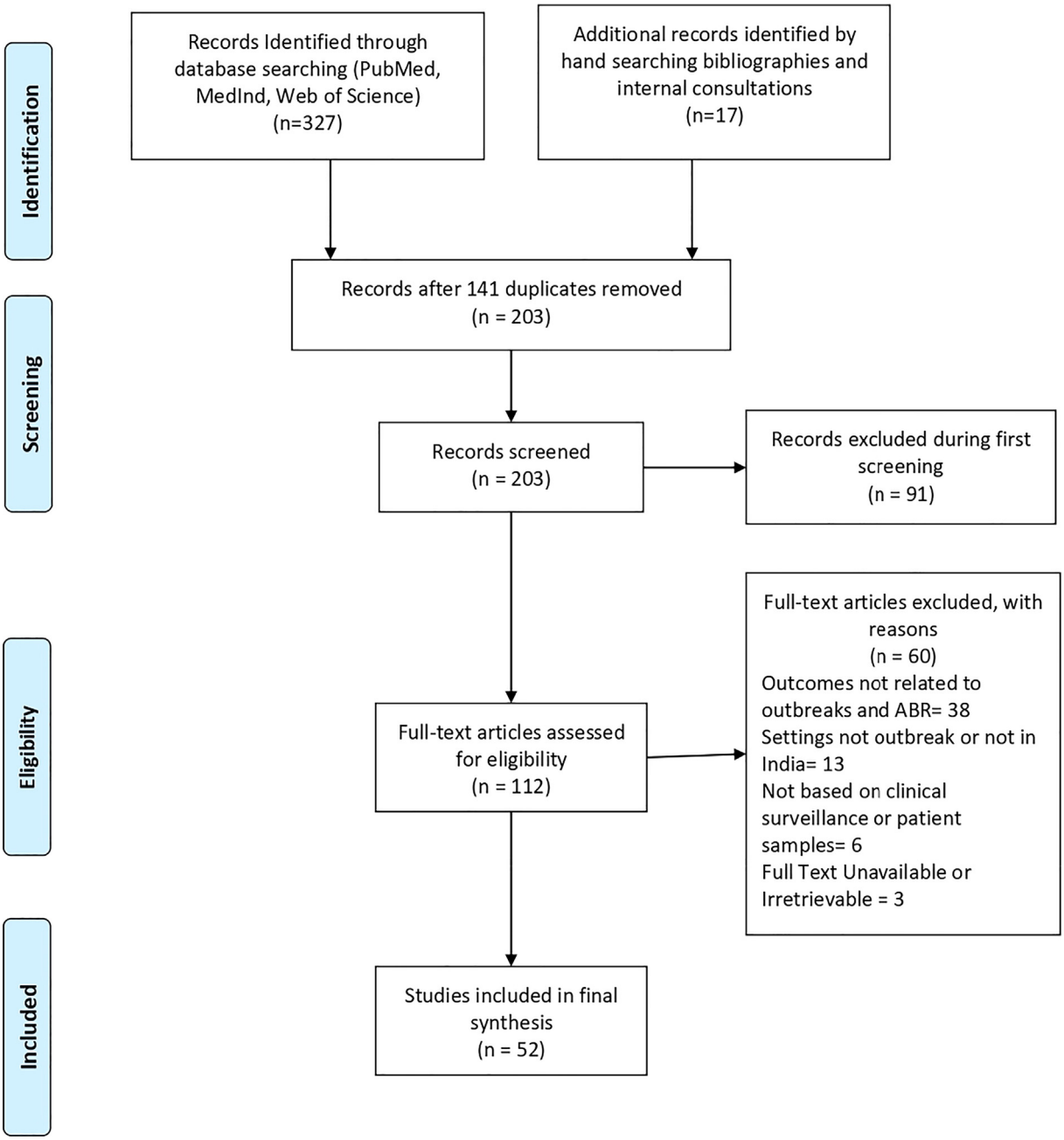


Fig. 1. PRISMA flow diagram showing selection of studies to be included in the scoping review.

last five years, or two or more outbreaks of cholera in the same year in two out of the last five years as outbreak-prone. Since the data for the year 2017 was till October, in order to apply the definitions for endemic states and outbreak prone vulnerable SUTs, we chose to concentrate on the latest five full years for which we had IDSP data, i.e. 2012–2016.

We created heat-maps of ABR rates over time to understand the trends of emergence of ABR against clinically important antibiotics. A large number of antibiotics have been studied, but we chose the ten antibiotics listed here for the analysis because they were most commonly reported by the studies, and were considered to be commonly used in clinical practice in the community setting: ampicillin, chloramphenicol, ciprofloxacin, cotrimoxazole, furazolidone, gentamicin, nalidixic acid, norfloxacin, streptomycin, and tetracycline.

Each of the publications reported the resistance rates either for a period of time or for individual years, over time. We wanted to see how many studies reported resistance rates in the four grades, for each of the ten antibiotics mentioned above. Given the low number of studies, we decided to divide the resistance rates into four grades based on the proportion of resistant isolates reported by the studies: 0–24%, 25–49%, 50–74% and 75–100%. In order to create these heat maps, we tabulated the frequency with which publications mentioned the grade of ABR noted in cholera samples, against time periods. Thus, the heat map would give us a qualitative idea about the spread of the resistance rates against a particular antibiotic over time. We created a heat map using the number of publications, in a particular year (or a range of years for studies that ran into multiple years), with the spectrum changing from green (no publications) to red (the maximum number of publications for the given antibiotic in a given year). Explanatory details accompany the footnote for the heatmap.

Stage 6: Consultation exercise and data from facility-based surveillance at Infectious Diseases Hospital, Kolkata

The consultation stage is considered to be an optional but valuable step in the process of conducting a scoping review following the Arksey and O'Malley framework [9–11,14]. We undertook an unstructured consultation involving the authors of the current manuscript to identify additional publications which could have been missed in the structured review; to understand the trends and patterns of outbreaks and outbreak-prone states in India; to identify the antibiotics which would be covered by the scoping review, and to identify any other secondary sources of information or data to help support our analyses. This consultation exercise was conducted after data charting was completed. The process led to the addition of three studies, the results of which were incorporated into the charted data.

It also led us to identify an additional dataset which helped us to reflect on the accuracy of the reported cases of and deaths from cholera in India. This dataset was built on the basis of the ongoing surveillance for diarrheal diseases at the Infectious Diseases Hospital (IDH) in Kolkata, which has been undertaken by the Indian Council of Medical Research, National Institute of Cholera and Enteric Diseases (ICMR-NICED), since the mid-1990s. The purpose of using this dataset was to compare the findings from a single, ongoing, quality assured, facility-based surveillance, to the nationally reported burden, to see if there were any broad discrepancies, which could indicate towards the existence of lacunae in the current reporting systems.

The IDH, Kolkata, is a tertiary care hospital dedicated to managing patients suffering from communicable diseases; a large proportion of the patients cared for at this hospital suffer from diarrhea. ICMR-NICED samples about 5% of the admitted patients to evaluate the etiology of acute diarrheal episodes. The detailed methodology and cumulative findings from the initial years of the facility-based surveillance at the Infectious Diseases Hospital, Kolkata, have been summarized elsewhere [21]. Cholera remains a leading diagnosis in adults. We extrapolated the isolation rates of cholera in the surveillance group to the annual cohort treated for diarrhea at the hospital and came up with a crude estimate of the number of cholera cases every year. We then compared it with the number of cases reported at the national level in the National Health Profile (NHP), which is published by the Central Bureau of Health Intelligence, Directorate General of Health Service (CBHI, DGHS) [22]. The CBHI,

Table 1
Year-wise number of reported cholera outbreaks from various states and union territories of India during 2009–2017.

States/UTs	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Andhra Pradesh	0	0	0	1	3	0	1	0	0	5
Assam	6	9	7	9	5	3	0	8	1	48
Bihar	0	0	0	0	0	2	0	0	0	2
Chandigarh	0	0	1	2	0	0	5	3	1	12
Chhattisgarh	0	0	4	1	1	1	0	3	1	11
Dadra & Nagar Haveli	0	0	0	0	1	0	2	1	0	4
Delhi	0	0	0	0	2	0	0	1	0	3
Goa	0	0	0	0	1	0	0	0	0	1
Gujarat	0	6	4	3	6	3	5	14	6	47
Haryana	3	3	1	5	4	3	0	0	1	20
Himachal Pradesh	0	2	0	0	0	0	0	0	0	2
Jammu & Kashmir	0	1	0	3	0	0	0	0	0	4
Jharkhand	0	0	0	1	0	0	0	0	0	1
Karnataka	7	4	13	22	23	3	12	16	1	101
Kerala	0	0	3	5	1	1	0	2	2	14
Madhya Pradesh	0	2	1	0	0	0	5	16	1	25
Maharashtra	0	3	5	7	14	1	2	11	2	45
Meghalaya	0	0	0	1	0	0	0	0	0	1
Odisha	0	1	0	2	2	6	0	4	0	15
Puducherry	0	5	0	1	0	0	0	0	0	6
Punjab	1	2	3	10	3	6	2	5	9	41
Rajasthan	0	7	2	1	0	0	2	8	0	20
Tamil Nadu	0	3	10	9	3	1	0	0	0	26
Telangana	0	0	0	0	0	0	2	3	0	5
Uttar Pradesh	0	0	0	0	0	0	0	1	0	1
Uttarakhand	1	0	1	0	0	0	0	0	0	2
West Bengal	1	4	11	15	30	12	7	17	0	97
Total	19	52	66	98	99	42	45	113	25	559

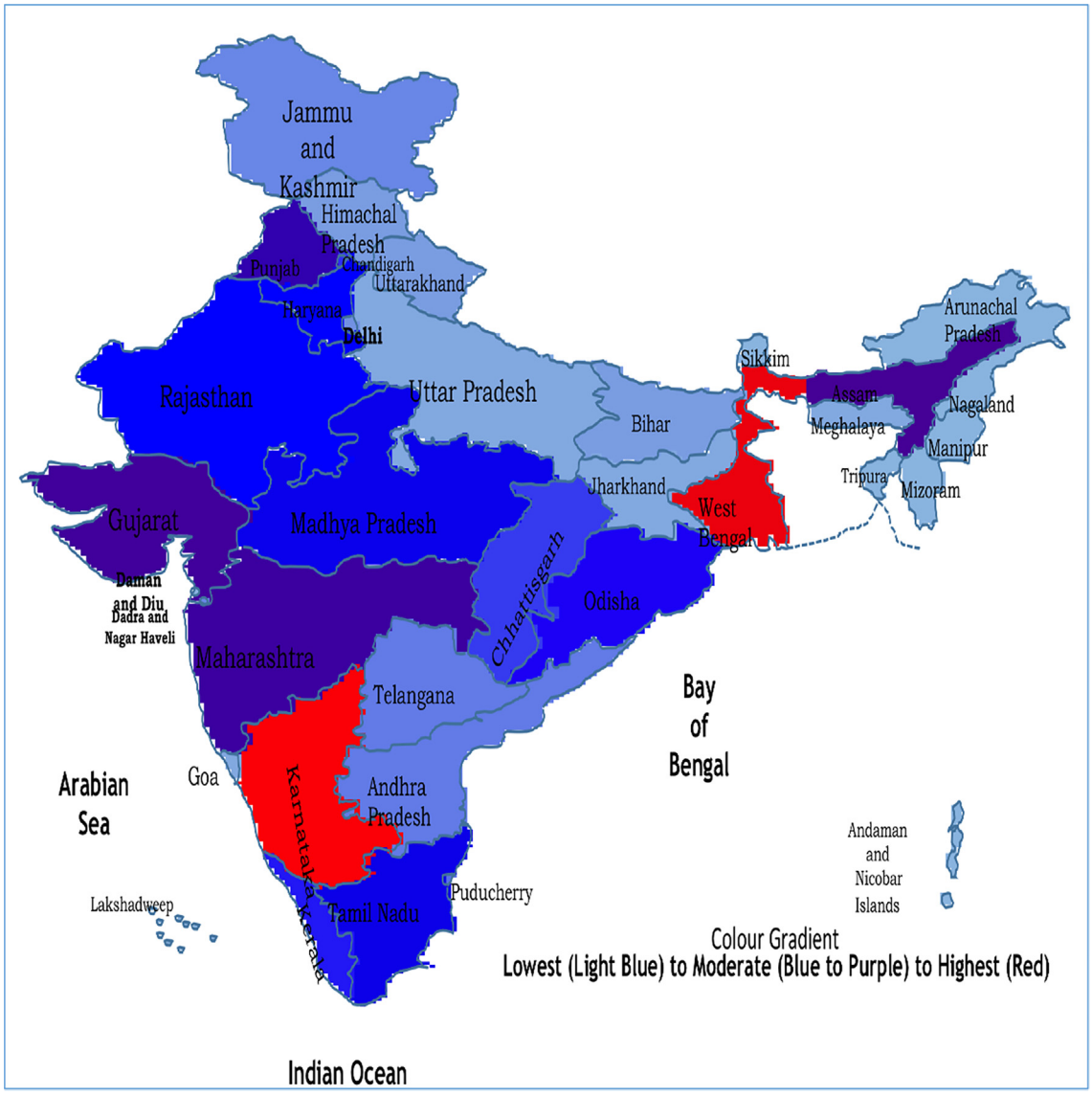


Fig. 2. Heat map showing number of cholera outbreaks based on IDSP data between 2009 and 2017. (Lowest: 0; Highest: 101).

DGHS collects reports on the burden of several diseases of public health importance, of which cholera is one, from health care systems across the nation and compiles them in an annual monograph, called the National Health Profile (NHP). It tabulates the case counts and deaths reported from individual diseases. This is separate from the outbreaks identified by the IDSP. The CBHI DGHS NHP creates burden estimates for diseases of public health importance, whereas the IDSP identifies and responds to outbreaks. Since the NHP provides the official, national estimates for the diseases concerned, we are using it to compare it against the case counts identified by our current efforts. The data has been presented in Table 3.

3. Results

From the three databases, we identified a total of 327 peer-reviewed publications using structured search strategies which were not limited by time periods. Screening through the bibliographies of the selected studies and internal consultations led to the

Table 2
Frequency at which various states and union territories contributed to the peer-reviewed literature on outbreak of ABR cholera.

State/UT	Frequency (%)
Andaman and Nicobar Islands	1 (1.6)
Assam	1 (1.6)
Bihar	1 (1.6)
Delhi	7 (11.3)
Himachal Pradesh	1 (1.6)
Karnataka	4 (6.5)
Kerala	2 (3.2)
Madhya Pradesh	1 (1.6)
Maharashtra	10 (16.1)
Mizoram	1 (1.6)
Odisha	10 (16.1)
Puducherry	2 (3.2)
Punjab	3 (4.8)
Tamil Nadu	4 (6.5)
West Bengal	14 (22.6)
Total	62 (100)

selection of 17 more records. After the selection process was over, we included 52 articles for this review. Fig. 1 summarizes the process.

3.1. Outbreaks

From the available IDSP data, we identified 559 outbreaks affecting 27 SUTs between 2009 and 2017. The outbreaks were defined by the IDSP in the IDSP training module for state and district surveillance officers, module 5. It is based on trigger definitions, as below:

- Trigger 1
  - o A single case of cholera / epidemiologically linked cases of diarrhea
  - o A case of severe dehydration / death due to diarrhea in a patient of greater than 5 years of age
  - o Clustering of cases in a particular village / urban ward where more than 10 houses have at least one case of loose stools irrespective of age per 1000 population
- Trigger 2
  - o More than 20 cases of diarrhea in a village/geographical area of 1000 population

The following SUTs did not report a single outbreak in this period: Arunachal Pradesh, Manipur, Mizoram, Nagaland, Sikkim, Tripura, Andaman and Nicobar Islands, Daman and Diu, and Lakshadweep. Six states accounted for 67% (379 out of 559) of all outbreaks: Karnataka (101), West Bengal (97), Assam (48), Gujarat (47), Maharashtra (45), and Punjab (41). Of the six most populous states of India (according to the 2011 census) [23], only one was represented in this list—West Bengal (7.55% of the national population); the other five, viz. Uttar Pradesh (16.49% of the national population), Maharashtra (9.28%), Bihar (8.58%), Madhya Pradesh (6%), and Tamil Nadu (5.96%), account for almost half of the nation's population (46.31%), but only about 18% of reported outbreaks of cholera.

The details of the year-wise number of outbreaks of cholera reported from various SUTs of India are given in Table 1. Fig. 2 maps out the same.

Sixteen SUTs fulfilled the definition we had set for cholera outbreak-prone SUT. These include: Andhra Pradesh, Assam, Chandigarh, Chhattisgarh, Dadra and Nagar Haveli, Gujarat, Haryana, Karnataka, Kerala, Maharashtra, Odisha, Punjab, Rajasthan, Tamil Nadu, Telangana, and West Bengal.

3.2. Publications

Although we included 52 publications, a small number of those covered sites in multiple SUTs, resulting in a total of 62 SUTs being represented in the analysis. The highest number of publications was based out of West Bengal (14), followed by Maharashtra (10), Odisha (10) and Delhi (7). Together, these four sites accounted for 66% of the publications (41/62). Table 2 outlines the frequency at which various SUTs contributed to the peer-reviewed literature on outbreak of ABR cholera.

3.3. Under reporting of cholera

In eight out of the nine years between 2008 and 2016, the crude estimates for cholera in IDH, Kolkata far surpassed the national estimate mentioned in the NHP (CBHI, DGHS). The only year which was an exception was 2010, when the national estimates surpassed the estimated crude cholera burden from the hospital. Year-wise details are provided in Table 3 here.

3.4. Antibiotic resistance

The extent of resistance against ten common and clinically relevant antibiotics was tabulated in the form of heat maps, as shown in Fig. 3 here. Resistance to ampicillin was lower in earlier years with a marked increase over time. Since 1999, almost all the studies have found a resistance rate between 75 and 100%. Resistance against chloramphenicol shows the opposite trend. Although the resistance rates have been low throughout, in recent years, the resistance rates have been lesser than 25%. Resistance to cotrimoxazole was low in the initial years, but since 1997, resistance rates have been over 75%. Resistance against ciprofloxacin has been largely less than 25% throughout the whole period, with a few studies showing an increasing trend since 2006. Similar trends have been observed for norfloxacin, with studies since 2012 suggesting rates of resistance in the 25–50% range. Nalidixic acid, a non-fluorinated quinolone, in comparison to fluoroquinolones like ciprofloxacin and norfloxacin, shows a very different ABR trend. Resistance rates have been consistently greater than 75% since as early as 1998. Studies throughout the period from the early 1990s have shown very high rates of resistance against furazolidone—consistently in the 75–100% range. Resistance against gentamicin has exhibited the opposite trend, with rates lower than 25% throughout the period. Resistance against streptomycin, though measured in fewer studies than the other antibiotics, has been consistently in the 75–100% range. Finally, an intriguing trend has been observed for tetracycline, the drug of choice for a long time. Until as recently as 2005, studies suggested relatively lower resistance rates, in the 0–25% range, but in the last decade, resistance rates have been steadily rising, with recent resistance rates in the 75–100% zone.

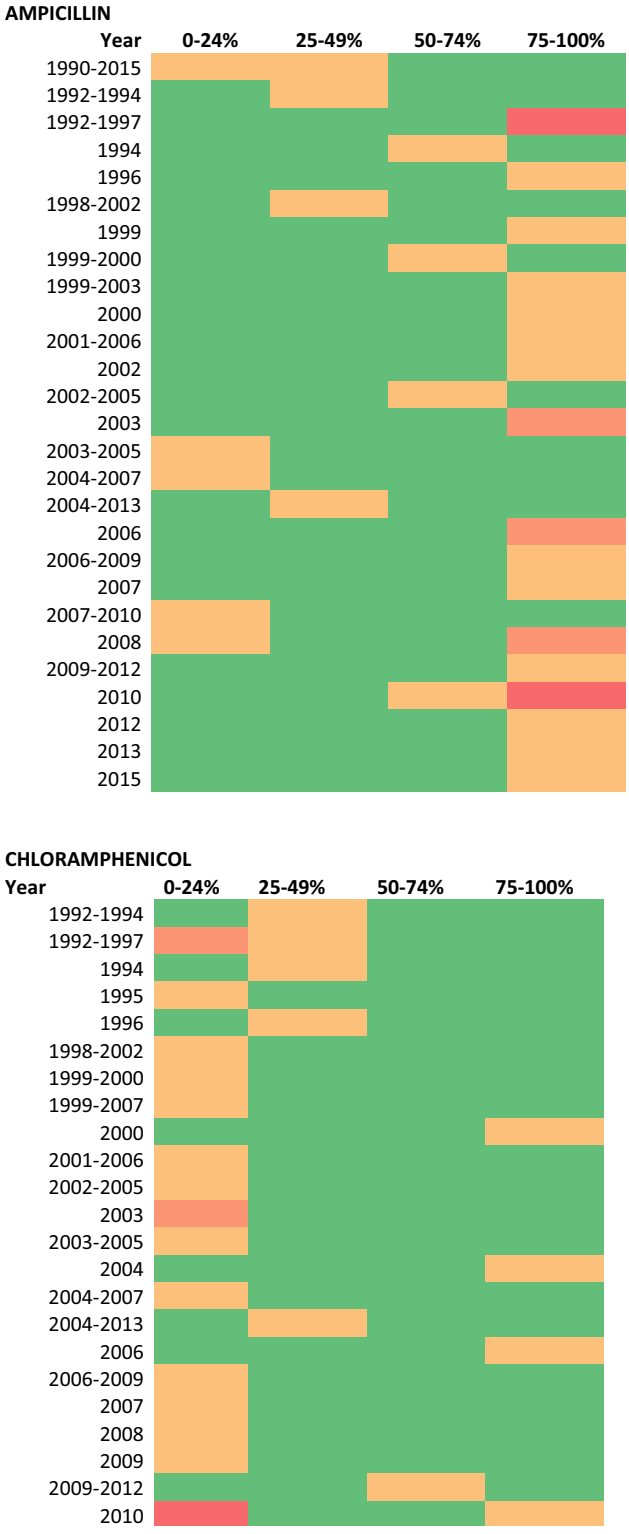
4. Discussion

Diarrheal diseases have been one of the most important causes of morbidity and mortality, and cholera, which continues to be a

Table 3
Comparison of crude estimate of confirmed cholera cases in Infectious Diseases Hospital, Beleghata, Kolkata, with those mentioned in the corresponding year-wise National Health Profile reports.

Year	Total admitted cases of diarrhea	Total cases under surveillance	Isolation Rate (%) of Cholera	Crude estimate of number of cholera cases	Cases Reported by CBHI, DGHS
2008	19,679	1122	250 (22.3)	4385	**2680**
2009	24,791	1393	376 (27.0)	6692	**3482**
2010	20,761	681	130 (19.1)	3963	5004
2011	20,558	644	126 (19.6)	4022	**2341**
2012	19,957	975	109 (11.2)	2231	**1688**
2013	22,378	1178	242 (20.5)	4597	**1130**
2014	22,566	1135	120 (10.6)	2386	**969**
2015	21,991	1193	163 (13.6)	3004	**913**
2016	22,963	1267	182 (14.4)	3299	**841**

The bolded numbers indicate that the total numbers of cases reported by the CBHI, DGHS, which represents the national cholera case load, is lower than the crude estimate of the number of cholera cases reported from a single hospital (ID Hospital, Kolkata).



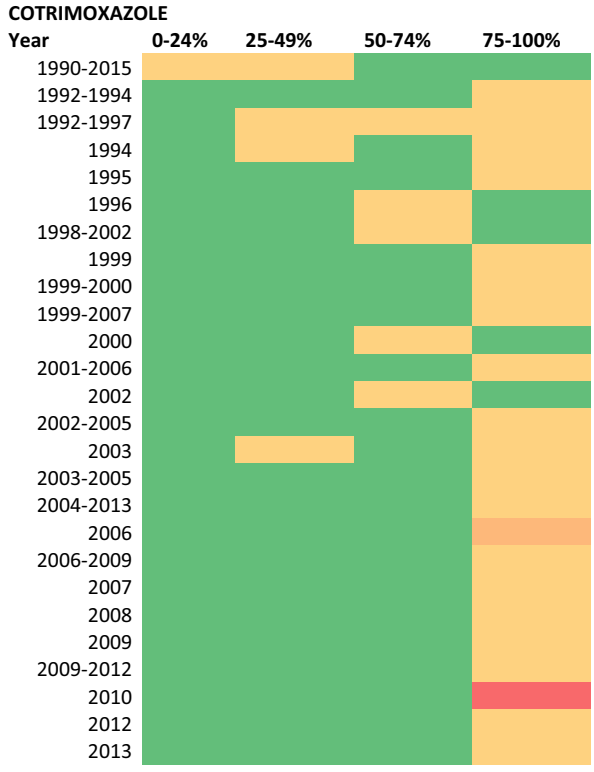
pandemic threat, remains a major causes of acute watery diarrhea [21]. Improved clinical management, particularly, early initiation of fluid and electrolyte replenishment using Oral Rehydration Salts (ORS) is one of the mainstays to prevent morbidity and mortality in cholera [25]. Antibiotic therapy, in addition to fluid replacement, substantially reduces the duration and volume of diarrhea [26]. The World Health Organization (WHO) advocates giving antibiotics only to patients of severe cholera [27]. However, contrary to WHO recommendations, studies conducted by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) concluded that antibiotic therapy should be considered for moderate cases of cholera as well [24,28]. Patients of cholera who receive appropriate antibiotics are more likely to suffer from a shorter duration of illness (50% reduction); excrete vibrios in the stool for fewer days; require less rehydration fluids and recover earlier; and require shorter in-patient care [7,29]. However, the long-term impact of antibiotic therapy, especially with respect to the emergence of plasmid-borne resistance in *V. cholerae*, has not been studied. We found 52 published instances of cholera outbreaks with an ABR *V cholerae* in 27 SUTs of India. This is especially significant at a time when global leaders have come together to commit to the containment and control of ABR [13].

The current review yields some worrying trends, especially with respect to emerging resistance patterns. There seems to be an association between antibiotic consumption and emergent ABR. This is obvious in the case of ampicillin, norfloxacin, ciprofloxacin and tetracycline. The reverse trend is apparent in the case of chloramphenicol. Chloramphenicol has had limited use in India in the past decade due to the availability of more effective antibiotics, which have dosing regimens which are easier to adhere to, and have fewer side effects. While this suggests that antibiotic cycling or antibiotic rotation could be a potential strategy to improve resistance profiles, previous clinical experiences, modeling studies, and guidelines do not support such a policy move [31–36].

To further complicate the epidemiology of drug resistant cholera, there is a wide range of drugs to which the pathogen can be resistant. Since vibrios do not have stable plasmids and plasmid-mediated mechanisms is one of the modes by which they may acquire drug resistance, resistance patterns fluctuate [37–42]. This observation is further supported by a number of reports noting the presence of resistance against multiple antibiotics. In 2006, there was an outbreak of multidrug resistant cholera in Odisha, followed by another one in 2007 [30,31]; high degrees of resistance were noted from samples examined in Kolkata between 2002 and 2010 as well [32,33].

A special concern has been the emergence and persistence of drug resistant *V. cholerae* in endemic areas [45]. Inappropriate antibiotic prescriptions for diarrhea patients, over-the-counter (OTC) availability of antibiotics without valid prescriptions and consumption of improper or incomplete antibiotic regimens have further contributed to this emerging crisis [46–49]. Furthermore, a lack of confidence in simple rehydration-based therapy for mild and moderate dehydration prompts the indiscriminate usage of antibiotics, either singly or in combination with anti-parasitic drugs, which may be prescribed even without a strong clinical suspicion of a parasitic infestation [36,37,50]. The utility of simple rehydration solutions has been well-known for over two decades now, and yet, people are loathe to rely on them [51]. This indis-

Fig. 3. Heat maps of time versus emerging resistance trends in *V. cholerae* against various antibiotics (Color legend: Green = None, Yellow = Few, Red = Many) # # These heat maps show the frequency with which publications report resistance rates against particular antibiotics over time. Years where no publications have reported rates of antimicrobial resistance have been considered to fall in the 0–24% range; with the increasing number of publications reporting resistance rates within a particular range, the color changes from green to yellow to red, where red cells indicate the largest number of publications. A heat map with more green on the left half of the heat map (covering the 0–24% and 25–49% ranges, as is seen for cotrimoxazole, streptomycin and furazolidone) is indicative of an antibiotic against which more studies report a higher proportion of resistant samples. Conversely, a heat map with the red cells on the left side represents an antibiotic against which studies report lower resistance rates (as is the case for gentamicin and ciprofloxacin). This allows a qualitative assessment of the extent of resistance against a particular antibiotic exhibited by *V. cholerae* isolates obtained from samples collected during outbreak situations.



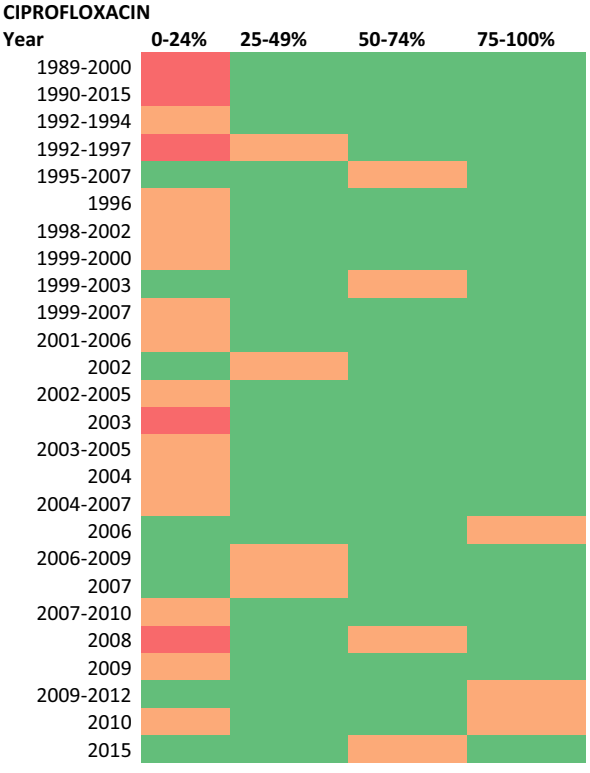
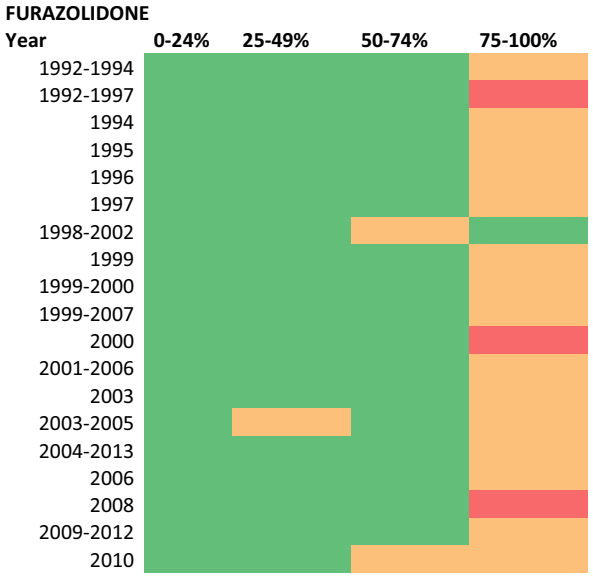


Fig. 3 (*continued*)

criminate prescription of antibiotics happens because of the lack of a proper understanding of the pathophysiology of diarrhea; lack of faith in ORS as a therapeutic product; patients' demand for "active" interventions by doctors (medication, injections, prescriptions for antibiotics, etc.); lack of time for dietary counseling



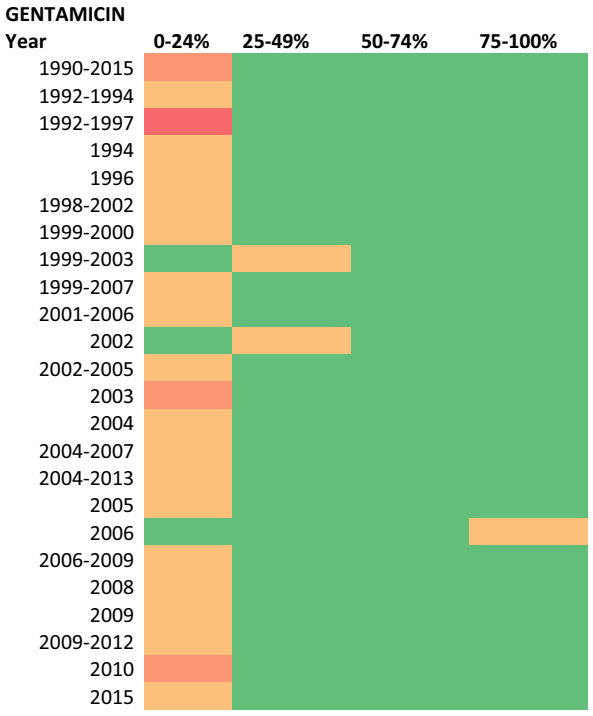


Fig. 3 (*continued*)

of patients and family members; financial incentives to prescribe medications like antibiotics; and a lack of control on OTC availability of antibiotics [52,53,68]. The inaccurate prescription habits of non-formal caregivers further intensifies the antibiotic selection pressure in endemic, vulnerable and underserved areas [54,55].

Against this background, the development of efficacious oral cholera vaccines (OCVs) presents an interesting policy alternative [42,43]. A modeling study from Bangladesh revealed that cholera transmission could be controlled in endemic areas with 50% OCV coverage [58]. An especially interesting facet has been the exploration of the effectiveness of single-dose based approaches. Although there have been no studies to evaluate this approach in

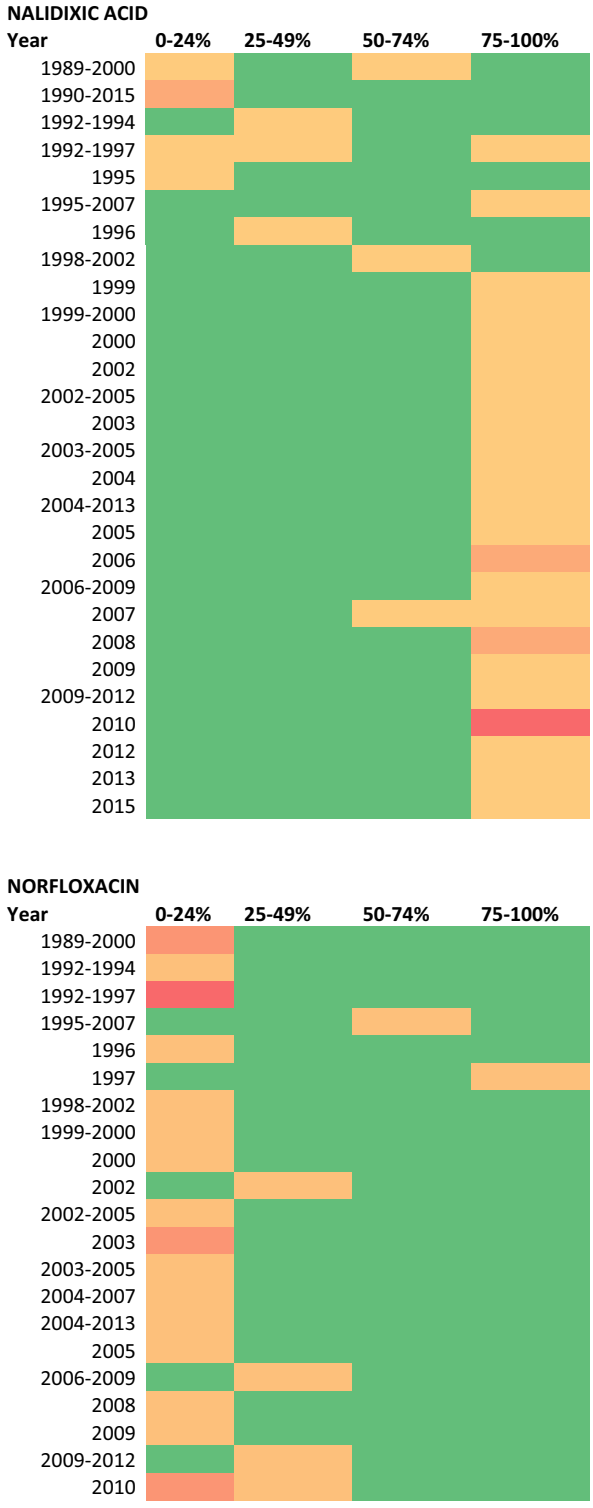


Fig. 3 (*continued*)

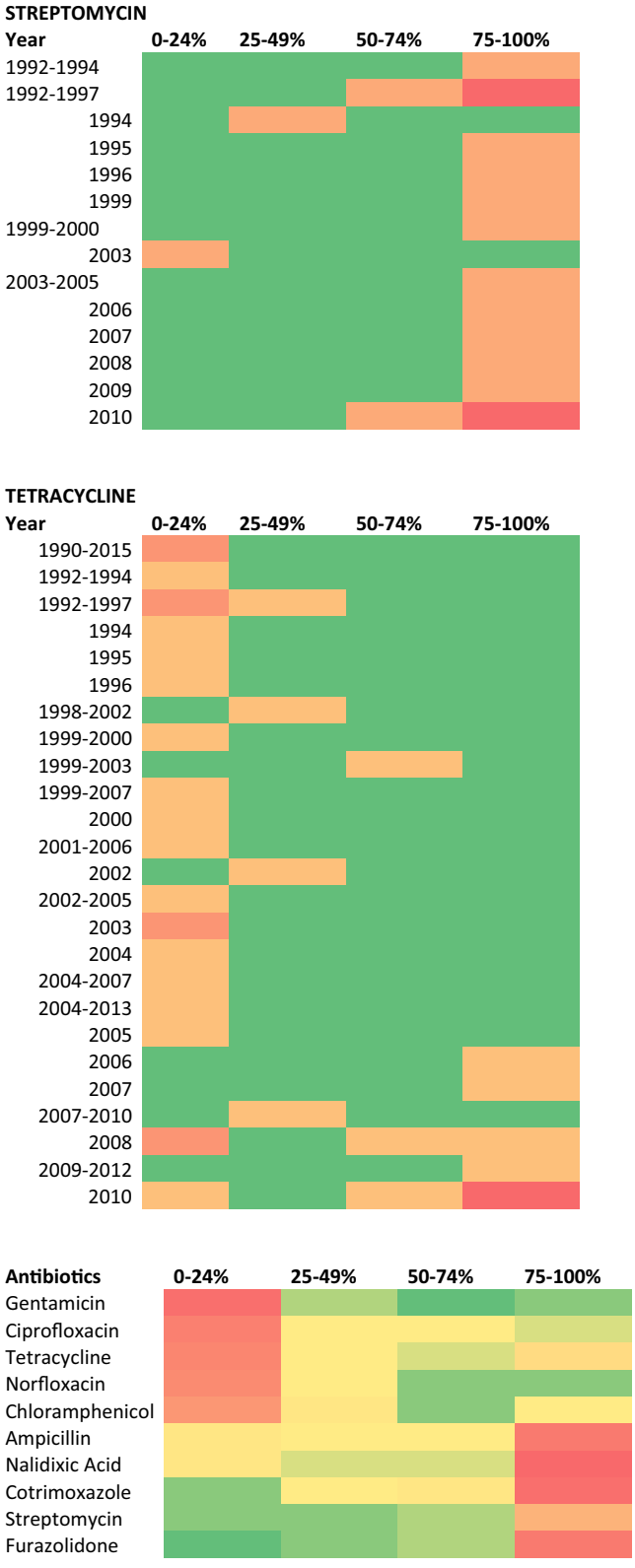


Fig. 3 (*continued*)

India, their effectiveness has been established in some other countries [59–63].

A recent review highlighted the fact that the institution of vaccination programs could potentially impact the emergence of ABR through multiple avenues: vaccination can be active against resistant strains, counteracting selection for resistance in vaccinated individuals; reducing colonization and preventing the exchange of genetic elements responsible for transmission of ABR; and reducing transmission of infection, leading to lowering of antibiotic consumption and selection pressure. Furthermore, due to the overall reduction of antibiotic consumption, there is likely to be lower levels of selection for resistance in "innocent bystanders" like commensal flora [64,67]. In an analogous example, the strategy of vaccinating against Pneumococcus and *Haemophilus influen-*

zae has led to the additional effect of mitigating the ABR threat in respiratory bacterial pathogens [56,57]. This has prompted some experts to advocate for investing in vaccines as a potential intervention to reduce the burden of ABR in other pathogenic bacteria as well [68,59,65,66].

An analysis of the SUTs from where a majority of the publications have stemmed reveals that the data is extremely skewed. States with medical institutes that have a special interest in the study of enteric infections figure in a disproportionately large number of publications. This points to a deeper issue—the lack of capacity in surveillance and research—that needs to be bolstered. This is also indicative of the fact that publications are driven by institutional mandates and not public health needs, which is exemplified by the divergence of the states which figure on the publications list versus the states which have reported higher number of outbreaks. Further, it needs to be noted that a large number of outbreaks of acute watery diarrhea has not been formally diagnosed or attributed to a pathogen. Further, states with improved IDSP infrastructure and diagnostic facilities are more likely to report a higher number of cholera outbreaks, while at the same time, reaching a final diagnosis successfully for a greater proportion of he acute watery diarrhea outbreaks, thus introducing a reporting bias in the given estimates.

Finally, another issue that needs to be addressed is the accuracy of the reported data. Cholera is known to be massively underreported internationally, with previous studies from India reckoning that there is an under-reporting of cases by a factor of at least six [5]. Recent modeling estimates reveal that the highest number of people susceptible to cholera reside in India, followed by Nigeria, China, Ethiopia and Bangladesh [1]. There remains a dissonance between the at risk population, and the reported burden, indicating possibilities of under-reporting. However, it needs to be noted that the model which arrived at these estimates used the population based cholera incidence rates obtained from the Diseases of the Most Impoverished (DOMI) cholera surveillance in Kolkata, which dates back to 2005, and may not represent the current incidence rates [69]. Virtually no cases have been reported from the states along the Gangetic plains of northern India, pointing at a divergence from the expected epidemiological trend, since these are areas where more cases are expected to accrue. The heat map (Fig. 2) highlights these findings, but also indicates to the underlying lacunae in reporting rates.

As the admissions data from the IDH, Kolkata illustrates, underreporting could be a bigger problem, since, in eight out of the last nine years, the crude estimate of the number of cases admitted to the IDH far outweighs the national estimates reported through the NHP. This calls for a more robust, transparent, and accurate surveillance system [70]. Given the case definitions and outbreak response triggers currently in use, it is also likely that the cholera burden for pediatric age groups is also under-estimated. This further strengthens the case for developing a sensitive surveillance mechanism to identify the disease burden.

In the absence of a National Cholera Control Plan for India, this review thus finds that understanding the true burden, and hotspots of occurrence of cholera are gaps which need to be addressed before comprehensive cholera control packages, as advocated by the Global Task Force on Cholera Control, can be deployed at the national level. Since India not only contributes the largest number of at-risk population, but also, perhaps, bears a major proportion of the true burden of cholera, without addressing these issues, the aspirations to end cholera by 2030 are likely to remain unmet [71].

The current review indicates potential policy responses that can be mounted to mitigate the emerging threat of ABR outbreaks of cholera in India. However, the findings are limited by the fact that there is a clear publication bias when it comes to reporting or publishing outbreak investigations. Although it is possible that even with the under-reporting of cases, the trends would remain unaffected, any under-reporting dwarfs the magnitude of the problem. This further intensifies the challenge of creating an adequate and appropriate investment strategy to combat the issue, since the real problem is larger than what is reported. Further, the different studies cover different time periods, and utilize different methods to estimate AMR burden. We have endeavored to incorporate all studies identified in the screening procedure resulting in some overlap. Since we have not been able to resolve this overlap without loss of evidence or exclusion of identified studies, we have chosen to present the data in a qualitative heat map rather than use quantitative statistical measures for assessing time trends. Despite these limitations, the current scoping review throws up findings which are enough to raise concerns about the emerging threat of ABR in cholera outbreaks, and points out gaps in the ongoing surveillance system that need to be addressed.

5. Conclusions

Conventionally, antibiotics in combination with rehydration therapy have been found to synergistically reduce the morbidity and severity of illness in cholera patients. However, with the threat of drug-resistant *V. cholerae* looming large, it seems to be more prudent to consider vaccines as an alternative to reduce caseloads as well as antibiotic selection pressure. There are no trials that have compared the two approaches and their long-term impact on the drug resistance profiles in *V. cholerae* isolated from cholera patients, either in an outbreak situation or in an endemic area. We need to better understand the additional benefits that may accrue from a more conservative use of antibiotics with wider coverage with OCVs. Modeled estimates posit that even modest immunization coverages can lead to an appreciable reduction in the caseload. Now is the time to nip the emergent issue of drug-resistant cholera in the bud.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Structured search strategies

PubMed

((“Cholera”[Mesh] OR “Cholera Vaccines”[Mesh]) AND (“Drug Resistance, Microbial”[Mesh] OR “Drug Resistance, Bacterial” [Mesh]) AND (“Disease Outbreaks”[Mesh] OR “Epidemiology”[Mesh] OR “Epidemics”[Mesh] OR “Pandemics”[Mesh])) AND “India”

Web of Science

TS = (cholera AND outbreaks AND antibiotic resistance AND india)

MedInd/IndMed

cholera AND outbreaks AND resistance

Appendix B. Inclusion and exclusion criteria

Inclusion Criteria

1. Study analyzing part or all samples sourced from an outbreak
2. Study site is in India
3. Studies based on clinical surveillance
4. Studies where *Vibrio cholerae* is one of several pathogens studied in an outbreak setting

Exclusion Criteria

1. Study relates to samples not originating from an outbreak.
2. Study not related to India
3. Study relating to describing the general epidemiology of ABR or cholera outbreaks and not discussing ABR in cholera outbreaks
4. Outbreak reports which discuss the field epidemiology or outbreak investigation without assessing the ABR profile of isolates
5. Studies which solely focus on the characterization of the genotype of isolates without clarifying their impact on ABR profiles of the pathogen
6. Studies based on environmental surveillance data or solely studying isolates from environmental samples or sources without relating the same to clinical cases or isolates or outbreaks.
7. Studies that focus solely on pathogens other than *Vibrio cholerae;* Other vibrios are also excluded.
8. Studies about environmental *Vibrio spp*.

Appendix C. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.12.003.

References

[1] Ali M, Nelson AR, Lopez AL, Sack DA, Ope M. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis 2015;9:e0003832. https://doi.org/10.1371/journal.pntd.0003832.

[2] Murugaiah C. The burden of cholera. Crit Rev Microbiol 2011;37:337–48. https://doi.org/10.3109/1040841X.2011.603288.

[3] Kelly-Hope LA. Conflict and emerging infectious diseases. Emerg Infect Dis 2008;14:1004–5. https://doi.org/10.3201/eid1406.080027. author reply 1005.

[4] Soto SM. Human migration and infectious diseases. Clin Microbiol Infect 2009;15:26–8. https://doi.org/10.1111/j.1469-0691.2008.02694.x.

[5] Kanungo S, Sah BK, Lopez AL, Sung JS, Paisley AM, Sur D, et al. Cholera in India: an analysis of reports, 1997–2006. Bull World Health Organ 2010. https://doi.org/10.2471/BLT.09.073460.

[6] Zuckerman Jane N, Rombo Lars, Fisch Alain. The true burden and risk of cholera: implications for prevention and control. Lancet Infect Dis 2007;7(8):521–30. https://doi.org/10.1016/S1473-3099(07)70138-X.

[7] Lindenbaum J, Greenough WB, Islam MR. Antibiotic therapy of cholera. Bull World Heal Organ 1967;36:871–83.

[8] Lindenbaum J, Greenough WB, Islam MR. Antibiotic Therapy of Cholera in Children,* In a controlled trial of the effects of oral antibiotics in treating cholera in children. Bull World Heal Organ 1967;37:529–38.

[9] Rijal N, Acharya J, Adhikari S, Upadhaya BP, Shakya G, Kansakar P, et al. Changing epidemiology and antimicrobial resistance in *Vibrio cholerae*: AMR surveillance findings (2006–2016) from Nepal. BMC Infect Dis 2019;19. https://doi.org/10.1186/s12879-019-4432-2.

[10] Das B, Verma J, Kumar P, Ghosh A, Ramamurthy T. Antibiotic resistance in *Vibrio cholerae*: understanding the ecology of resistance genes and mechanisms. Vaccine 2020;38(S1):A83–92.

[11] Panda S, Chatterjee P, Deb A, Kanungo S, Dutta S. Preventing cholera in India: synthesizing evidences through a systematic review for policy discussion on the use of oral cholera vaccine. Vaccine 2020;38(S1):A148–56.

[12] United Nations News Service Section. UN announces interagency group to coordinate global fight against antimicrobial resistance. UN News Cent; 2017:3. http://www.un.org/apps/news/story.asp?NewsID=56365#.WNJGWRJ95lB [accessed March 22, 2017].

[13] World Health Organization. United Nations high-level meeting on antimicrobial resistance. Antimicrob Resist 2016:3. http://www.who.int/antimicrobial-resistance/events/UNGA-meeting-amr-sept2016/en/ [accessed September 30, 2016].

[14] National Centre for Disease Control. Integrated Disease Surveillance Programme. Dir Gen Heal Serv Minist Heal Fam Welfare, Gov India; 2017:1. http://idsp.nic.in/index.php [accessed May 14, 2017].

[15] National Centre for Disease Control DG of HS. Outbreaks:: Integrated Disease Surveillance Programme(IDSP); n.d.

[16] Integrated Disease Surveillance Project. Training manual for state and district surveillance officers: Module 5 – Case definitions of diseases and syndromes under surveillance. New Delhi; 2008.

[17] Ml Daudt H, Van Mossel C, Scott SJ. Enhancing the scoping study methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. BMC Med Res Method 2013;13:1. https://doi.org/10.1186/1471-2288-13-48.

[18] Arksey Hilary, O'Malley Lisa. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19–32. https://doi.org/10.1080/1364557032000119616.

[19] Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation Sci 2010. https://doi.org/10.1186/1748-5908-5-69.

[20] Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Method 2018;18:143. https://doi.org/10.1186/s12874-018-0611-x.

[21] Nair GB, Ramamurthy T, Bhattacharya MK, Krishnan T, Ganguly S, Saha DR, et al. Emerging trends in the etiology of enteric pathogens as evidenced from an active surveillance of hospitalized diarrhoeal patients in Kolkata, India. Gut Pathog 2010;2:4. https://doi.org/10.1186/1757-4749-2-4.

[22] Central Bureau of Health Intelligence. National health profile 2005 onwards. Natl Heal Profile; n.d. http://cbhidghs.nic.in/index1.asp?linkid=267 [accessed November 22, 2017].

[23] Census of India Website : Office of the registrar general & census commissioner, India; n.d. http://censusindia.gov.in/ [accessed July 22, 2015].

[24] Guerrant RL, Carneiro-Filho BA, Dillingham RA. Cholera, diarrhea, and oral rehydration therapy: triumph and indictment. Clin Infect Dis 2003;37:398–405. https://doi.org/10.1086/376619.

[25] Musekiwa A, Volmink J. Oral rehydration salt solution for treating cholera: ? 270 mOsm/L solutions vs ? 310 mOsm/L solutions. In: Musekiwa A, editor. Cochrane database syst rev. Chichester, UK: John Wiley & Sons, Ltd; 2011. https://doi.org/10.1002/14651858.CD003754.pub3.

[26] Leibovici-Weissman Y, Neuberger A, Bitterman R, Sinclair D, Salam MA, Paul M. Antimicrobial drugs for treating cholera. In: Leibovici-Weissman Y, editor. Cochrane database syst rev. Chichester, UK: John Wiley & Sons, Ltd; 2014. https://doi.org/10.1002/14651858.CD008625.pub2.

[27] Pan-American Health Organization, World Health Organization. PAHO/WHO expert consultation on pharmacological measures for prevention of cholera introduction in non endemic areas; n.d.

[28] Nelson EJ, Nelson DS, Salam MA, Sack DA. Antibiotics for both moderate and severe cholera. New England J Med 2011;364:5–7. https://doi.org/10.1056/NEJMp1013771.

[29] Saha D, Karim MM, Khan WA, Ahmed S, Salam MA, Bennish ML. Single-dose azithromycin for the treatment of cholera in adults. N Engl J Med 2006;354:2452–62. https://doi.org/10.1056/NEJMoa054493.

[30] Rahaman MM, Majid MA, Alam AKMJ, Islam MR. Effects of doxycycline in actively purging cholera patients: a double-blind clinical trial. Antimicrob Agents Chemother 1976;10:610–2.

[31] Doron S, Davidson LE. Antimicrobial stewardship. Mayo Clin Proc 2011;86:1113–23. https://doi.org/10.4065/mcp.2011.0358.

[32] Lee C-R, Cho IH, Jeong BC, Lee SH. Strategies to minimize antibiotic resistance. Int J Environ Res Public Health 2013;10:4274–305. https://doi.org/10.3390/ijerph10094274.

[33] van Loon HJ, Vriens MR, Fluit AC, Troelstra A, van der Werken C, Verhoef J, et al. Antibiotic rotation and development of gram-negative antibiotic resistance. Am J Respir Crit Care Med 2005;171:480–7. https://doi.org/10.1164/rccm.200401-070OC.

[34] Warren DK, Hill HA, Merz LR, Kollef MH, Hayden MK, Fraser VJ, et al. Cycling empirical antimicrobial agents to prevent emergence of antimicrobial-resistant Gram-negative bacteria among intensive care unit patients. Crit Care Med 2004;32:2450–6.

[35] Bergstrom CT, Lo M, Lipsitch M. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. Proc Natl Acad Sci 2004;101:13285–90. https://doi.org/10.1073/pnas.0402298101.

[36] Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, et al. Infectious diseases society of america and the society for healthcare epidemiology of america guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159–77. https://doi.org/10.1086/510393.

[37] Kuwahara S. Antibiotic resistance of *vibrio cholerae*: special considerations of R-plasmids. Zhonghua Min Guo Wei Sheng Wu Xue Za Zhi 1978;11:99–103.

[38] Manjusha S, Sarita G. Plasmid associated antibiotic resistance in Vibrios isolated from coastal waters of Kerala. Int Food Res J 2011;18:1171–81.

[39] Kitaoka M, Miyata ST, Unterweger D, Pukatzki S. Antibiotic resistance mechanisms of *Vibrio cholerae*. J Med Microbiol 2011;60:397–407. https://doi.org/10.1099/jmm.0.023051-0.

[40] Letchumanan V, Yin W-F, Lee L-H, Chan K-G. Prevalence and antimicrobial susceptibility of Vibrio parahaemolyticus isolated from retail shrimps in Malaysia. Front Microbiol 2015;6:33. https://doi.org/10.3389/fmicb.2015.00033.

[41] Letchumanan V, Pusparajah P, Tan LT-H, Yin W-F, Lee L-H, Chan K-G. Occurrence and antibiotic resistance of vibrio parahaemolyticus from shellfish in Selangor, Malaysia. Front Microbiol 2015;6:1417. https://doi.org/10.3389/fmicb.2015.01417.
[42] Hayashi F, Harada K, Mitsuhashi S, Inoue M. Conjugation of drug-resistance plasmids from vibrio anguillarum to vibrio parahaemolyticus. Microbiol Immunol 1982;26:479–85.
[43] Khuntia HK, Samal SK, Kar SK, Pal BB. An ogawa cholera outbreak 6 months after the inaba cholera outbreaks in India, 2006. J Microbiol Immunol Infect 2010;43:133–7. https://doi.org/10.1016/S1684-1182(10)60021-7.
[44] Dutta D, Chowdhury G, Pazhani GP, Guin S, Dutta S, Ghosh S, et al. *Vibrio cholerae* non-O1, non-O139 serogroups and cholera-like diarrhea, Kolkata, India. Emerg Infect Dis 2013;19:464–7. https://doi.org/10.3201/eid1903.121156.
[45] Garg P, Chakraborty S, Basu I, Datta S, Rajendran K, Bhattacharya T, et al. Expanding multiple antibiotic resistance among clinical strains of *Vibrio cholerae* isolated from 1992–7 in Calcutta, India. Epidemiol Infect 2000;124:393–9.
[46] Global Antibiotic Resistance Partnership (GARP) – India Working Group, Ganguly NK, Arora NK, Chandy SJ, Fairoze MN, Gill JPS, et al. Rationalizing antibiotic use to limit antibiotic resistance in India. Indian J Med Res 2011;134:281–94.
[47] Kanungo S, Mahapatra T, Bhaduri B, Mahapatra S, Chakraborty ND, Manna B, et al. Diarrhoea-related knowledge and practice of physicians in urban slums of Kolkata, India. Epidemiol Infect 2014;142:314–26. https://doi.org/10.1017/S0950268813001076.
[48] Chauhan AS, George MS, Chatterjee P, Lindahl J, Grace D, Kakkar M. The social biography of antibiotic use in smallholder dairy farms in India. Antimicrob Resist Infect Control 2018;7:60. https://doi.org/10.1186/s13756-018-0354-9.
[49] Singh J, Bora D, Sachdeva V, Sharma RS, Verghese T. Prescribing pattern by doctors for acute diarrhoea in children in Delhi, India. J Diarrhoeal Dis Res 1995;13:229–31.
[50] Reis EC, Goepp JG, Katz S, Santosham M. Barriers to use of oral rehydration therapy. Pediatrics 1994;93.
[51] Gore SM, Fontaine O, Pierce NF. Impact of rice based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials. BMJ 1992;304.
[52] Vashishtha VM. Oral Rehydration Salts solution use in India: why are doctors still not convinced?. BMJ 2001;323:81. https://doi.org/10.1136/bmj.323.7304.81.
[53] Kakkar M, Walia K, Vong S, Chatterjee P, Sharma A. Antibiotic resistance and its containment in India. Br Med J 2017;358:j2687. https://doi.org/10.1136/BMJ.J2687.
[54] Kotwani A, Wattal C, Katewa S, Joshic PC, Holloway K. Factors influencing primary care physicians to prescribe antibiotics in Delhi India. Fam Pract 2010. https://doi.org/10.1093/fampra/cmq059.
[55] Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi. India. BMC Infect Dis 2011;11:99. https://doi.org/10.1186/1471-2334-11-99.
[56] Sur D, Kanungo S, Sah B, Manna B, Ali M, Paisley AM, et al. Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: results from 3 years of Follow-Up of a randomized, controlled trial. PLoS Negl Trop Dis 2011;5:1–6. https://doi.org/10.1371/journal.pntd.0001289.
[57] Bhattacharya SK, Sur D, Ali M, Kanungo S, You YA, Manna B, et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. Lancet Infect Dis 2013;13:1050–6. https://doi.org/10.1016/S1473-3099(13)70273-1.
[58] Longini IM, Nizam A, Ali M, Yunus M, Shenvi N, Clemens JD. Controlling endemic cholera with oral vaccines. PLoS Med 2007;4:1776–83. https://doi.org/10.1371/journal.pmed.0040336.
[59] Qadri F, Wierzba TF, Ali M, Chowdhury F, Khan AIA, Saha A, et al. Efficacy of a single-dose, inactivated oral cholera vaccine in Bangladesh. N Engl J Med 2016;374:1723–32. https://doi.org/10.1056/NEJMoa1510330.
[60] Azman AS, Parker LA, Rumunu J, Tadesse F, Grandesso F, Deng LL, et al. Effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. Lancet Glob Heal 2016;4:e856–63. https://doi.org/10.1016/S2214-109X(16)30211-X.
[61] Parker LA, Rumunu J, Jamet C, Kenyi Y, Lino RL, Wamala JF, et al. Adapting to the global shortage of cholera vaccines: targeted single dose cholera vaccine in response to an outbreak in South Sudan. Lancet Infect Dis 2017;17:e123–7. https://doi.org/10.1016/S1473-3099(16)30472-8.
[62] Reyburn R, Deen JL, Grais RF, Bhattacharya SK, Sur D, Lopez AL, et al. The case for reactive mass oral cholera vaccinations. PLoS Negl Trop Dis 2011;5:e952. https://doi.org/10.1371/journal.pntd.0000952.
[63] Azman AS, Luquero FJ. Single-dose oral cholera vaccine in Bangladesh. N Engl J Med 2016;375:. https://doi.org/10.1056/NEJMc1607285e12.
[64] Lipsitch M, Siber GR. How can vaccines contribute to solving the antimicrobial resistance problem?. MBio 2016;7:e00428–e516. https://doi.org/10.1128/mBio. 00428-16.
[65] von Gottberg A, de Gouveia L, Tempia S, Quan V, Meiring S, von Mollendorf C, et al. Effects of vaccination on invasive pneumococcal disease in South Africa. N Engl J Med 2014;371:1889–99. https://doi.org/10.1056/NEJMoa1401914.
[66] Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. N Engl J Med 2006;354:1455–63. https://doi.org/10.1056/NEJMoa051642.
[67] Ginsburg AS, Klugman KP. Vaccination to reduce antimicrobial resistance. Lancet Glob Heal 2017;5:e1176–7. https://doi.org/10.1016/S2214-109X(17)30364-9.
[68] O'Neill J. Vaccines and alternative approaches: reducing our dependence on antimicrobials. The review on antimicrobial resistance. London; 2016.
[69] Sur D, Deen JL, Manna B, Niyogi SK, Deb AK, Kanungo S, et al. The burden of cholera in the slums of Kolkata, India: data from a prospective, community based study. Arch Dis Child 2005;90:1175–81. https://doi.org/10.1136/adc.2004.071316.
[70] Tacconelli E, Sifakis F, Harbarth S, Schrijver R, van Mourik M, Voss A, et al. Surveillance for control of antimicrobial resistance. Lancet Infect Dis 2017. https://doi.org/10.1016/S1473-3099(17)30485-1.
[71] Global Task Force on Cholera Control. Ending cholera: a global roadmap to 2030. Geneva: World Health Organization; 2017.