# Delineating the impact of COVID-19 on antimicrobial resistance: an Indian perspective

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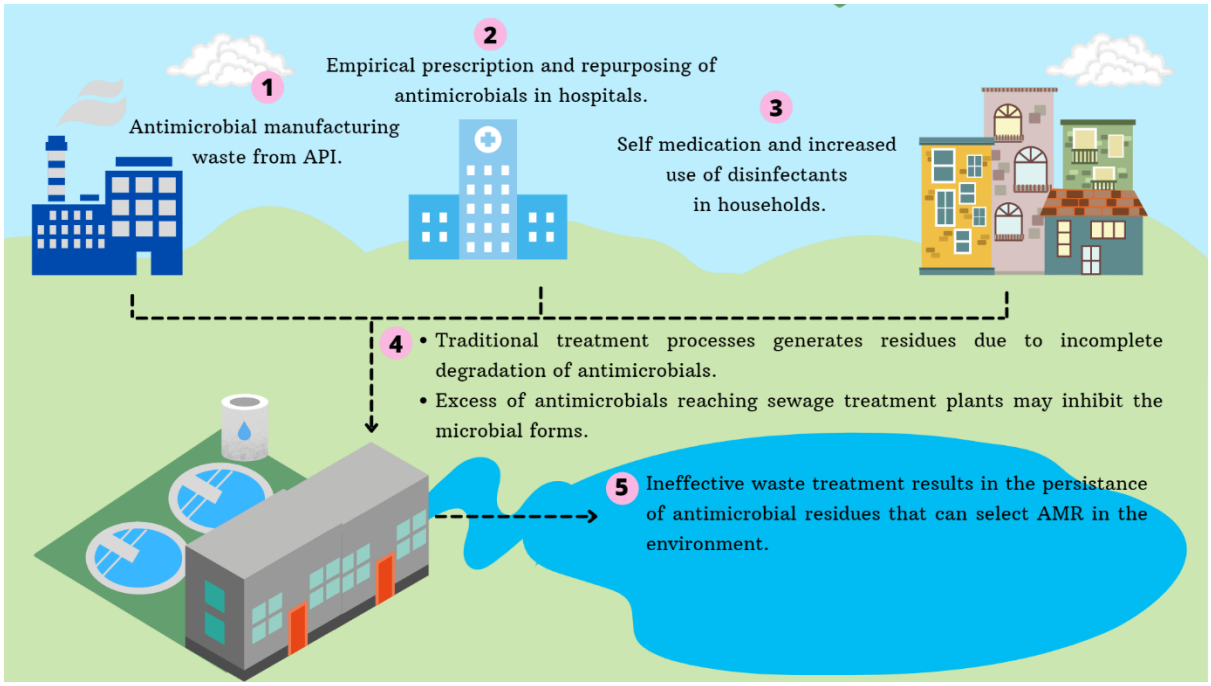
**Abstract**

The COVID-19 pandemic has shattered millions of lives globally and continues to be a challenge to public health due to the emergence of variants of concern. Fear of secondary infections following COVID-19 has led to an escalation in antimicrobial use during the pandemic, while some antimicrobials have been repurposed as treatments for SARS-CoV-2, further driving antimicrobial resistance. India is one of the largest producers and consumers of antimicrobials globally, hence the task of curbing antimicrobial resistance is a huge challenge. Practices like empirical antimicrobial prescription and repurposing of drugs in clinical settings, self-medication and excessive use of antimicrobial hygiene products may have deteriorated the prevalence of antimicrobial resistance in India. However, the expanded production of antimicrobials and disinfectants during the pandemic in response to increased demand may have had an even greater impact on the threat of antimicrobial resistance through major impacts on the environment. The review provides an outline of the impact COVID-19 can have on antimicrobial resistance in clinical settings and the possible outcomes of the same on environment. This review calls for the up gradation of existing antimicrobial policies and emphasizes the need for research studies to understand the impact of the pandemic on antimicrobial resistance in India.

**Keywords:** COVID-19, AMR, empirical consumption, antimicrobial residues, antimicrobial manufacturing waste.

## Graphical Abstract




## 1. Introduction

Antimicrobial resistance (AMR) and COVID-19 are the two looming pandemics the world is currently challenged with and poses a significant threat to public health in a global scale. Infections resulting from antimicrobial resistant bacteria are expected to claim 10 million lives globally, per year by 2050 (O'Neill 2014). COVID-19 and AMR are interacting health emergencies which can have mutual impact due to the obligation of using existing antimicrobials for the treatment of COVID-19 patients since a specific treatment is absent for the disease (Nieuwlaat et al. 2012). If the current trend of AMR goes unchecked, it would result in the shortage of available therapeutics in future and may even mark an end to the conventional drug discovery pipeline (Kaul et al. 2019). By the year 2050, infections caused by antimicrobial resistant bacteria is projected to cause 2 million deaths in India. Considering India's huge population, the threat of AMR extends to other nations as well. International travel results in the dissemination of antimicrobial resistant bacteria to different nations and continents, extending the threat of AMR in India to a global scale (Frost et al. 2019a). New Delhi metallo-

β-lactamase (NDM-1) producing bacteria which are resistant to carbapenems emerged in India and have rapidly disseminated to other nations causing a havoc in health care, worldwide (Nordmann et al. 2011).

India observed a sudden spike of COVID-19 cases from Mid-March of 2021 which rose steeply to more than 300,000 COVID-19 cases consecutively for 10 days (Samarasekera 2021). The crisis worsened with shortages of hospital beds, oxygen supplies, overwhelmed hospitals and exhausted health staff (The Lancet 2021). Prior to the pandemic, India was already facing major challenges in antimicrobial resistance, with prevalence of highly resistant Gram-negative bacteria orders of magnitude higher than many high-income countries (Gandra et al. 2019; Gandra et al. 2018; Walia 2019). Amongst the hospitalized COVID-19 patients in India, a predominance of Gram-negative bacteria resistant to higher generation of antimicrobials was observed (Vijay et al. 2021). It is indefinite to what extent COVID-19 will raise AMR and impede the efforts taken to curb its spread, however, there are several determinants of the ongoing pandemic which could possibly fuel the prevailing AMR threat in India.

With attention focused on tackling COVID-19, efforts to curb antimicrobial resistance have largely been put on hold in community and healthcare settings. The current pandemic will amplify the threat of antimicrobial resistance in India: practices that were already prevalent such as over-the-counter use of antimicrobial drugs and empirical prescription of broad-spectrum antibiotics will have increased with any increase in febrile respiratory illness, while COVID-19 has more specifically led to increased use of antimicrobials through re-purposing and management of secondary infections. While the negative impact of the pandemic on antimicrobial stewardship and excessive consumption has been highlighted around the globe (Rawson et al. 2020; Ghosh et al. 2021), India as a world leader in production faces a greater threat; environmental contamination with antimicrobial waste resulting from a pandemic-altered manufacturing landscape. Excessive use of hygienic products, practice of self-

93 medication, and expanded production of antimicrobials associated with COVID-19, could
94 amplify the concentration of these compounds in the environment. This is further challenged
95 by weak waste management infrastructure and poor sanitation observed in developing
96 communities like India. Antimicrobial residues accumulating in the environment can induce
97 the development of resistance in bacteria to antibiotics.

98 In this review we provide an overview of the AMR situation in clinical settings of India
99 during the pandemic and explain in detail how the consumption and production of
100 antimicrobials exacerbated by COVID-19 can overwhelm the crisis of AMR in India.

101 **2. AMR in the backdrop of COVID-19: a clinical overview**

102 **2.1 Co-infections and secondary infections in healthcare during the COVID-19 pandemic**

103 Viral respiratory infections have been closely linked to increased chances of bacterial co-
104 infections (Rawlinson et al. 2003; Beadling and Slifka 2004). Although secondary infections
105 caused by bacteria and fungal pathogens were reported frequently in severe cases of COVID-
106 19 (Chen et al. 2020), this finding is not universal (Hughes et al. 2020; Rawson et al. 2020;
107 Garcia-Vidal et al. 2021). Preliminary reports from China suggested 50% patients who died
108 of COVID-19 were affected by secondary bacterial infections (Zhou et al. 2020). Concern
109 about bacterial co-infections in COVID-19 will have been augmented by reports of co-
110 infections in MERS-CoV intensive care patients (Memish et al. 2020). It is apparent that co-
111 infection may be more related to hospital-acquired and intensive care-associated secondary
112 infection than COVID-19 alone and may not be the leading cause of death in contrast to co-
113 infection in influenza (Morens et al. 2008).

114 Several mechanisms could underlie a co-infection risk in COVID-19 patients: During viral
115 infections, viruses can obstruct the configuration required for mucociliary clearance which
116 could enhance the adherence of bacteria to mucins. In addition to this the dense mucus will

prevent the entry of immune cells and antimicrobial substances (Wilson et al. 1996). The inflammation stimulated by viral infection activates epithelial cells to alter the expression pattern of surface receptors which can also favor attachment of bacteria (Morris et al. 2007). SARS-CoV-2 may facilitate colonization of bacterial pathogens to host tissues in a similar manner and result in systemic dissemination of the virus and bacteria (Bengoechea and Bamford 2020). Health conditions such as severe lymphopenia and respiratory failure observed in COVID-19 patients can also increase the chance of acquiring secondary infections (Ripa et al. 2020).

There are several healthcare practises that have augmented the risk of secondary infection. Mechanical ventilation, consumption of steroidal drugs and other comorbidities can act as a predisposing factor for secondary infections in critically ill COVID-19 patients (Chowdhary et al. 2020). Susceptibility to unusual infections in the intensive care unit has been linked in part to the practise of "proning" patients (placing patients prone, face down, to improve ventilations), leading to greater risk of skin maceration and contact with fomites. Excessive use of personal protective equipment coupled with reduced attention to contact precautions when caring for patients has also been highlighted as a risk for nosocomial infection. Increasing use of steroids in COVID-19 and biological therapies that impair cytokine responses may further augment the risk of fungal and bacterial co-infections. This may underlie the reasons why COVID-19 patients are reportedly vulnerable to opportunistic fungal infections such as pulmonary aspergillosis, mucormycosis, cryptococcosis, and pneumocystis pneumonia which have a high mortality rate (Song et al. 2020; Salehi et al. 2020).

In India, a high rate of secondary infections was observed in hospitalized COVID-19 patients of both intensive care unit (ICU) and non-ICU wards during the first wave of the pandemic (Vijay et al. 2021; Khurana et al. 2021). A study by Vijay et al. (2021) found that 3.6% of COVID-19 patients developed secondary infections following hospitalization and the mortality

142 rate amongst these patients was estimated to be 56.7%. The B.1.617 variant resulted in a
143 massive surge of COVID-19 cases in India during the second wave (Vaidyanathan 2021).
144 Unexpectedly, India witnessed an increasing trend of mucormycosis in COVID-19 recovered
145 patients during the second wave of the pandemic (Gade et al. 2021). Mucormycosis, an
146 infection with high mortality even when treated, occurred either during or subsequent SARS-
147 CoV-2 infection. Unmanageable diabetes mellitus and immune suppression linked to intake of
148 steroids in COVID-19 patients are known to escalate the risk of fungal infections (Sen et al.
149 2021). Among the 101 cases of COVID-19-associated mucormycosis reported globally, 82
150 cases are from India (Singh, A et al. 2021). Cases of fatal mucormycosis were reported amongst
151 COVID-19 patients of India where the condition of patient deteriorated even after
152 administration of amphotericin B (Nehara et al. 2021). With a lack of population-based studies,
153 the exact incidence of mucormycosis in India is not yet clear (Prakash et al. 2021).

154 The evidence base regarding secondary and co-infection in COVID-19 is hampered in two
155 ways. Firstly, there is little contextual epidemiological information that allows COVID-19 to
156 be compared with other, similar respiratory viral infections, except in large intensive care
157 databases. As such, although secondary infections are documented in patients diagnosed with
158 COVID-19, whether these are any more frequently observed than in other patients ventilated
159 for pneumonia is unclear. Apart from highly virulent infections such as from species of
160 Mucorales, it is also difficult to comment whether hospital acquired infections are connected
161 to increased COVID-19 severity and mortality. Secondly, invasive diagnostic methods are not
162 routinely undertaken in COVID-19 patients, in part related to infection control considerations,
163 leading to an increase in empiric prescribing.

164 **2.2. Antimicrobial resistance in healthcare during the COVID-19 pandemic**

COVID-19 patients in ICU are subject to antimicrobial therapy more often and the decision to treat is based on laboratory markers of inflammation and severity of the disease (Mustafa et al. 2021). Indeed, COVID-19 patients have been subject to antibiotic therapy even in the absence of underlying secondary infections (Moretto et al. 2021). A meta-analysis carried out in the initial six months of the pandemic observed that three-quarters of COVID-19 patients received antibiotic therapy globally (Langford et al. 2021). A recent review by Chedid et al. (2021) reveals that the mean antibiotic use for COVID-19 management is 74% where only 17. 6% patients are tested positive for secondary infections. This underlines the extent to which un-targeted and empiric use of antimicrobials has increased in the wake of the pandemic.

The intersection between AMR and COVID-19 was highlighted by many researchers at the beginning of pandemic (Bengoechea and Bamford 2020; Cantón et al. 2020; Murray 2020). AMR in hospitalized COVID-19 patients have been reported from many countries. A study by Kampmeier et al. (2020) reported *vanB* clones of *Enterococcus faecium* in COVID-19 subjects from intensive care wards in Germany. New Delhi metallo-beta-lactamase (NDM) producing *Enterobacter cloacae* were isolated from critically-ill COVID-19 patients in New York City, which resulted in the death of four out of five patients admitted at the medical center (Nori et al. 2020). NDM-beta-lactamase-producing carbapenem-resistant Enterobacterales isolated from COVID-19 patients of a teaching hospital from Italy worsened the outcome of patients significantly by prolonging length of stay (Porretta et al. 2020). A higher incidence of invasive antimicrobial resistant fungal infections has also been documented in COVID-19 patients: Posteraro et al. (2020) reported a fatal COVID-19 case in Italy where the patient succumbed to death due to co-infection with resistant bacteria and pan-echinocandin-resistant *Candida glabrata*. Several studies have also pointed out the failure of antimicrobial therapy in *Aspergillus* infections (Koehler et al. 2020; Alanio et al. 2020; Rutsaert et al. 2020; Blaize et al. 2020; Arastehfar et al. 2020). Evidence comparing prevalence of AMR in specific bacterial

and fungal species during the pandemic and pre-pandemic will no doubt emerge in countries where AMR is subject to routine mandatory surveillance.

A tertiary hospital in India reported an overall antimicrobial resistance up to 84% in COVID-19 patients with secondary infections between April 3 and July 11, 2020 (Khuranna et al. 2021). The pathogens isolated from these patients exhibited resistance to: amoxicillin/clavulanic acid, levofloxacin, ciprofloxacin, piperacillin/tazobactam, and trimethoprim/sulfamethoxazole with an overall resistance of 64% to 69% to third-generation cephalosporins and carbapenems (Khuranna et al. 2021). Another study carried out by Vijay et al. (2021) reported nosocomial pathogens exhibiting resistance to cephalosporins, fluoroquinolones and β-lactam/β-lactamase inhibitor combinations, piperacillin/tazobactam and cefoperazone-sulbactam in COVID-19 patients. A greater occurrence of *Candida auris* blood stream infection was reported in India in COVID-19 patients; most of the *C. auris* clinical isolates were found to be resistant to antifungal agents such as amphotericin B and fluconazole (Chowdhary et al. 2020). *Candida* infections resistant to these fungal agents is a matter of concern for low-resource countries where there is limited accessibility to echinocandins and is likely to eventually result in treatment failure (Chowdhary et al. 2020). Certain isolates of *Syncephalastrum monosporum* which caused mucormycosis in COVID-19 patients were found to exhibit elevated minimum inhibitory concentration of itraconazole and posaconazole (Singh, S et al. 2021).

The Indian Council of Medical Research have reported a higher prevalence of AMR infections in hospitals of India during the pre-COVID-19 period (ICMR 2019) and the surge of COVID-19 cases in India will likely exacerbate the overall prevalence of AMR infections in hospitals. Studies that have reported the incidence of AMR stem mainly from the first wave of COVID-19 infections in India, while the impact of second wave of COVID-19 in the incidence of AMR infections is not yet clear. The second wave of COVID-19 in India resulted

an overflow of patients in hospitals impacting the ability to implement routine infection control practices, paving the way to nosocomial transmission of both SARS-CoV-2 and multi-drug resistant microorganisms. Scarcity in available data makes it difficult to determine if the prevalence of AMR has escalated in India, potentially compounded by under-reporting of antimicrobial surveillance data from hospitals already overwhelmed by the workload of the second pandemic wave. The few studies that do exist, conducted on secondary infections in COVID-19 patients, suggests that AMR may well have worsened. Incorporating AMR surveillance and stewardship alongside the COVID-19 response will be greatly advantageous (Getahun et al. 2020).

## 3. Antimicrobials used for COVID-19 management in India

Several different guidelines have operated worldwide since the onset of the pandemic. Combination therapy with azithromycin and hydroxychloroquine (HCQ) has been recommended in COVID-19 patients due to its antiviral potential despite its risk of prolonging the QT interval (Gautret et al. 2020). In China, empirical use of antibiotics like azithromycin, amoxicillin or fluroquinolones has been recommended in mild cases of COVID-19 while broad-spectrum antibiotics were advocated in severe cases to eliminate all possible bacterial co-pathogens (Jin et al. 2020). Initially in the UK, empirical oral administration of doxycycline was suggested in patients who were at increased risk of COVID-19-associated complications or when it was difficult to determine if the causative agent was bacterial or viral, perhaps because patients were asked to remain at home and not present to healthcare (NICE 2020). Later, antibiotic treatment was limited to confirmed bacterial co-infections (NICE 2021). Treatment guidelines for COVID-19 management in African countries recommend antibiotics, with Liberia suggesting use of antibiotics for COVID-19 associated symptoms such as cough, diarrhea and sore throat (Adebisi et al. 2021). A survey on antibiotic use in COVID-19 patients reported piperacillin/tazobactam as the most used antibiotic in general, whereas a

preponderance in the use of fluoroquinolones in combination with other antibiotics and carbapenems was observed in Italy (Beović et al. 2020).

India is one of the countries most severely affected by COVID-19 with approximately 31 million cases reported in India as of July 2021 (Arogya setu mobile app). For patients with severe illness, a combination of HCQ and the antibiotic azithromycin was initially recommended by the Ministry of Health and Family Welfare in India. The anti-malarial drug HCQ was recommended for asymptomatic healthcare personnel, asymptomatic frontline personnel, and asymptomatic household contacts of the confirmed patients (MoHFW 2020). Later ivermectin, another antiparasitic drug, was introduced as an alternative for HCQ in COVID-19 management in India (MoHFW 2021). The standard operating protocol for COVID-19 management is different throughout Indian states. For example, the state health boards of the Indian states Bihar and West Bengal recommend the use of ivermectin and doxycycline in all patients diagnosed with severe COVID-19 (Government of Bihar 2021; Health and Family welfare department 2021). In the Indian state of Maharashtra, use of antimicrobials is based on the severity of COVID-19 illness. For those with mild symptoms and other comorbidities the antibiotic cefixime or amoxicillin clavulanate along with HCQ is recommended, whereas in patients with moderate illness and pneumonia, empiric intravenous administration of ceftriaxone for 5-10 days has been recommended. In severe cases with pneumonia, septic shock, or acute respiratory distress syndrome (ARDS), intravenous administration of meropenem is suggested (Government of Maharashtra 2020). The latest guidelines for treatment by the Maharashtra COVID-19 task force have revised the protocol to recommend piperacillin-tazobactam in cases of pneumonia with respiratory failure (Nagpur Municipal Corporation 2021). Use of carbapenems and even the so-called “last resort” antibiotic colistin have been reported in COVID-19 patients in India (Gale and Shrivastava 2020). Most of the antibiotics prescribed in treatment of bacterial infections in COVID-19

patients in India come under the category of 'Watch' and 'Reserve' in the WHO Aware, Watch and Reserve (AWaRe) classification. The WHO advises against the prescription of antimicrobial agents in mild to moderate cases of COVID-19 cases without clear indication of bacterial infections (WHO 2020). Ideally, local guidelines set by public health agencies should adhere to WHO guidelines and the choice of antibiotic for treatment should be based on confirmation of bacterial infection and antibiogram profiling rather than empirical prescription.

Although repurposing antimicrobials such as HCQ, azithromycin and doxycycline might appear to be a reasonable approach to COVID-19 management, it is by no means clear that such drugs have any activity against COVID-19 apart from their already known anti-bacterial or anti-malarial activity; their injudicious use can have setbacks. The use of HCQ is a big concern for India as malaria is endemic in the country (WHO 2018; Principi and Esposito 2020), and its indiscriminatory use may contribute to resistance in *Plasmodium* sp. (Sutherland et al. 2007). Typhoid fever is an important health concern for India specifically because of the emergence of azithromycin resistance in *Salmonella enterica* serovar Typhi (Carey et al. 2021). In such a situation, the decision to repurpose azithromycin in India could endanger the treatment of typhoid fever. Irrational use of doxycycline in poultry rearing is already a prevailing issue in developing communities (Waghamare et al. 2020; Ali et al. 2020) and introduction of the antibiotic as a treatment regimen for COVID-19 may exacerbate the risk of doxycycline resistance. Ivermectin resistance has also been documented in several studies (Dent et al. 2000; Osei-Atweneboana et al. 2011) highlighting the need for surveillance of these antimicrobial drugs in developing countries before its implementation as an anti-SARS-CoV-2 drug.

## 4. The AMR burden of antimicrobial production and consumption: a pandemic point of view

The consumption of antimicrobials by humans and animals and their subsequent excretion is considered a major source of antimicrobial residues in the environment. Even though the concentration of antimicrobials is in low ranges of μg/kg to mg/kg (soil) and ng/L to μg/L (water), their presence in such levels have been found to promote antimicrobial resistance (Gilbertson et al. 1990; Boxall et al. 2003; Göbel et al. 2004; Roberts and Thomas 2006; Watkinson et al. 2009). In addition to consumption of antimicrobials, the pharmaceutical industry acts as another important source for antimicrobial residues in the environment. The pharmaceutical industry comprises of active pharmaceutical ingredient (API) units that manufacture the raw materials of antimicrobials and units that formulate antimicrobials to finished pharmaceutical product (FPP) (Nahar 2020). Residues emerging from these sources lays grounds for the development of AMR in bacteria.

While the Republic of China is the chief global hub for API production, the Indian pharmaceutical industry is oriented towards the formulation of FPP (Arnum 2013; Gandra et al. 2017). The environment surrounding API manufacturing units has been identified as an important source of AMR bacteria, especially in India (Larsson et al. 2007; Rutgersson et al. 2014; Bengtsson-Palme et al. 2014). Despite an order by the Supreme Court of India to treat wastewater and reuse it, pharmaceutical industries have breached these regulations (The Hans India 2015; Changing Markets 2016). Technologies to ensure zero liquid discharge are expensive, and pharmaceutical industries may elect to dispose residues and waste directly into surrounding environments surreptitiously (The Hans India 2015; Changing Markets 2016). A lack of effective waste management in the API manufacturing and formulating industries leads to dispersal of manufacturing wastes to water bodies and further leads to the development of AMR. Aquatic environments surrounded by bulk drug manufacturing companies in India was found to exhibit 1000 times higher concentration of antimicrobials than what is generally found in rivers of high-income countries (Gothwal and Shashidhar 2016).

The pandemic has also resulted in more pharmaceutical companies commencing production of azithromycin and HCQ in India (The Times of India 2020; The Economic Times 2020). It can therefore be expected that the overall production of antimicrobials, especially those that have been recommended for treating COVID-19 is likely to have escalated. Increased production of antimicrobials coupled with poor waste management strategies is predicted to intensify the prevalence of AMR in environmental settings. Environment (Protection) Amendment Rules, 2019 (set by the Ministry of Environment, Forest and Climate Change, Government of India) have released emission standards for 111 antimicrobials in treated effluent originating from bulk drug and formulation units (The Gazette of India 2020). However, HCQ, ivermectin and other antivirals are not listed. Since the pandemic has resulted in an increased demand for HCQ and antivirals, inclusion of emission standards for these APIs are desirable.

***Landfills and wastewater treatment plants***

Hospitals, municipal sewage and manufacturing plants are important sources of both antimicrobials and antibiotic-resistance genes to freshwater bodies. Municipal WWTPs with or without an *in-situ* pre-treatment step (Giger et al., 2003) do not often sufficiently neutralize antibiotic resistant bacteria and genes, nor remove antimicrobial residues which are further shed into the local environment. For example, WWTPs receiving effluents from hospitals with considerable numbers of COVID-19 patients could be potential reservoirs of antimicrobial residues, antimicrobial resistant bacteria as well as AMR genes that are capable of horizontal transmission into other bacterial species. A risk assessment study conducted in an emergency hospital in the UK suggested that the ratio of predicted environmental concentration to predicted no-effect concentration (PEC: PNEC) would be above 1 for amoxicillin, if around 70% of patients consumed the antibiotic, highlighting a realistic environmental concern for selection of AMR during a pandemic where large proportions of the population are consuming

antibiotics, particularly in healthcare settings (Comber et al. 2020). Considering the widespread use of antimicrobials during the pandemic it can be expected that municipal and hospital WWTPs may receive a heavy load of antimicrobials. Microbial forms such as flocs and biofilms are essential for the functioning and stability of sewage treatment plants and high concentrations of antibiotics in wastewaters may exert inhibitory effect on these microbial forms and subsequently compromise the efficacy of sewage treatment (Singer et al. 2008).

Sales of antimicrobial disinfectants and soaps have soared during the pandemic in India (Tandon 2020). Soaps and disinfectants containing antimicrobials could persist in wastewater biosolids at higher concentrations than that of antibiotics, imposing damage to the ecosystem (McClellan and Halden, 2010). Depending on the physical and chemical properties of the antimicrobial compound and the technology of WWTPs, antimicrobials may undergo precipitation, biodegradation, transformation or sorption onto the activated sludge (Ternes and Joss, 2006). Conventional WWTP processes either partially mineralise antimicrobials or transform them into metabolites with biological activity, resulting in the generation of residues, thereby allowing the entry of these compounds into the environment through effluent discharges or applications of sewage sludge (Miranda and Castillo 1998; Marcinek et al. 1998; Reinthaler et al. 2003; Lindberg et al. 2005; Silva et al. 2006). Some antimicrobials get transformed into molecules that may have higher or similar antimicrobial effect than that of parent molecule. For example, transformed products of the antibiotic sulfamethoxazole modified at the *para*-amino group exhibits antibacterial effects like that of parent molecule whereas its 4-$NO_2$ and 4-OH derivates have higher inhibitory activity than the parent molecule (Majewsky et al. 2013). Methyltriclosan, a by-product of triclosan following biological treatment, has a mode of action similar to parent molecule and occurs even when triclosan levels are below measurable limits (Lindström et al. 2002). Thus, antimicrobial residues and transformed by products of antimicrobials originating from WWTPs may enable

364 microorganisms to develop resistance through selective sweeps of point mutations or
365 horizontally transferred AMR genes due to selection driven by exposure to these compounds
366 at sub-inhibitory concentrations. Antimicrobials at sub-inhibitory concentrations could exalt
367 the expression of efflux pumps and promote efflux-mediated resistance to antimicrobials
368 (Poole 2005; Maillard 2007). Additionally, WWTPs act as a fulcrum in the generation of AMR
369 bacteria due to the high microbial load present and increased availability of nutrients within
370 them (Threedeach et al. 2012; Zhang et al. 2015) which may enable their dissemination into
371 various environments.

372 Municipal solid waste landfills are also sentinels of antimicrobials and AMR residues
373 which can disperse into surrounding environments (Li et al. 2017). It has been predicted that
374 the risk of AMR is even serious in economies when a population of 20 million reside within <
375 2 kilometers away from landfills (Wilson et al. 2016). Antimicrobial residues in landfills could
376 even result in depletion of microbes essential in biogeochemical cycles. This has been
377 demonstrated in a study by Wu et al. (2017) where oxytetracycline present in landfill refuse
378 reduced $N_2$ production capacity by >50% linked to depletion of *Rhodothermus* sp. and inhibits
379 denitrification in the long term. Practices like long-term landfilling enriches the abundance of
380 antimicrobial resistant genes (Wu et al. 2017) and abandoning these landfills are not an
381 effective solution as they can still diffuse out for years (Velpandian et al. 2018). Alarming
382 levels of pharmaceuticals have been recorded in aquifers adjoined to the Ghazipur landfill of
383 the year 1984 and the leachate from the landfill was found to be continuously drained into the
384 river Yamuna (Velpandian et al. 2018). The overuse and misuse of antimicrobials linked to the
385 continuing global pandemic can concentrate such landfills with antimicrobials and may present
386 vital damage to the natural ecosystems.

387 ***Water bodies***

Lack of access to clean water is one of the pressing issues the world is facing. Studies have documented antimicrobial contamination in water resources including surface water, groundwater and seawater (López-Serna et al. 2013; Zhao et al. 2015; Mahmood et al. 2019). In addition, water mixes up bacteria from the environment, humans and animals which enables the transfer of AMR encoding mobile elements between bacteria and evolution of new AMR encoding mobile elements through recombination of AMR genes and genes for mobile element transfer from an enhanced gene pool. Aquatic ecosystems have a significant ecological and evolutionary role in influencing the emergence, transmission and persistence of AMR and can dampen the efforts taken to reduce the prevalence of AMR in clinical settings (Taylor et al. 2011).

AMR is a huge burden for highly populated areas where clean water, sanitation and hygiene (WaSH) are not stringently followed and unrestricted use of antimicrobials prevails. Since COVID-19 has brought an unprecedented change in antimicrobial consumption and production, it can be presumed that the composition of wastewater generated has changed, introducing new challenges to wastewater management. This inevitably leaves water resources at stake and the biota dependent on it. One study in India has confirmed an increased incidence of *Escherichia coli* resistant to non-fluoroquinolone antibiotics during the pandemic in ambient waterbodies in the city of Ahmedabad where many COVID-19 cases were being reported (Kumar et al. 2021). In many cities of India, a proper WWTP is absent and domestic sewage is directly discharged into aquatic ecosystems. Of crucial importance, AMR is not included in the water quality standards and guidelines of India precisely because of this reason (IS10500, 2012; Kumar et al. 2021).

***Human beings***

411 Besides the empirical use of antimicrobials in clinical settings, another important factor
412 leading to increased antimicrobial consumption is self-medication. Misuse of antimicrobial
413 drugs is common in urban and rural parts of India, due to ease in procuring over-the-counter
414 use of antibiotics. Social stigma associated with declaring oneself affected by the virus can
415 tempt people to self-medicate. The knowledge that antimicrobials recommended for COVID-
416 19 are readily available without prescription further facilitates the practice of self-medication.
417 The lack of regulation in antimicrobial self-medication in India has supported an increase in
418 the consumption of antimicrobials by 105% between 2000 and 2015, a metric that is expected
419 to increase globally by 63% during 2010–2030 (Klein et al. 2018; GARP-India Working
420 Group, 2011; Van Boeckel et al. 2015). Furthermore, since the beginning of pandemic, the
421 public has been directed to use hand sanitizers and disinfectants as a key infection control
422 intervention. Quaternary ammonium compounds, a common ingredient in many commercially
423 available disinfectants can affect the susceptibility of bacteria to other antibacterial agents
424 when they are present at sub-inhibitory concentrations (Soumet et al. 2012). According to the
425 State of the World's Antibiotics 2021 report, the change in per capita use of antibiotics in India
426 between 2010-2020 is 30.64% (Sriram et al. 2021). The increased use of antimicrobials like
427 HCQ and azithromycin during COVID-19 can disrupt the composition of human gut
428 microbiome (Finlay et al. 2021) which could result in serious health consequences. Moreover,
429 consumption of azithromycin has proven to alter the metabolic functioning of gut microbiome
430 and select for azithromycin resistance in the gut (Doan et al. 2019). Antimicrobial consumption
431 also results in the loss of microbial taxa which are low in number and more susceptible to
432 antimicrobials, and this can alter metabolic and immune functioning of the host (Neuman et al.
433 2018). The altered manufacturing landscape of APIs during the pandemic can also magnify the
434 risk of AMR. Untreated effluents from manufacturing industries contaminates surface, ground,

435 and drinking water with antimicrobials and human consumption of such polluted water could
436 select for AMR in the intestine.

437 ***Animals and aquatic biota***

438 With numerous studies confirming the presence of antimicrobial resistant bacteria in
439 the gut microbiota of wildlife species such as birds, reptiles, mammals and fish (Gilliver et al.
440 1999; Sjölund et al. 2008; Wheeler et al. 2012; Bonnedahl et al. 2014), it is apparent that the
441 issue of AMR is not confined to food animals. Ensuing the selection of antimicrobial resistance
442 in the intestinal flora of humans receiving antimicrobial therapy, antimicrobial resistant
443 bacteria and antimicrobial residues are released into the environment through excreta. The
444 antimicrobial residues and their metabolites reaching aquatic resources exert toxic effects to
445 various biological systems (Bilal et al. 2020). Their presence in water causes the enteric
446 bacteria in the gut of aquatic animals to evolve resistance through selection of already existing
447 environmental AMR genes (Arnold et al. 2016). Long-range animal movement further assists
448 the circulation of resistant genes in a global scale making them potential vectors of AMR
449 (Dolejska and Papagiannitsis 2018).

450 Aquatic environments provide perfect conditions for horizontal gene transfer and
451 establishment of antimicrobial resistant bacteria (Bhattacharyya et al. 2019). Effluents from
452 sewage treatment plants contain heavy metals, detergents and other pollutants along with
453 antimicrobials that can co-select AMR (Baker-Austin et al. 2006). Run offs from agricultural
454 lands, aquaculture facilities and pharmaceutical industries also introduces antimicrobial
455 products and resistant bacteria into marine and other aquatic ecosystems (Baquero et al. 2008).
456 Antimicrobial resistant genes from aquatic organisms can re-enter into the human and animal
457 microbiota via food chain resulting in a vicious cycle of AMR.

458 **5. Concluding remarks and recommendations**

459 The current pandemic demonstrates how poor planning and preparedness can impact
460 public health. There are no defined borders for microorganisms which can spread easily from
461 one source to another. Infectious diseases with no reliable therapeutic options can further
462 decimate public health infrastructure. AMR is however a silent pandemic that has worsened in
463 the face of COVID-19 (Mahoney et al. 2021). Ironically, lack of access to antimicrobials and
464 healthcare currently costs more lives than AMR, particularly in resource limited countries
465 (Frost et al. 2019b). However, if the bacteria impacting resource-limited countries develop
466 AMR, then a more catastrophic situation will arise where even those who reach healthcare
467 cannot be treated. The solution will be to address AMR without delay and ensure rational use
468 without affecting accessibility to antimicrobials for those who need them most (Ginsburg and
469 Klugman 2020). Research studies assessing the prevalence of AMR in humans, animals and
470 environment is required urgently to assess the overall impact of COVID-19 and plan mitigation
471 strategies for the future. Accelerating the COVID-19 vaccination drive in India can also help
472 reduce the incidence of AMR to an extent, as vaccines can reduce the need for hospitalization
473 in patients infected with the virus (Sheikh et al. 2021) and dependency on antimicrobials.

474 India's national action plan for AMR is a well-structured proposal inclusive of all
475 realms of One Health to tackle AMR. However, the execution of the plan has been slow- paced
476 and requires momentum. So far, only three states of India have proposed an action plan for the
477 containment of AMR (Government of Kerala 2018; Government of Madhya Pradesh 2019;
478 Government of NCT of Delhi 2020). Such initiatives must be introduced from other states as
479 well, since this enables the direct involvement of state governments for effective monitoring
480 and assessment of programs and policies. The absence of a surveillance system monitoring
481 antibiotic usage and AMR from manufacturing sources, animal husbandry, aquaculture and
482 other environmental settings, restricts our understanding on the overall burden of AMR. Hence,
483 it will be necessary to develop an integral AMR surveillance system that is fully inclusive of

all sectors of One Health. COVID-19 can increase the prevalence of AMR even in natural environments due to the increase in production and consumption of antimicrobials. According to the Scoping Report on Antimicrobial Resistance in India, only 7% of the research studies conducted on AMR in the environmental scale accounts to industrial effluents (Gandra et al. 2017), a number which is too small considering the volume of antimicrobial production in India. The AMR risk associated with hospital and industrial effluents are largely unknown and therefore demands further research to come up with real solutions for the management of AMR. About 50% of people in rural parts of India are still dependent on pharmacies for treatment as their first choice due to the geographical constraints, affordability and inaccessibility to health care (DownToEarth 2020). Even though Schedule H1 prohibits the sale of antimicrobials without any prescription, it is often not enforced extensively and over-the-counter sale of antimicrobials still prevails in some parts of India (Satyanarayana et al. 2016). AMR is an issue of social construct and it requires the collective efforts of psychologists, social and environmental scientists in order to frame strategies for behaviour and technical interventions in minimising the irrational use of antimicrobials and their inputs to the environment. As much as it is important to educate pharmacists, it is equally important to educate the public on the injudicious use of antimicrobials and its relation to AMR. Inculcating knowledge on AMR and the sensible use of antimicrobials in early education can amend the knowledge gap that exists within the public regarding AMR. India has a history of successful health campaigns like the pulse polio and BCG vaccination drive where social media has aided in reaching out to the masses. Social media has played an immense role in creating awareness about COVID-19 and instilling COVID-19 appropriate behaviours amongst the public. This model could be extended to disseminate knowledge regarding AMR and appropriate behavioural interventions by public health authorities.

Improving AMR surveillance capacity and antimicrobial stewardship activities will be essential if we are to effectively manage AMR in India. Reinforcement of AMR stewardship activities, revision of environmental policies and antimicrobial policies will not only help in mitigating the current challenge of AMR but could prevent a worsening crisis in any forthcoming third wave of COVID-19 in India.

**Acknowledgements:** Authors are thankful to DBT-NERC AMRWATCH research grant.

**Compliance with Ethical Standards:**

Research involving human participants and/or animals: This article does not contain any studies with human participants or animals performed by any of the authors

Informed consent: This article does not contain any studies with human participants performed by any of the authors.

**References**

Adebisi, Y. A., Jimoh, N. D., Ogunkola, I. O., Uwizeyimana, T., Olayemi, A. H., Ukor, N. A., & Lucero-Prisno, D. E., 3rd (2021). The use of antibiotics in COVID-19 management: a rapid review of national treatment guidelines in 10 African countries. *Tropical medicine and health*, *49*(1), 51. https://doi.org/10.1186/s41182-021-00344-w

Alanio, A., Dellière, S., Fodil, S., Bretagne, S., & Mégarbane, B. (2020). Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *The Lancet Respiratory Medicine*, *8*(6), e48-e49. https://doi.org/10.1016/S2213-2600(20)30237-X

Ali, M. R., Sikder, M. M. H., Islam, M. S., & Islam, M. S. (2020). Investigation of discriminate and indiscriminate use of doxycycline in broiler: An indoor research on antibiotic doxycycline residue study in edible poultry tissue. *Asian Journal of Medical and Biological Research*, *6*(1), 1-7. https://doi.org/10.3329/ajmbr.v6i1.46472

Annual Report 2019-20, Central Pollution Control Board (CPCB), Ministry of Environment, Forest & Climate Change (2020). https://cpcb.nic.in/openpdffile.php?id=UmVwb3J0RmlsZXMvMTI0M18xNjE2NTYxOTAxX21lZGlhcGhvdG8xMTgzNi5wZGY= (accessed 14 July 2021).

Antimicrobial Research and Surveillance Network, Annual report January 2019- December 2019, Indian Council of Medical Research (ICMR), 2019. http://iamrsn.icmr.org.in/index.php/resources/amr-icmr-data (accessed 1 July 2021).

Arastehfar, A., Carvalho, A., van de Veerdonk, F. L., Jenks, J. D., Koehler, P., Krause, R., ... & Hoenigl, M. (2020). COVID-19 associated pulmonary aspergillosis (CAPA)—from immunology to treatment. *Journal of Fungi*, *6*(2), 91. https://doi.org/10.3390/jof6020091

Arnold, K. E., Williams, N. J., & Bennett, M. (2016). 'Disperse abroad in the land': the role of wildlife in the dissemination of antimicrobial resistance. *Biology Letters*, *12*(8), 20160137. https://doi.org/10.1098/rsbl.2016.0137

Arnum PV (2013) The Weaknesses and Strengths of the Global API Market. PTSM: Pharmaceutical Technology Sourcing and Management 9. Available at: https://www.pharmtech.com/view/weaknesses-and-strengths-global-api-market. (accessed 14 July 2021).

Ashbolt, N. J., Amézquita, A., Backhaus, T., Borriello, P., Brandt, K. K., Collignon, P., ... & Topp, E. (2013). Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. *Environmental health perspectives*, *121*(9), 993-1001. https://doi.org/10.1289/ehp.1206316

Baker-Austin, C., Wright, M. S., Stepanauskas, R., & McArthur, J. V. (2006). Co-selection of antibiotic and metal resistance. *Trends in microbiology*, *14*(4), 176-182.

554 Baquero, F., Martínez, J. L., & Cantón, R. (2008). Antibiotics and antibiotic resistance in water
555 environments. *Current opinion in biotechnology*, *19*(3), 260-265.
556 https://doi.org/10.1016/j.copbio.2008.05.006

557 Beadling, C., & Slifka, M. K. (2004). How do viral infections predispose patients to bacterial
558 infections?. *Current opinion in infectious diseases*, *17*(3), 185-191.
559 https://doi.org/10.1097/00001432-200406000-00003

560 Bengoechea, J. A., & Bamford, C. G. (2020). SARS-CoV-2, bacterial co-infections, and AMR:
561 the deadly trio in COVID-19?. *EMBO molecular medicine*, *12*(7), e12560.
562 https://doi.org/10.15252/emmm.202012560

563 Bengtsson-Palme, J., & Larsson, D. J. (2016). Concentrations of antibiotics predicted to select
564 for resistant bacteria: proposed limits for environmental regulation. *Environment*
565 *international*, *86*, 140-149. https://doi.org/10.1016/j.envint.2015.10.015

566 Bengtsson-Palme, J., Boulund, F., Fick, J., Kristiansson, E., & Larsson, D. G. (2014). Shotgun
567 metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a
568 polluted lake in India. *Frontiers in microbiology*, *5*, 648.
569 https://doi.org/10.3389/fmicb.2014.00648

570 Beović, B., Doušak, M., Ferreira-Coimbra, J., Nadrah, K., Rubulotta, F., Belliato, M., Berger-
571 Estilita, J., Ayoade, F., Rello, J., & Erdem, H. (2020). Antibiotic use in patients with COVID-
572 19: a 'snapshot' Infectious Diseases International Research Initiative (ID-IRI) survey. *The*
573 *Journal of antimicrobial chemotherapy*, *75*(11), 3386–3390.
574 https://doi.org/10.1093/jac/dkaa326

575 Bhattacharyya, A., Haldar, A., Bhattacharyya, M., & Ghosh, A. (2019). Anthropogenic
576 influence shapes the distribution of antibiotic resistant bacteria (ARB) in the sediment of

577 Sundarban estuary in India. *Science of the Total Environment*, *647*, 1626-
578 1639.https://doi.org/10.1016/j.scitotenv.2018.08.038

579 Bilal, M., Mehmood, S., Rasheed, T., & Iqbal, H. M. (2020). Antibiotics traces in the aquatic
580 environment: persistence and adverse environmental impact. *Current opinion in environmental*
581 *science & health*, *13*, 68-74. https://doi.org/10.1016/j.coesh.2019.11.005

582 Blaize, M., Mayaux, J., Nabet, C., Lampros, A., Marcelin, A. G., Thellier, M., Piarroux, R.,
583 Demoule, A., & Fekkar, A. (2020). Fatal Invasive Aspergillosis and Coronavirus Disease in an
584 Immunocompetent Patient. *Emerging infectious diseases*, *26*(7), 1636–1637.
585 https://doi.org/10.3201/eid2607.201603

586 Bonnedahl, J., & Järhult, J. D. (2014). Antibiotic resistance in wild birds. *Upsala journal of*
587 *medical sciences*, *119*(2), 113-116.

588 Boxall, A. B., Kolpin, D. W., Halling-Sørensen, B., & Tolls, J. (2003). Peer reviewed: are
589 veterinary medicines causing environmental risks?. *Environmental science &*
590 *technology*, *37*(15), 286A-294A.

591 Cantón, R., Gijón, D., & Ruiz-Garbajosa, P. (2020). Antimicrobial resistance in ICUs: an
592 update in the light of the COVID-19 pandemic. *Current Opinion in Critical Care*, *26*(5), 433-
593 441. https://doi.org/10.1097/mcc.0000000000000755

594 Carey, M. E., Jain, R., Yousuf, M., Maes, M., Dyson, Z. A., Thu, T. N. H., ... & Taneja, N.
595 (2021). Spontaneous emergence of azithromycin resistance in independent lineages of
596 *Salmonella Typhi* in Northern India. *Clinical Infectious Diseases*, *72*(5), e120-e127.
597 https://doi.org/10.1093/cid/ciaa1773

598 Center for Drug Evaluation, Research. FDA cautions use of hydroxychloroquine/chloroquine
599 for COVID-19, 2020. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-

cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (accessed 15 June 2021).

Changing Markets. Superbugs in the Supply Chain, 2016: how pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. https://epha.org/wp-content/uploads/2016/10/Superbugsinthesupplychain_CMreport.pdf (accessed 14 July 2021).

Chedid, M., Waked, R., Haddad, E., Chetata, N., Saliba, G., & Choucair, J. (2021). Antibiotics in treatment of COVID-19 complications: a review of frequency, indications, and efficacy. *Journal of infection and public health*, *14*(5), 570. https://dx.doi.org/10.1016%2Fj.jiph.2021.02.001

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., ... & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The lancet*, *395*(10223), 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

Chowdhary, A., Tarai, B., Singh, A., & Sharma, A. (2020). Multidrug-Resistant *Candida auris* Infections in Critically Ill Coronavirus Disease Patients, India, April-July 2020. *Emerging infectious diseases*, 26(11), 2694–2696. https://dx.doi.org/10.3201%2Feid2611.203504

Cleaning Matters, 2020. Coronavirus: supplies run low of anti-bacterial hand-soaps. https://www.cleaning-matters.co.uk/Coronavirus-anti-bacterial-soaps (accessed 14 July 2021).

Comber, S. D., Upton, M., Lewin, S., Powell, N., & Hutchinson, T. H. (2020). COVID-19, antibiotics and One Health: a UK environmental risk assessment. *Journal of Antimicrobial Chemotherapy*, *75*(11), 3411-3412. https://doi.org/10.1093/jac/dkaa338

622 Contou, D., Claudinon, A., Pajot, O., Micaëlo, M., Flandre, P. L., Dubert, M., ... & Plantefève,
623 G. (2020). Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia
624 admitted to a French ICU. *Annals of Intensive Care*, *10*(1), 1-9.
625 https://doi.org/10.1186/s13613-020-00736-x

626 COVID-19 rapid guideline: managing COVID-19 NICE guideline Published: 23 March 2021
627 https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-
628 covid19-pdf-51035553326 (accessed 2 July 2021).

629 COVID-19 rapid guideline: managing suspected or confirmed pneumonia in adults in the
630 community NICE guideline [NG165] (2020).
631 https://www.nice.org.uk/guidance/ng165#antibiotic-treatment (accessed 2 July 2021).

632 Cucinotta, D., & Vanelli, M. (2020). WHO declares COVID-19 a pandemic. *Acta Bio Medica:*
633 *Atenei Parmensis*, *91*(1), 157. https://dx.doi.org/10.23750%2Fabm.v91i1.9397

634 Dent, J. A., Smith, M. M., Vassilatis, D. K., & Avery, L. (2000). The genetics of ivermectin
635 resistance in *Caenorhabditis elegans*. *Proceedings of the National Academy of Sciences*, *97*(6),
636 2674-2679. https://doi.org/10.1073/pnas.97.6.2674

637 Doan, T., Hinterwirth, A., Worden, L., Arzika, A. M., Maliki, R., Abdou, A., ... & Lietman, T.
638 M. (2019). Gut microbiome alteration in MORDOR I: a community-randomized trial of mass
639 azithromycin distribution. *Nature medicine*, *25*(9), 1370-1376.
640 https://doi.org/10.1038/s41591-019-0533-0

641 Dolejska, M., & Papagiannitsis, C. C. (2018). Plasmid-mediated resistance is going
642 wild. *Plasmid*, *99*, 99-111. https://doi.org/10.1016/j.plasmid.2018.09.010

643 DownToEarth: What should India do to control antimicrobial resistance (2020).
644 https://www.downtoearth.org.in/blog/health/what-should-india-do-to-control-antimicrobial-
645 resistance-74267 (Accessed: 17 October 2021).

646 Dutta, V., Dubey, D., & Kumar, S. (2020). Cleaning the River Ganga: Impact of lockdown on
647 water quality and future implications on river rejuvenation strategies. *Science of the Total*
648 *Environment*, *743*, 140756. https://doi.org/10.1016/j.scitotenv.2020.140756

649 Finlay, B. B., Amato, K. R., Azad, M., Blaser, M. J., Bosch, T. C., Chu, H., ... & Giles-Vernick,
650 T. (2021). The hygiene hypothesis, the COVID pandemic, and consequences for the human
651 microbiome. *Proceedings of the National Academy of Sciences*, *118*(6).

652 Francisco EM. COVID-19: reminder of the risks of chloroquine and hydroxychloroquine,
653 2020. Available: https://www.ema.europa.eu/en/news/covid-19-reminder-risks-chloroquine-
654 hydroxychloroquine (accessed 2 July 2021).

655 Frost, I., Craig, J., Joshi, J., Faure, K., & Laxminarayan, R. (2019b). Access barriers to
656 antibiotics. Washington, DC: *Center for Disease Dynamics, Economics & Policy*.
657 https://cddep.org/wp-
658 content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf (accessed 12 July
659 2021).

660 Frost, I., Van Boeckel, T. P., Pires, J., Craig, J., & Laxminarayan, R. (2019a). Global
661 geographic trends in antimicrobial resistance: the role of international travel. *Journal of travel*
662 *medicine*, *26*(8), taz036. https://doi.org/10.1093/jtm/taz036

663 Fu, Y., Yang, Q., Xu, M., Kong, H., Chen, H., Fu, Y., ... & Zhou, J. (2020). Secondary bacterial
664 infections in critical ill patients of COVID-19. In *Open forum infectious diseases*.
665 https://dx.doi.org/10.1093%2Fofid%2Fofaa220

Gade, V., Bajaj, N., Sonarkar, S., Radke, S., Kokane, N., & Rahul, N. (2021). Mucormycosis: Tsunami of Fungal Infection after Second Wave of COVID-19. *Annals of the Romanian Society for Cell Biology*, *25*(6), 6383-6390. Retrieved from https://www.annalsofrscb.ro/index.php/journal/article/view/6700

Gale, J; Shrivastava, B. (2020, May 25). Antibiotics for Covid Cases Worsen India's Superbug Crisis. *BloombergQuint*. https://www.bloombergquint.com/coronavirus-outbreak/antibiotics-for-covid-patients-worsen-india-s-superbug-plight (accessed 14 July 2021).

Gandra S, Joshi J, Trett A, Lamkang AS, Laxminarayan R (2017). Scoping report on antimicrobial resistance in India. Center for Disease Dynamics, Economics & Policy, Washington, DC. https://cddep.org/wp-content/uploads/2017/11/AMR-INDIA-SCOPING-REPORT.pdf (accessed 14 July 2021).

Gandra, S., Mojica, N., Klein, E. Y., Ashok, A., Nerurkar, V., Kumari, M., ... & Laxminarayan, R. (2016). Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. *International Journal of Infectious Diseases*, *50*, 75-82. https://doi.org/10.1016/j.ijid.2016.08.002

Gandra, S., Tseng, K. K., Arora, A., Bhowmik, B., Robinson, M. L., Panigrahi, B., ... & Klein, E. Y. (2019). The mortality burden of multidrug-resistant pathogens in India: a retrospective, observational study. *Clinical Infectious Diseases*, *69*(4), 563-570. https://doi.org/10.1093/cid/ciy955

Garcia-Vidal, C., Sanjuan, G., Moreno-García, E., Puerta-Alcalde, P., Garcia-Pouton, N., Chumbita, M., ... & Torres, A. (2021). Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clinical Microbiology and Infection*, *27*(1), 83-88. https://doi.org/10.1016/j.cmi.2020.07.041

690 Gautret, P., Lagier, J. C., Parola, P., Meddeb, L., Mailhe, M., Doudier, B., ... & Raoult, D.
691 (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-
692 label non-randomized clinical trial. *International journal of antimicrobial agents*, *56*(1),
693 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949

694 Getahun, H., Smith, I., Trivedi, K., Paulin, S., & Balkhy, H. H. (2020). Tackling antimicrobial
695 resistance in the COVID-19 pandemic. *Bulletin of the World Health Organization*, *98*(7), 442.
696 https://dx.doi.org/10.2471%2FBLT.20.268573

697 Ghosh, S., Bornman, C., & Zafer, M. M. (2021). Antimicrobial Resistance Threats in the
698 emerging COVID-19 pandemic: Where do we stand?. *Journal of infection and public*
699 *health*, *14*(5), 555–560. https://doi.org/10.1016/j.jiph.2021.02.011

700 Gilbertson, T. J., Hornish, R. E., Jaglan, P. S., Koshy, K. T., Nappier, J. L., Stahl, G. L., ... &
701 Kubicek, M. F. (1990). Environmental fate of ceftiofur sodium, a cephalosporin antibiotic.
702 Role of animal excreta in its decomposition. *Journal of Agricultural and Food*
703 *Chemistry*, *38*(3), 890-894.

704 Gilliver, M. A., Bennett, M., Begon, M., Hazel, S. M., & Hart, C. A. (1999). Antibiotic
705 resistance found in wild rodents. *Nature*, *401*(6750), 233-234.

706 Ginsburg, A. S., & Klugman, K. P. (2020). COVID-19 pneumonia and the appropriate use of
707 antibiotics. *The Lancet Global Health*, *8*(12), e1453-e1454. https://doi.org/10.1016/S2214-
708 109X(20)30444-7

709 Global Antibiotic Resistance Partnership (GARP)-India Working Group. (2011). Rationalizing
710 antibiotic use to limit antibiotic resistance in India+. *The Indian journal of medical*
711 *research*, *134*(3), 281.

712 Göbel, A., McArdell, C. S., Suter, M. J. F., & Giger, W. (2004). Trace determination of
713 macrolide and sulfonamide antimicrobials, a human sulfonamide metabolite, and trimethoprim
714 in wastewater using liquid chromatography coupled to electrospray tandem mass
715 spectrometry. *Analytical Chemistry*, *76*(16), 4756-4764.

716 Gothwal, R., & Shashidhar. (2017). Occurrence of high levels of fluoroquinolones in aquatic
717 environment due to effluent discharges from bulk drug manufacturers. *Journal of Hazardous,*
718 *Toxic, and Radioactive Waste*, *21*(3), 05016003.

719 Government of Bihar (2021), *Management of* COVID-19 *cases in Bihar.*
720 https://state.bihar.gov.in/health/cache/19/17-Jun-21/SHOW_DOCS/74(H.S)%20-
721 %2021.04.2021%20(1).pdf (accessed 10 May 2021).

722 Government of India, Aarogya setu mobile app. https://www.mygov.in/aarogya-setu-app/
723 (accessed 1 July 2021).

724 Government of Kerala (2018). Kerala Antimicrobial Resistance Strategic Action Plan One
725 health response to AMR containment. https://cdn.who.int/media/docs/default-
726 source/searo/india/antimicrobial-resistance/karsap-
727 keralaantimicrobialresistancestrategicactionplan.pdf?sfvrsn=ccaa481a_2 (Accessed on 16
728 October 2021).

729 Government of Madhya Pradesh (2019). Madhya Pradesh State Action Plan to Combat
730 Antimicrobial Resistance in Delhi. https://cdn.who.int/media/docs/default-
731 source/searo/india/antimicrobial-resistance/mp-state-action-plan-for-containment-of-
732 antimicrobial-resistance-final.pdf?sfvrsn=a06ee216_2 (Accessed on 16 October 2021).

733 Government of Maharashtra (2020), Standard Treatment Protocol for COVID-19.
734 https://www.nmcnagpur.gov.in/assets/250/2020/07/mediafiles/22_July_2020_Standard_Treat
735 ment_Protocol_Revision_4.pdf (accessed 10 May 2021).

736 Government of NCT of Delhi (2020). State Action Plan to Combat Antimicrobial Resistance
737 in Delhi. https://cdn.who.int/media/docs/default-source/searo/india/antimicrobial-
738 resistance/sapcard-final.pdf?sfvrsn=83eb02f4_2 (Accessed on 16 October 2021).

739 Health and Family welfare department. Government of West Bengal. (2021), *Top sheet for the*
740 *management of COVID-19 patients*.
741 https://www.wbhealth.gov.in/uploaded_files/corona/Top_Sheet_for_Covid-19_with_sig.pdf
742 (accessed 10 May 2021).

743 Hughes, S., Troise, O., Donaldson, H., Mughal, N., & Moore, L. S. (2020). Bacterial and fungal
744 coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK
745 secondary-care setting. *Clinical Microbiology and Infection*, *26*(10), 1395-1399.
746 https://doi.org/10.1016/j.cmi.2020.06.025

747 Huijbers, P. M., Blaak, H., de Jong, M. C., Graat, E. A., Vandenbroucke-Grauls, C. M., & de
748 Roda Husman, A. M. (2015). Role of the environment in the transmission of antimicrobial
749 resistance to humans: a review. *Environmental science & technology*, *49*(20), 11993-12004.

750 Human pharmaceuticals, hormones and fragrances. In: Ternes, T., Joss, A. (Eds.), The
751 Challenge of Micropollutants in Urban Water Management. IWA Publishing.
752 https://doi.org/10.2166/9781780402468.

753 IS10500, B. I. S. (2012). Indian standard drinking water–specification (second
754 revision). *Bureau of Indian Standards (BIS), New Delhi*. http://cgwb.gov.in/Documents/WQ-
755 standards.pdf (accessed 14 July 2021).

756 Jain, V. K., Iyengar, K. P., & Vaishya, R. (2021). Differences between First wave and Second
757 wave of COVID-19 in India. *Diabetes & metabolic syndrome*, *15*(3), 1047–1048.
758 https://doi.org/10.1016/j.dsx.2021.05.009

759 Jin, Y. H., Cai, L., Cheng, Z. S., Cheng, H., Deng, T., Fan, Y. P., ... & Wang, X. H. (2020). A
760 rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV)
761 infected pneumonia (standard version). *Military Medical Research*, *7*(1), 1-23.
762 https://doi.org/10.1186/s40779-020-0233-6

763 Kampmeier, S., Tönnies, H., Correa-Martinez, C. L., Mellmann, A., & Schwierzeck, V. (2020).
764 A nosocomial cluster of vancomycin resistant enterococci among COVID-19 patients in an
765 intensive care unit. *Antimicrobial Resistance & Infection Control*, *9*(1), 1-6.
766 https://doi.org/10.1186/s13756-020-00820-8

767 Kaul, G., Shukla, M., Dasgupta, A., & Chopra, S. (2019). Update on drug-repurposing: is it
768 useful for tackling antimicrobial resistance? https://doi.org/10.2217/fmb-2019-0122

769 Khurana, S., Singh, P., Sharad, N., Kiro, V. V., Rastogi, N., Lathwal, A., ... & Mathur, P.
770 (2021). Profile of co-infections & secondary infections in COVID-19 patients at a dedicated
771 COVID-19 facility of a tertiary care Indian hospital: Implication on antimicrobial
772 resistance. *Indian journal of medical microbiology*, *39*(2), 147-153.
773 https://doi.org/10.1016/j.ijmmb.2020.10.014

774 Klein, E. Y., Van Boeckel, T. P., Martinez, E. M., Pant, S., Gandra, S., Levin, S. A., ... &
775 Laxminarayan, R. (2018). Global increase and geographic convergence in antibiotic
776 consumption between 2000 and 2015. *Proceedings of the National Academy of*
777 *Sciences*, *115*(15), E3463-E3470. https://doi.org/10.1073/pnas.1717295115

778 Koehler, P., Cornely, O. A., Böttiger, B. W., Dusse, F., Eichenauer, D. A., Fuchs, F., ... &
779 Shimabukuro-Vornhagen, A. (2020). COVID-19 associated pulmonary
780 aspergillosis. *Mycoses*, *63*(6), 528-534. https://doi.org/10.1111/myc.13096

781 Kumar, M., Dhangar, K., Thakur, A. K., Ram, B., Chaminda, T., Sharma, P., ... & Barcelo, D.
782 (2021). Antidrug Resistance in the Indian Ambient Waters of Ahmedabad during the COVID-

19 Pandemic. *Journal of Hazardous Materials*, 126125. https://doi.org/10.1016/j.jhazmat.2021.126125

Langford, B. J., So, M., Raybardhan, S., Leung, V., Soucy, J. P. R., Westwood, D., ... & MacFadden, D. R. (2021). Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. *Clinical Microbiology and Infection*. https://doi.org/10.1016/j.cmi.2020.12.018

Lansbury, L., Lim, B., Baskaran, V., & Lim, W. S. (2020). Co-infections in people with COVID-19: a systematic review and meta-analysis. https://doi.org/10.1016/j.jinf.2020.05.046

Larsson, D. J., de Pedro, C., & Paxeus, N. (2007). Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *Journal of hazardous materials*, *148*(3), 751-755. https://doi.org/10.1016/j.jhazmat.2007.07.008

Li, L. G., Xia, Y., & Zhang, T. (2017). Co-occurrence of antibiotic and metal resistance genes revealed in complete genome collection. *The ISME journal*, *11*(3), 651-662. https://doi.org/10.1038/ismej.2016.155

Lindberg, R. H., Wennberg, P., Johansson, M. I., Tysklind, M., & Andersson, B. A. (2005). Screening of human antibiotic substances and determination of weekly mass flows in five sewage treatment plants in Sweden. *Environmental science & technology*, *39*(10), 3421-3429. https://doi.org/10.1021/es048143z

Lindström, A., Buerge, I. J., Poiger, T., Bergqvist, P. A., Müller, M. D., & Buser, H. R. (2002). Occurrence and environmental behavior of the bactericide triclosan and its methyl derivative in surface waters and in wastewater. *Environmental science & technology*, *36*(11), 2322-2329.

López-Serna, R., Jurado, A., Vázquez-Suñé, E., Carrera, J., Petrović, M., & Barceló, D. (2013). Occurrence of 95 pharmaceuticals and transformation products in urban groundwaters

805 underlying the metropolis of Barcelona, Spain. *Environmental Pollution*, *174*, 305-315.
806 https://doi.org/10.1016/j.envpol.2012.11.022

807 Mahmood, A. R., Al-Haideri, H. H., & Hassan, F. M. (2019). Detection of antibiotics in
808 drinking water treatment plants in Baghdad City, Iraq. *Advances in Public Health*, *2019*.
809 https://doi.org/10.1155/2019/7851354

810 Mahoney, A. R., Safaee, M. M., Wuest, W. M., & Furst, A. L. (2021). The silent pandemic:
811 Emergent antibiotic resistances following the global response to SARS-CoV-2. *Iscience*,
812 102304. https://doi.org/10.1016/j.isci.2021.102304

813 Maillard, J. Y. (2007). Bacterial resistance to biocides in the healthcare environment: should it
814 be of genuine concern?. *Journal of Hospital Infection*, *65*, 60-72.
815 https://doi.org/10.1016/S0195-6701(07)60018-8

816 Majewsky, M., Wagner, D., Delay, M., Bräse, S., Yargeau, V., & Horn, H. (2014).
817 Antibacterial activity of sulfamethoxazole transformation products (TPs): general relevance
818 for sulfonamide TPs modified at the para position. *Chemical research in toxicology*, *27*(10),
819 1821-1828.

820 Marathe, N. P., Regina, V. R., Walujkar, S. A., Charan, S. S., Moore, E. R., Larsson, D. J., &
821 Shouche, Y. S. (2013). A treatment plant receiving waste water from multiple bulk drug
822 manufacturers is a reservoir for highly multi-drug resistant integron-bearing bacteria. *PLoS*
823 *One*, *8*(10), e77310. https://doi.org/10.1371/journal.pone.0077310

824 Marcinek, H., Wirth, R., Muscholl-Silberhorn, A., & Gauer, M. (1998). *Enterococcus faecalis*
825 gene transfer under natural conditions in municipal sewage water treatment plants. *Applied and*
826 *Environmental Microbiology*, *64*(2), 626-632. https://doi.org/10.1128/AEM.64.2.626-
827 632.1998

McClellan, K., & Halden, R. U. (2010). Pharmaceuticals and personal care products in archived US biosolids from the 2001 EPA national sewage sludge survey. *Water research*, *44*(2), 658-668. https://doi.org/10.1016/j.watres.2009.12.032

Memish, Z. A., Perlman, S., Van Kerkhove, M. D., & Zumla, A. (2020). Middle East respiratory syndrome. *The Lancet*, *395*(10229), 1063-1077. https://doi.org/10.1016/S0140-6736(19)33221-0

Ministry of Health & Family Welfare (MoHFW) - Government of India Guidelines on Clinical Management of COVID-19 (2020). https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf (accessed 10 May 2021).

Ministry of Health & Family Welfare (MoHFW), Government of India. Clinical guidance for management of adult COVID-19 patients (2021). https://www.icmr.gov.in/pdf/covid/techdoc/COVID_Management_Algorithm_17052021.pdf (accessed 10 May 2021).

Miranda, C. D., & Castillo, G. (1998). Resistance to antibiotic and heavy metals of motile aeromonads from Chilean freshwater. *Science of the total environment*, *224*(1-3), 167-176. https://doi.org/10.1016/S0048-9697(98)00354-4

Morens, D. M., Taubenberger, J. K., & Fauci, A. S. (2008). Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *The Journal of infectious diseases*, *198*(7), 962–970. https://doi.org/10.1086/591708

Moretto, F., Sixt, T., Devilliers, H., Abdallahoui, M., Eberl, I., Rogier, T., ... & Piroth, L. (2021). Is there a need to widely prescribe antibiotics in patients hospitalized with COVID-

19?. *International Journal of Infectious Diseases*, *105*, 256-260. https://doi.org/10.1016/j.ijid.2021.01.051

Murray, A. K. (2020). The novel coronavirus COVID-19 outbreak: global implications for antimicrobial resistance. *Frontiers in microbiology*, *11*, 1020. https://doi.org/10.3389/fmicb.2020.01020

Mustafa, L., Tolaj, I., Baftiu, N., & Fejza, H. (2021). Use of antibiotics in COVID-19 ICU patients. *The Journal of Infection in Developing Countries*, *15*(04), 501-505. https://doi.org/10.3855/jidc.14404

Nagpur Municipal Corporation (2021). Maharashtra COVID-19 task force recommendations for the management of hospitalised COVID-19 patients. https://www.nmcnagpur.gov.in/assets/250/2021/04/mediafiles/COVID_latest_guidelines.pdf (accessed 10 May 2021).

Nahar S (2020) Understanding How The Indian Pharmaceutical Industry Works – Part 2. https://www.alphainvesco.com/blog/understanding-how-the-indian-pharmaceutical-industry-works-part-2/ (accessed 10 May 2021).

Nehara, H. R., Puri, I., Singhal, V., Sunil, I. H., Bishnoi, B. R., & Sirohi, P. (2021). Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: Case series from the north-western part of India. *Indian Journal of Medical Microbiology*. https://doi.org/10.1016/j.ijmmb.2021.05.009

Neuman, H., Forsythe, P., Uzan, A., Avni, O., & Koren, O. (2018). Antibiotics in early life: dysbiosis and the damage done. *FEMS microbiology reviews*, *42*(4), 489-499. https://doi.org/10.1093/femsre/fuy018

873 Nordmann, P., Naas, T., & Poirel, L. (2011). Global spread of Carbapenemase-producing
874 Enterobacteriaceae. *Emerging infectious diseases*, *17*(10), 1791–1798.
875 https://doi.org/10.3201/eid1710.110655

876 Nori, P., Szymczak, W., Puius, Y., Sharma, A., Cowman, K., Gialanella, P., Fleischner, Z.,
877 Corpuz, M., Torres-Isasiga, J., Bartash, R., Felsen, U., Chen, V., & Guo, Y. (2020). Emerging
878 Co-Pathogens: New Delhi Metallo-beta-lactamase producing Enterobacterales Infections in
879 New York City COVID-19 Patients. *International journal of antimicrobial agents*, *56*(6),
880 106179. https://dx.doi.org/10.1016%2Fj.ijantimicag.2020.106179

881 O'Neill, J. (2014). Antimicrobial resistance. *Tackling a crisis for the health and wealth of*
882 *nations*. https://www.who.int/antimicrobial-resistance/news/amr-newsletter-no13-
883 july2016.pdf (Accessed: 17 October 2021)

884 Osei-Atweneboana, M. Y., Awadzi, K., Attah, S. K., Boakye, D. A., Gyapong, J. O., &
885 Prichard, R. K. (2011). Phenotypic evidence of emerging ivermectin resistance in Onchocerca
886 volvulus. *PLoS neglected tropical diseases*, *5*(3), e998.
887 https://doi.org/10.1371/journal.pntd.0000998

888 Poole K. (2005). Efflux-mediated antimicrobial resistance. *The Journal of antimicrobial*
889 *chemotherapy*, *56*(1), 20–51. https://doi.org/10.1093/jac/dki171

890 Porretta, A. D., Baggiani, A., Arzilli, G., Casigliani, V., Mariotti, T., Mariottini, F., ... &
891 Privitera, G. P. (2020). Increased risk of acquisition of New Delhi metallo-beta-lactamase-
892 producing carbapenem-resistant enterobacterales (NDM-CRE) among a cohort of COVID-19
893 patients in a teaching hospital in Tuscany, Italy. *Pathogens*, *9*(8), 635.
894 https://doi.org/10.3390/pathogens9080635

Posteraro, B., Torelli, R., Vella, A., Leone, P. M., De Angelis, G., De Carolis, E., ... & Fantoni, M. (2020). Pan-echinocandin-resistant *Candida glabrata* bloodstream infection complicating COVID-19: a fatal case report. *Journal of Fungi*, *6*(3), 163. https://doi.org/10.3390/jof6030163

Prakash, H., & Chakrabarti, A. (2021). Epidemiology of Mucormycosis in India. *Microorganisms*, *9*(3), 523. https://doi.org/10.3390/microorganisms9030523

Principi, N., & Esposito, S. (2020). Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. *The Lancet. Infectious diseases*, *20*(10), 1118. https://doi.org/10.1016/S1473-3099(20)30296-6

Rawlinson, W. D., Waliuzzaman, Z., Carter, I. W., Belessis, Y. C., Gilbert, K. M., & Morton, J. R. (2003). Asthma exacerbations in children associated with rhinovirus but not human metapneumovirus infection. *The Journal of infectious diseases*, *187*(8), 1314-1318. https://doi.org/10.1086/368411

Rawson, T. M., Ming, D., Ahmad, R., Moore, L., & Holmes, A. H. (2020). Antimicrobial use, drug-resistant infections and COVID-19. *Nature reviews. Microbiology*, *18*(8), 409–410. https://doi.org/10.1038/s41579-020-0395-y

Rawson, T. M., Moore, L. S., Zhu, N., Ranganathan, N., Skolimowska, K., Gilchrist, M., ... & Holmes, A. (2020). Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clinical Infectious Diseases*, *71*(9), 2459-2468.https://doi.org/10.1093/cid/ciaa530

Reinthaler, F. F., Posch, J., Feierl, G., Wüst, G., Haas, D., Ruckenbauer, G., ... & Marth, E. (2003). Antibiotic resistance of *E. coli* in sewage and sludge. *Water research*, *37*(8), 1685-1690. https://doi.org/10.1016/S0043-1354(02)00569-9

Ripa, M., Galli, L., Poli, A., Oltolini, C., Spagnuolo, V., Mastrangelo, A., ... & Vinci, C. (2021). Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. *Clinical Microbiology and Infection*, *27*(3), 451-457. https://doi.org/10.1016/j.cmi.2020.10.021

Rutgersson, C., Fick, J., Marathe, N., Kristiansson, E., Janzon, A., Angelin, M., ... & Larsson, D. J. (2014). Fluoroquinolones and qnr genes in sediment, water, soil, and human fecal flora in an environment polluted by manufacturing discharges. *Environmental science & technology*, *48*(14), 7825-7832. https://doi.org/10.1021/es501452a

Rutsaert, L., Steinfort, N., Van Hunsel, T., Bomans, P., Naesens, R., Mertes, H., ... & Van Regenmortel, N. (2020). COVID-19-associated invasive pulmonary aspergillosis. *Annals of Intensive Care*, *10*, 1-4. https://dx.doi.org/10.1186%2Fs13613-020-00686-4

Salehi, M., Ahmadikia, K., Badali, H., & Khodavaisy, S. (2020). Opportunistic fungal infections in the epidemic area of COVID-19: a clinical and diagnostic perspective from Iran. *Mycopathologia*, *185*(4), 607-611. https://doi.org/10.1007/s11046-020-00472-7

Satyanarayana, S., Kwan, A., Daniels, B., Subbaraman, R., McDowell, A., Bergkvist, S., ... & Pai, M. (2016). Use of standardised patients to assess antibiotic dispensing for tuberculosis by pharmacies in urban India: a cross-sectional study. *The Lancet Infectious Diseases*, *16*(11), 1261-1268.

Sen, M., Lahane, S., Lahane, T. P., Parekh, R., & Honavar, S. G. (2021). Mucor in a Viral Land: A Tale of Two Pathogens. *Indian journal of ophthalmology*, *69*(2), 244–252. https://doi.org/10.4103/ijo.IJO_3774_20

Sharifipour, E., Shams, S., Esmkhani, M., Khodadadi, J., Fotouhi-Ardakani, R., Koohpaei, A., ... & Golzari, S. E. (2020). Evaluation of bacterial co-infections of the respiratory tract in

940 COVID-19 patients admitted to ICU. *BMC infectious diseases*, *20*(1), 1-7.
941 https://doi.org/10.1186/s12879-020-05374-z

942 Sheikh, A; McMenamin, J; Taylor, B; Robertson, C. (2021). SARS-CoV-2 Delta VOC in
943 Scotland: demographics, risk of hospital admission, and vaccine effectiveness, *The lancet*,
944 https://doi.org/10.1016/S0140-6736(21)01358-1

945 Silva, J., Castillo, G., Callejas, L., López, H., & Olmos, J. (2006). Frequency of transferable
946 multiple antibiotic resistance amongst coliform bacteria isolated from a treated sewage effluent
947 in Antofagasta, Chile. *Electronic Journal of Biotechnology*, *9*(5), 0-0.

948 Singer, A. C., Howard, B. M., Johnson, A. C., Knowles, C. J., Jackman, S., Accinelli, C., ... &
949 Watts, C. (2008). Meeting report: risk assessment of Tamiflu use under pandemic
950 conditions. *Environmental health perspectives*, *116*(11), 1563-1567.
951 https://doi.org/10.1289/ehp.11310

952 Singh, A. K., Singh, R., Joshi, S. R., & Misra, A. (2021). Mucormycosis in COVID-19: A
953 systematic review of cases reported worldwide and in India. *Diabetes & Metabolic Syndrome:*
954 *Clinical Research & Reviews*. https://doi.org/10.1016/j.dsx.2021.05.019

955 Singh, S., Pal, N., Chander, J., Sardana, R., Mahajan, B., Joseph, N., ... & Ghosh, A. (2021).
956 Mucormycosis caused by *Syncephalastrum* spp.: clinical profile, molecular characterization,
957 antifungal susceptibility and review of literature. *Clinical Infection in Practice*, 100074.
958 https://doi.org/10.1016/j.clinpr.2021.100074

959 Sjölund, M., Bonnedahl, J., Hernandez, J., Bengtsson, S., Cederbrant, G., Pinhassi, J., ... &
960 Olsen, B. (2008). Dissemination of multidrug-resistant bacteria into the Arctic. *Emerging*
961 *infectious diseases*, *14*(1), 70.

962 Song, G., Liang, G., & Liu, W. (2020). Fungal co-infections associated with global COVID-
963 19 pandemic: a clinical and diagnostic perspective from China. *Mycopathologia*, 1-8.
964 https://doi.org/10.1007/s11046-020-00462-9

965 Soumet, C., Fourreau, E., Legrandois, P., & Maris, P. (2012). Resistance to phenicol
966 compounds following adaptation to quaternary ammonium compounds in Escherichia
967 coli. *Veterinary microbiology*, *158*(1-2), 147-152.

968 Sriram, A., Kalanxhi, E., Kapoor, G., Craig, J., Balasubramanian, R., Brar, S., Criscuolo, N.,
969 Hamilton, A., Klein, E., Tseng, K., Van Boeckel, T., Laxminarayan, R. (2021). State of the
970 world's antibiotics 2021: A global analysis of antimicrobial resistance and its drivers. Center
971 for Disease Dynamics, Economics & Policy, Washington DC. https://cddep.org/wp-
972 content/uploads/2021/02/The-State-of-the-Worlds-Antibiotics-2021.pdf (Acessed 02 October
973 2021).

974 Standard treatment protocol for COVID-19 Revision 4: 22-7 -2020. Government of
975 Maharashtra.
976 https://www.nmcnagpur.gov.in/assets/250/2020/07/mediafiles/22_July_2020_Standard_Treat
977 ment_Protocol_Revision_4.pdf (accessed 14 July 2021).

978 Sulis, G., Batomen, B., Kotwani, A., Pai, M., & Gandra, S. (2021). Sales of antibiotics and
979 hydroxychloroquine in India during the COVID-19 epidemic: An interrupted time series
980 analysis. *PLoS medicine*, *18*(7), e1003682. https://doi.org/10.1371/journal.pmed.1003682

981 Sutherland, C. J., Haustein, T., Gadalla, N., Armstrong, M., Doherty, J. F., & Chiodini, P. L.
982 (2007). Chloroquine-resistant Plasmodium falciparum infections among UK travellers
983 returning with malaria after chloroquine prophylaxis. *Journal of Antimicrobial*
984 *Chemotherapy*, *59*(6), 1197-1199. https://doi.org/10.1093/jac/dkm104

985 Tandon, S. (2020, July 12) Covid drives growth in germ-protection soaps category over beauty.
986 *Mint*. https://www.livemint.com/industry/retail/covid-drives-growth-in-anti-bacterial-soaps-
987 category-over-beauty-11594537156083.html (accessed 12 July 2021).

988 Taylor, N. G., Verner-Jeffreys, D. W., & Baker-Austin, C. (2011). Aquatic systems:
989 maintaining, mixing and mobilising antimicrobial resistance?. *Trends in ecology &*
990 *evolution*, *26*(6), 278-284. https://doi.org/10.1016/j.tree.2011.03.004

991 The Economic Times: Eight global pharmaceutical firms evince interest in India's plan to ramp
992 up API production: Mansukh Mandaviya (2020).
993 https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/eight-
994 global-pharmaceutical-firms-evince-interest-in-indias-plan-to-ramp-up-api-production-
995 mansukh-mandaviya/articleshow/76201809.cms?from=mdr (accessed 1 July 2021).

996 The Gazette of India. Ministry of Environment, Forest and Climate Change Notification
997 (2020). http://moef.gov.in/wp-content/uploads/2020/01/finalization.pdf (accessed 14 July
998 2021).

999 The Hans India. Pharma still pollutes Patancheru,
1000 2015. http://www.thehansindia.com/posts/index/Telangana/2015-11-28/Pharma-still-pollutes-
1001 Patancheru/189407. (accessed 14 July 2021).

1002 The Lancet (2021). India's COVID-19 emergency. *Lancet (London, England)*, *397*(10286),
1003 1683. https://doi.org/10.1016/S0140-6736(21)01052-7

1004 The Times of India: 37 pharma firms get Gujarat FDCA nod for azithromycin (2020).
1005 https://timesofindia.indiatimes.com/city/ahmedabad/37-pharma-firms-get-gujarat-fdca-nod-
1006 for-azithromycin/articleshow/75730482.cms (accessed 14 July 2021).

1007 Threedeach, S., Chiemchaisri, W., Watanabe, T., Chiemchaisri, C., Honda, R., & Yamamoto,
1008 K. (2012). Antibiotic resistance of *Escherichia coli* in leachates from municipal solid waste
1009 landfills: comparison between semi-aerobic and anaerobic operations. *Bioresource*
1010 *technology*, *113*, 253-258. https://doi.org/10.1016/j.biortech.2012.01.086

1011 Vaidyanathan, G. (2021). Coronavirus variants are spreading in India—what scientists know
1012 so far. *Nature*, *593*, 321. (accessed 1 July 2021).

1013 Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., ...
1014 & Laxminarayan, R. (2015). Global trends in antimicrobial use in food animals. *Proceedings*
1015 *of the National Academy of Sciences*, *112*(18), 5649-5654.
1016 https://doi.org/10.1073/pnas.1503141112

1017 Velpandian, T., Halder, N., Nath, M., Das, U., Moksha, L., Gowtham, L., & Batta, S. P. (2018).
1018 Un-segregated waste disposal: an alarming threat of antimicrobials in surface and ground water
1019 sources in Delhi. *Environmental Science and Pollution Research*, *25*(29), 29518-29528.
1020 https://doi.org/10.1007/s11356-018-2927-9

1021 Vijay, S., Bansal, N., Rao, B. K., Veeraraghavan, B., Rodrigues, C., Wattal, C., ... & Walia, K.
1022 (2021). Secondary Infections in Hospitalized COVID-19 Patients: Indian Experience. *Infection*
1023 *and drug resistance*, *14*, 1893. https://dx.doi.org/10.2147%2FIDR.S299774

1024 Voumard, M., Venturelli, L., Borgatta, M., Croxatto, A., Kasas, S., Dietler, G., ... & von
1025 Gunten, U. (2020). Adaptation of *Pseudomonas aeruginosa* to constant sub-inhibitory
1026 concentrations of quaternary ammonium compounds. *Environmental Science: Water Research*
1027 *& Technology*, *6*(4), 1139-1152. https://doi.org/10.1039/C9EW01056D

1028 Waghamare, R. N., Paturkar, A. M., Vaidya, V. M., Zende, R. J., Kumar, A., & Bedi, J. S.
1029 (2020). Screening of antimicrobial residues and confirmation of doxycycline in samples

collected from chicken farms and processing units located around Mumbai, India. *Indian Journal of Animal Research*, *54*(11), 1415-1421. http://dx.doi.org/10.18805/ijar.B-3899

Walia, K., Madhumathi, J., Veeraraghavan, B., Chakrabarti, A., Kapil, A., Ray, P., ... & Ohri, V. C. (2019). Establishing antimicrobial resistance surveillance & research network in India: journey so far. *The Indian journal of medical research*, *149*(2), 164. https://dx.doi.org/10.4103%2Fijmr.IJMR_226_18

Wang, L., Amin, A. K., Khanna, P., Aali, A., McGregor, A., Bassett, P., & Gopal Rao, G. (2021). An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London. *Journal of Antimicrobial Chemotherapy*, *76*(3), 796-803. https://doi.org/10.1093/jac/dkaa475

Watkinson, A. J., Murby, E. J., Kolpin, D. W., & Costanzo, S. D. (2009). The occurrence of antibiotics in an urban watershed: from wastewater to drinking water. *Science of the total environment*, *407*(8), 2711-2723.

Weekly epidemiological update on COVID-19 - 13 July 2021. World Health Organisation (WHO) (2020). https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-july-2021 (accessed 15 July 2021).

Wheeler, E., Hong, P. Y., Bedon, L. C., & Mackie, R. I. (2012). Carriage of antibiotic-resistant enteric bacteria varies among sites in Galapagos reptiles. *Journal of Wildlife Diseases*, *48*(1), 56-67.

Wilson, D. C., Rodic, L., Modak, P., Soos, R., Carpintero, A., Velis, K., ... & Simonett, O. (2015). *Global waste management outlook*. UNEP.. https://doi.org/10.18356/765baec0-en.

World Health Organization (WHO), World malaria report 2018. https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf (accessed 13 July 2021).

Wu, D., Chen, G., Zhang, X., Yang, K., & Xie, B. (2017). Change in microbial community in landfill refuse contaminated with antibiotics facilitates denitrification more than the increase in ARG over long-term. *Scientific reports*, *7*(1), 1-9. https://doi.org/10.1038/srep41230

Zhang, S., Han, B., Gu, J., Wang, C., Wang, P., Ma, Y., ... & He, Z. (2015). Fate of antibiotic resistant cultivable heterotrophic bacteria and antibiotic resistance genes in wastewater treatment processes. *Chemosphere*, *135*, 138-145. https://doi.org/10.1016/j.chemosphere.2015.04.001

Zhao, H., Zhou, J. L., & Zhang, J. (2015). Tidal impact on the dynamic behavior of dissolved pharmaceuticals in the Yangtze Estuary, China. *Science of the Total Environment*, *536*, 946-954. https://doi.org/10.1016/j.scitotenv.2015.06.055

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet*, *395*(10229), 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3