



# Potential ways to address antimicrobial resistance across India and wider exacerbated by COVID-19

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Rising rates of antimicrobial resistance (AMR) are a concern across all countries as AMR increases morbidity, mortality and costs (Cassini *et al.*, 2019, Founou *et al.*, 2017, Godman *et al.*, 2021a, Haque and Godman, 2021a, Hofer, 2019, Shrestha *et al.*, 2018, Swaminathan *et al.*, 2017). The World Bank in 2017 believed even in a low-AMR scenario, the loss on output as a result of AMR across the world could exceed US\$1 trillion annually after 2030 unless addressed, which is equivalent to 3.8% of annual Gross Domestic Product (GDP) (World Bank, 2017). In addition, the overall costs of AMR appreciably exceed those of any of the antibiotics prescribed or dispensed (Shrestha *et al.*, 2018). It is also estimated that in India there will be more than two million deaths a year due to AMR by 2050 unless the factors causing AMR, including excessive and inappropriate use of antibiotics, are addressed (Chandra *et al.*, 2020).

The concerns with rising AMR rates have resulted in multiple activities by the World Health Organization (WHO) and others, including the development of national action plans (NAP) as well as the classification of antibiotics into Access, Watch, or Reserve (AWaRe) antibiotics in the WHO Essential Medicines List (EML), to guide and assess the quality of antimicrobial utilization (Gandra and Kotwani, 2019, Rogers Van Katwyk *et al.*, 2019, Saleem *et al.*, 2020, Seale *et al.*, 2017, Sharland *et al.*, 2019, Skosana *et al.*, 2021, World Health Organization, 2015, World Health Organization, 2018). India is no exception. National activities include instigating AMR surveillance networks in 2013, launching national treatment guidelines directing antimicrobial use in infectious diseases in 2016 and publishing its own NAP on AMR in 2017 (Chandra *et al.*, 2020, Government of India, 2017, National Centre for Disease Control, 2016, Swaminathan *et al.*, 2017). More recent initiatives in India include the introduction of national guidelines on Infection, Prevention and Control among healthcare facilities in 2020 as well as encouraging antimicrobial stewardship programs (ASPs) via a series of training workshops (Ministry of Health and Family Welfare 2020, Ministry of Health and Family Welfare, 2021a).

These programs are seen as essential given current concerns with AMR rates in India exacerbated by the current consumption of antimicrobials in India being among the highest in the world (Gandra and Kotwani, 2019). ASPs have been successful in hospitals even in low- and middle-income countries (LMICs), with their greater pressure on resources (Cox *et al.*, 2017), to improve antibiotic use. This includes programs to stop the prolonged administration of antibiotics to prevent surgical site infections as well as other targets (Ahmed *et al.*, 2018, Akpan, 2020; Godman *et al.*, 2021a, Majumder *et al.*, 2020, Mwita *et al.*, 2021, Nathwani *et al.*, 2019). We are

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also seeing successful programs introduced in ambulatory care, including LMICs, to reduce unnecessary prescribing and dispensing of antibiotics for essentially viral infections such as respiratory tract infections (Godman *et al.*, 2021a, Godman *et al.*, 2020a, Haque and Godman, 2021b). However, multiple activities are still needed given continual concerns with AMR rates and the lack of new antibiotics being developed (O'Neill, 2015).

The COVID-19 pandemic has further exacerbated the inappropriate use of antimicrobials across countries (Langford *et al.*, 2021). This includes the increasing use of hydroxychloroquine among countries following the initial hype, leading to shortages, price rises and deaths (Abena *et al.*, 2020, Haque *et al.*, 2021a, Haque *et al.*, 2021b, Sefah *et al.*, 2021). However, this was not the case in ambulatory care in countries where there were regulations outlawing the purchasing of antibiotics without a prescription and these were being followed, including Namibia and Vietnam, or where pharmacists in dispensaries provided appropriate guidance on managing COVID-19 including symptomatic relief such as Kenya (Godman *et al.*, 2020b, Kibuule *et al.*, 2021, Opanga *et al.*, 2021). This was encouraging as the well-constructed Solidarity (WHO) and UK Recovery trials showed no clinical benefit from using hydroxychloroquine in the management of patients with COVID-19; consequently, no longer recommended (Abubakar *et al.*, 2021, Horby *et al.*, 2020, Rochwerg *et al.*, 2020, World Health Organization, 2020). Interestingly in India, sales of hydroxychloroquine peaked in March 2020 but slowed down thereafter as more clinical trial data became available (Sulis *et al.*, 2021).

There has also been increasing use of antibiotics including azithromycin across health care sectors and countries, including India, as a result of the pandemic (Langford *et al.*, 2021, Sulis *et al.*, 2021). Published studies have suggested that up to 70% or more of patients with COVID-19 received antibiotics as part of their management (Knight *et al.*, 2021, Langford *et al.*, 2021, Rawson *et al.*, 2020), with appreciable over-use also recorded in India (Gale and Shrivastava, 2021). This includes azithromycin (Sulis *et al.*, 2021), with such overuse of antimicrobials likely to drive up AMR rates (Hsu, 2020, Saini *et al.*, 2021). This is despite less than 10% of patients with COVID-19 appearing to have either bacterial or fungal infections (Hsu, 2020), with some studies suggesting as few as 3.2% of patients with COVID-19 warrant an antibiotic (Langford *et al.*, 2021, Sriram *et al.*, 2021). This is similar to the findings of Rajni *et al.* (2021), who found that out of 1578 COVID-19 positive patients that were admitted to their tertiary hospital in India over a 5-month period, only 9.4% of the blood cultures were positive out of the 158 blood cultures taken (Rajni *et al.*, 2021).

Potential ways forward in India and wider to reduce AMR include assessing the current situation regarding antimicrobial use in hospitals. Subsequently, using the findings to instigate appropriate ASPs in line with national recommendations. This strategy is motivated by the fact that whilst national guidelines advocate prudent use of antimicrobials among adult patients with suspected or actual COVID-19 in hospitals, there is currently a dearth of publications documenting their use among admitted patients in India. This includes assessing patient management, including antimicrobials, against national or local guidelines with only a limited number of patients likely to have either bacterial or fungal co-infections (Government of India, 2021, Rajni *et al.*, 2021, Langford *et al.*, 2021). This is a concern since, as mentioned, adherence to agreed guidelines is increasingly seen as good quality prescribing resulting in a reduction of inappropriate antibiotic utilization in hospitals (Campbell *et al.*, 2021, Godman *et al.*, 2021a, Mwita *et al.*, 2021, Versporten *et al.*, 2018).

However, we are aware that there can be secondary infections among patients admitted to hospitals in India with COVID-19, which requires active ASPs to monitor and improve their future outcomes as well as reduce resistance rates (Khurana *et al.*, 2021, Saini *et al.*, 2021). Overall though, in the study by Vijay *et al.* (2021), out of 17,534 admitted patients to hospitals in India, only 3.6% developed secondary fungal or bacterial infections (Vijay *et al.*, 2021). There has also been limited research to date regarding the management of children with COVID-19 admitted to hospitals in India, although guidelines have also been published (Ministry of Health and Family Welfare, 2021b, Sankar *et al.*, 2020). We are aware of the high use of antimicrobials among hospitalized children with COVID-19 in Bangladesh, and we will be investigating this further in India to provide future guidance (Nusrat *et al.*, 2021).

Instigating vaccination programs with effective vaccines, including booster doses, is also seen a critical step to reduce hospitalizations, as well as the unnecessary use of antimicrobials, in patients with COVID-19, given concerns with AMR rates in India (Lopez Bernal *et al.*, 2021a, Lopez Bernal *et al.*, 2021b, Iheanacho *et al.*, 2021, Majumder *et al.*, 2020). This builds on previous findings with other vaccines that reduced subsequent antimicrobial utilization and AMR (Buchy *et al.*, 2020, Godman *et al.*, 2021a, Jansen and Anderson, 2018, Lewnard *et al.*, 2020, Troisi *et al.*, 2020). However, there are real concerns with vaccine hesitancy towards COVID-19 vaccines across countries, including India, fueled by the spread of misinformation (Danabal *et al.*, 2021, Khan *et al.*, 2020, Sallam *et al.*, 2021, Wilson and Wiysonge, 2020). Overall vaccine hesitancy rates do appear to be higher in some high-income countries versus LMICs; however, this is not always the

case (Solís Arce *et al.*, 2021, Lazarus *et al.*, 2021). Consequently, it is critical that any misinformation regarding COVID-19 vaccines is rapidly addressed through various channels, including from Governments, healthcare associations and patient groups, with the positive help of social media messaging, harnessed to increase confidence and use of vaccines. This can include making vaccinations easy to access and inducing feelings of ownership among those vaccinated (Dai *et al.*, 2021). Alongside this, ensuring access to effective vaccines by making them free-of-charge (BBC News, 2021).

In ambulatory care, we have seen that multiple coordinated activities have reduced antimicrobial utilization as well as limited any increase among countries where there is already low antimicrobial utilization (Abilova *et al.*, 2018, Furst *et al.*, 2015, Bojanic *et al.*, 2018, Godman *et al.*, 2020b, Wilkinson *et al.*, 2018). This contrasts with Poland where the authorities and other groups have only instigated limited activities. This resulted in Poland having one of the highest rates of antibiotic consumption across Europe between 2007 and 2016 (Wojkowska-Mach *et al.*, 2018). Similarly, multiple activities including education, removal of licenses to practice, and potentially fines, have reduced the extent of inappropriate prescribing and self-purchasing of antibiotics without a prescription in numerous studies (Alrasheedy *et al.*, 2020, Godman *et al.*, 2020a, Godman *et al.*, 2021a, Godman *et al.*, 2021b, Haque and Godman, 2021b, Jacobs *et al.*, 2019). This is similar to the situation in other disease areas and circumstances providing direction to the Government in India and elsewhere (Godman *et al.*, 2021b, Godman, 2021, Godman *et al.*, 2021c, Kroon *et al.*, 2021).

In conclusion, we have seen that the inappropriate use of antimicrobials has risen across countries, including India, during the current COVID-19 pandemic. This urgently needs to be addressed to reduce current AMR rates and their impact on morbidity, mortality and costs. There are a number of coordinated strategies that key stakeholder groups, including Governments, can undertake to improve the future use of antimicrobials during pandemics, and other circumstances, to address concerns with rising AMR rates. Typically, multiple strategies have greater impact. Furthermore, effective programs to prevent vaccine-preventable diseases, as well as the associated reduction in antimicrobial use, should be expedited along with programs to reduce vaccine hesitancy in the community. These activities can build on agreed NAPs and other national activities to reduce AMR. We will continue to monitor the situation.

## CONFLICTS OF INTEREST

The authors declare they have no relevant conflicts of interest.

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