



# Impact of COVID-19 on Antimicrobial Resistance in Paediatric Population: a Narrative Review

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## Abstract

**Purpose of Review** Irrational use of antimicrobials has been reported in paediatric population during the COVID-19 time period. This may lead to potential development of antimicrobial resistance and increased morbidity and mortality among this vulnerable population. The purpose of this review is to ascertain the impact of COVID-19 pandemic on antimicrobial resistance among paediatrics and the possible strategies to minimize the menace of antimicrobial resistance.

**Recent Findings** Recent findings indicate that the COVID-19 pandemic has direct as well as indirect impact on the development of antimicrobial resistance among paediatric population.

**Summary** This review article shows the impact of COVID-19 on the development of antimicrobial resistance and strategies to prevent it with special reference to antimicrobial stewardship programmes among paediatric population.

**Keywords** Antimicrobials · Antimicrobial resistance · Paediatrics · COVID-19 · Antimicrobial stewardship · Antibiotics

## Abbreviations

AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
FDA	Food and Drug Administration
WHO	World Health Organization

PICU	Paediatric intensive care unit
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>

## Introduction

SARS-CoV-2 was discovered in November 2019 and it was declared a global pandemic by WHO in March 2020 [1]. Even though various syndromic manifestations were documented, comprehensive data about the impact of SARS-CoV-2 on the paediatric population (0–21 years) is missing. A relatively limited percentage of COVID-19 cases have been documented in this age group [2]. Children constitute about 1–3% of COVID-19 cases reported across the world, with substantially fewer critical incidence and mortality [3–6]. As per WHO, between December 2019 to September 2021, children under 5 years of age constituted 1.8% and 0.1% of the global cases and global deaths respectively, children aged 5 to 14 years represented 6.3% and 0.1% of global cases and deaths respectively and the adolescents between 10 and 24 years represented 14.5% and 0.4% of global cases and deaths respectively [7]. The incidence of SARS-CoV-2 in children is not a direct marker of vulnerability or spreading, because the anticipated incidence is dependent on

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exposure, susceptibility, the proportion and mixing rates among children, and the social distancing initiatives that restrict gathering [8]. Furthermore, the present illness categorization is based on radiologic diagnosis, which includes computed tomography (CT) scans [9].

As the world responds towards COVID-19, a greater implicit menace of antimicrobial resistance (AMR) is emerging, which is harming thousands of individuals across the globe. Considering SARS-CoV-2, a viral illness that is mild among children, it is indeed doubtful that a child having COVID-19 should be prescribed antimicrobials on a regular basis. During the COVID-19 pandemic as such, there are rising concerns about the pandemic's potential influence on antimicrobial usage patterns. Antimicrobial utilization in paediatric inpatients could be significantly impacted by the pandemic outbreak. Although the outbreak had only a few visible effects on children, improper prescriptions have the capacity to exacerbate an existing serious problem, namely antibiotic resistance [10, 11, 12•].

The aim of this review article is to explore the impact of COVID-19 on the usage of antimicrobials and the possible development of resistance in the paediatric population, and strategies to minimize antimicrobial resistance with special reference to antimicrobial stewardship programmes during the ongoing pandemic time period.

## Methods

Searches were carried out on the study objectives with the help of search engines: Google Scholar, PubMed/Medline and Scopus. The search items used were a compendium of keywords such as antimicrobials use in paediatrics and COVID-19, COVID-19 and antimicrobial resistance, antimicrobial stewardship and COVID-19. Additional keywords were used either alone or in combination with COVID-19 such as infection prevention and control, control strategies and antimicrobial stewardship.

The articles included in this narrative review are most recent after the COVID-19 pandemic. Earlier material as early as year 2015 is also included based on its requirement and relevance. Related journals and articles were searched and selected, and their references were set aside for further information collection. The findings from this search are discussed under different heads within the preview of selected objectives.

## Guidelines on Antimicrobial Prescribing

Various health organizations have developed guidelines on the clinical management of COVID-19 in both adult and paediatric populations. The WHO's interim guidelines

recommend that certain antimicrobials should not be administered as treatment or prophylaxis for COVID-19 outside of clinical trials [13••]. The National Institute of Health (NIH), Infectious Diseases Society of America (IDSA) and Michigan medicine guidelines are the other guidelines that recommend against antimicrobial use in COVID-19 patients. The antimicrobials that should not be used without any supportive evidence/or associated with potential harm include Hydroxychloroquine, Hydroxychloroquine with Azithromycin, Lopinavir/Ritonavir, Oseltamivir, Nitazoxanide, Baloxavir and Ribavirin [14••, 15, 16••].

## Effect of COVID-19 on Antimicrobial Resistance in Paediatrics

The impact of an uncontrolled infection on the society is already proved by the COVID-19 pandemic, which is comparable to what have been prophesied for AMR in several papers. One of the many results of the pandemic is the significant impact on AMR with changes in antimicrobial usage, healthcare behaviour and also infection-control strategies [17]. The impact of COVID-19 on antimicrobial resistance in paediatric population is shown in Fig. 1.

## In Clinical Settings

In a study conducted by Ashikkali et al. in Scotland, it was found that during the first wave of pandemic there was a noticeable reduction in paediatric emergency department (ED) visits and hospital admission of the paediatric population probably related to diminished general infection spread, restricted ED and also ED underuse because of parental worry of children being susceptible to SARS-CoV-2 [18]. In a research study conducted in the UK by Isba et al., it is revealed that according to regional records, the number of kids going to the paediatric emergency department has decreased by more than 30% by March 2020. This has undoubtedly contributed to preventing overcrowding and provided time for new health-protection plans to be implemented. While this change in behaviour reduced unnecessary ED visits, it could also place children with significant diseases requiring treatment at higher risk [19].

## On Antimicrobial Usage Pattern

A research study conducted in Spain by Velasco-Arnaiz et al. indicated that the use of antimicrobials was significantly higher, particularly in the paediatric intensive care units, during the first wave of COVID-19. The use of

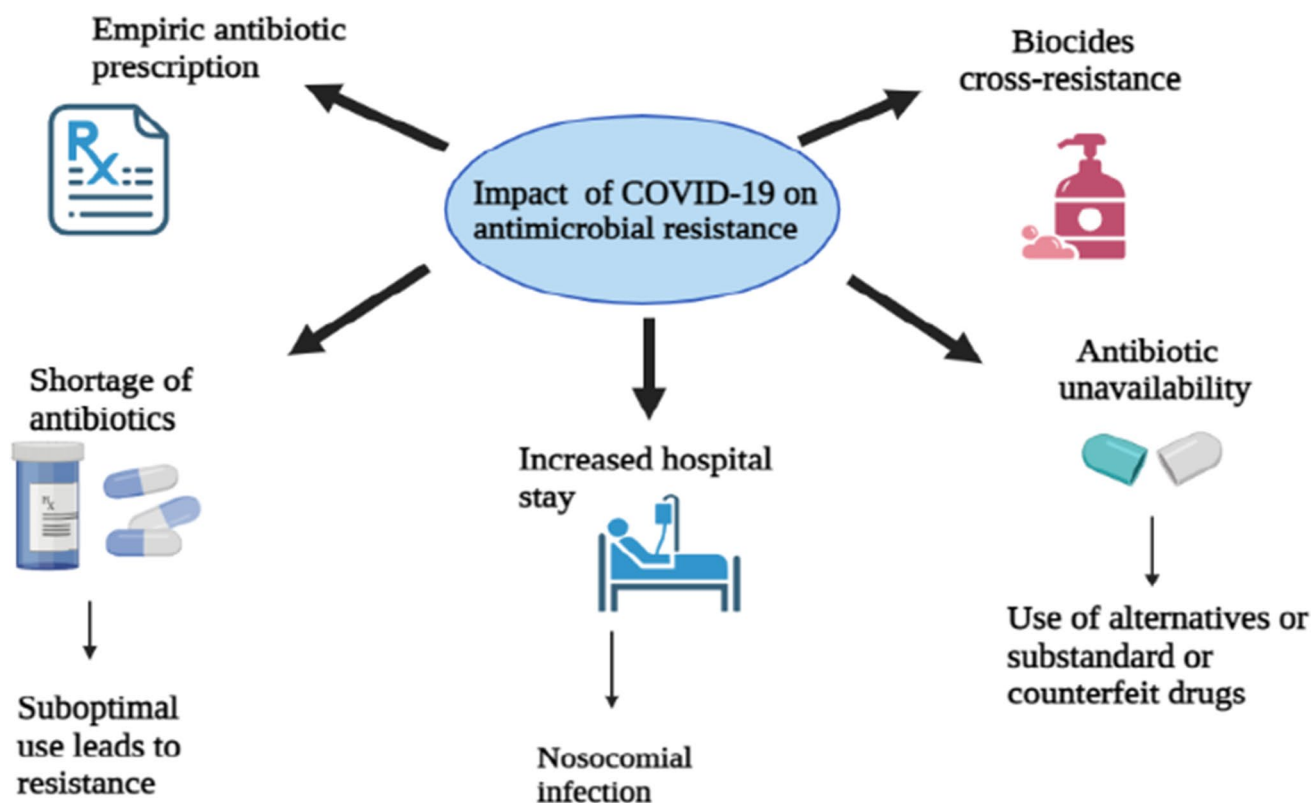


Fig. 1 Impact of COVID-19 on antimicrobial resistance in paediatric population

Azithromycin along with hydroxychloroquine increased during the same time period. Ceftriaxone and teicoplanin use in PICU doubled in April 2020 compared to April 2019. In non-PICU, the use of piperacillin-tazobactam and ciprofloxacin increased [12•, 20]. In another US-based study, researchers highlighted that infections were discovered in 31% of COVID-19 patients, and antimicrobials were provided to 56% of patients during hospitalization; however, 100% of patients who required ICU care were given antibiotics [21–23]. Antimicrobials commonly used in the paediatric population during COVID-19 are shown in Table 1.

The symptoms of COVID-19 infection resemble that of respiratory tract infections like pneumonia [24]. Thus, the improper diagnosis leads to empiric antibiotic prescribing that may include the prescribing of broad-spectrum antibiotics or commonly used narrow-spectrum antibiotics which further leads to increased risk of mortality because of inappropriate therapy [25••, 26]. Stewardship advice, which is based on susceptibility evidence, has an impact on clinicians' choice of antibiotic prescribing. Empiric therapy

aims to manage a wide range of suspected microorganisms. As a result, AMR influences the antimicrobial choice recommended to COVID-19 patients [25••, 27].

### On Antimicrobial Availability

In LMICs, economic impacts from COVID-19 regulations enhanced the demand of consumers for using OTC products, including unregulated antimicrobials, in an effort to cut costs on treatment. This increases the possibility of sub therapeutic medication dosages and antimicrobial course lengthening, as well as enhanced mortality [25••, 28•]. During the COVID-19 pandemic, there is the unavailability of recommended antimicrobials; thus, alternatives or substandard or counterfeit drugs may be overused. This further results in AMR due to suboptimal antibiotic use [25••, 29]. Due to COVID-19, in India and Pakistan, BCG vaccination coverage has indeed decreased. This might have disastrous repercussions for TB meningitis rates among children [25••, 30•, 31].

**Table 1** Antimicrobials used in paediatrics during COVID-19 [43–54]

Study design	Study title	Country	Target population	Antimicrobials used	Expected outcome	Reference
Case series	Early-onset symptomatic neonatal COVID-19 infection with high probability of vertical transmission	India	Neonate	Ampicillin, amoxicillin/clavulanate, meropenem, vancomycin	Shows the possibility for COVID-19 infection to spread directly from a symptomatic, RT-PCR negative but antibody-positive mother to a severe symptomatic, early-onset new-born infection	Kulkarni R et al. [43]
Case report	Case report of a neonate with high viral SARSCoV-2 loads and long-term virus shedding	Netherland	Neonate	Amoxicillin	According to the findings, new-borns may have a greater viral load of SARSCoV-2 and can spread the virus in their faeces for up to a month	Slaats MA et al. [44]
Case report	A Fatal Case of COVID-19 in an Infant with Severe Acute Malnutrition Admitted to a Paediatric Ward in Niger	Niger	Neonate	Ceftriaxone, gentamycin	Early diagnosis will contribute to improved patient care and hence prevent the transmission of the disease in the absence of a vaccine and appropriate therapy	Soumana A et al. [45]
Case report	Non-operative management of acute appendicitis in a pediatric patient with concomitant COVID-19 infection	USA	Early adolescence	Ceftriaxone, metronidazole	In the study they are able to properly cure the patient's acute appendicitis using a non-operative treatment plan	Jones BA et al. [46]
Case report	Novel coronavirus in a 15-day-old neonate with clinical signs of sepsis, a case report	Iran	Neonate	Vancomycin and amikacin	PCR testing should be done for a new-born if parents have a history of COVID-19	Kamali Aghdam M et al. [47]
Prospective study	Detectable SARS-CoV-2 viral RNA in faeces of three children during recovery period of COVID-19 pneumonia	China	Middle childhood	Ceftriaxone	This study shows the possibility of transmission of SARSCoV-2 through faecal-oral route in children	Zhang T et al. [48]
Case series	COVID-19 in Neonates and Infants: Progression and Recovery	NA	Neonates	Amoxicillin, cefotaxime and gentamicin	Neonates acquire SARSCoV-2 postnatally	Bandi S et al. [49]
Multicentre case series	Clinical and epidemiological characteristics of paediatric SARS-CoV-2 infections in China: A multicenter case series	China	Preadolescence	Azithromycin	Clinical and epidemiological characteristics of COVID-19 sufferers in children	Zhang C et al. [50]

**Table 1** (continued)

Study design	Study title	Country	Target population	Antimicrobials used	Expected outcome	Reference
Retrospective study	Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China	China	Preadolescence	Cefoperazone/sulbactam, meropenem, linezolid	The majority of cases were found to be in children under the age of three	Zheng F et al. [51]
Cross-sectional study	Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units	North America	Paediatric	Hydroxychloroquine, Azithromycin, Remdisivir	Children hospitalized to PICUs with diagnosed COVID-19: prehospital features, clinical trend and hospitalization results	Shekerdemian LS et al. [52]
Retrospective study	Coronavirus disease 2019 in children: Characteristics, antimicrobial treatment and outcomes	China	Preadolescence	Ribavirin, Arbidol, Oseltamivir, Antibacterial agents, Azithromycin	Antiviral treatment in children need to be considered	Peng H et al. [53]
Cross-sectional descriptive study	Clinical Profile, Hospital Course and Outcome of Children with COVID-19	North India	Infants Toddler Adolescence	Antibiotics, Azithromycin, Oseltamivir	Serious infection was observed in infants and with comorbidity	Nallasamy K et al. [54]

## Other Infections

Co-infections involving frequent pulmonary organisms are much more prominent in children compared to adults, and pneumococcus plays a significant role in the progression of lower respiratory tract infections related to paediatric COVID infection [32•]. The increased hospital stays because of COVID-19 hasten the peril of acquiring nosocomial infections to resistant pathogens (MRSA, *Candida auris*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) [25••, 33]. *Clostridioides difficile* infection (CDI) is one of the most severe HAIs, presenting a major health issue. However, there seems reduction in CDI reporting due to boosting of infection prevention strategies; moreover, many hospitals have reduced the efficacy of these strategies, raising the chances of hospital-acquired CDI. The reduction in *C. difficile* tests and rising usage of broad-spectrum antibiotics during the pandemic have aroused new concerns. Overuse of antibiotics and disinfectants may result in the emergence of resistant *C. difficile* variants [34•]. In a study conducted by Bhatt et al., secondary infections in COVID-19 patients have been reported. Among these, 91.4% were having bacterial infections and 5.5% had fungal infections. Patients with secondary blood-stream infections have more severe respiratory difficulty, as reflected by reduced oxygen saturation. These symptoms could be a result of bacterial or fungal sepsis compounded by severe COVID-19, or they could be a sign of COVID-19-related critical condition. Children with secondary infections and influenza have shown similar symptoms of respiratory distress and sepsis. In this condition, we could not neglect the use of antimicrobial agents [35•].

## Indirect Impact

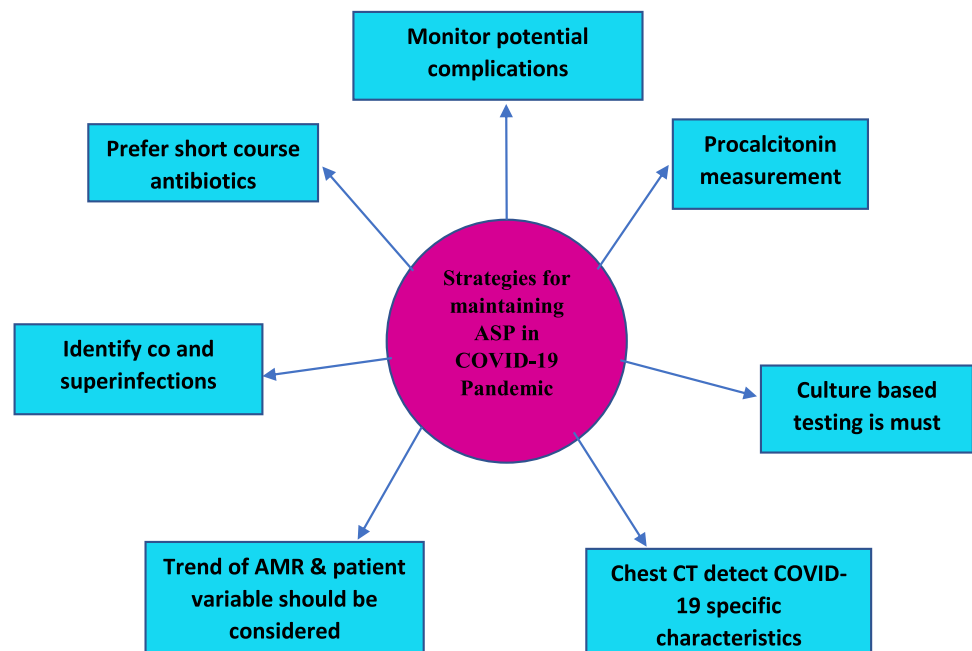
Attention is given to the immediate effects of the disease during the pandemic. Vulnerable children are subjected to poor treatment at home due to the limited access of healthcare facilities during the pandemic [36]. Inadequate immunisation is always a concern and during pandemics, it is easy to overlook this situation. This could put populations in danger of a vaccine-preventable illness outbreak [37, 38]. An indirect effect of COVID-19 is a surge in vaccine-preventable diseases and related issues that leads to elevated antimicrobial use and the likelihood of resistance [25••, 39, 40]. The economic ramifications of the disaster imply that the healthcare services that are already struggling to offer adequate access to antimicrobials may face new obstacles, and for those who are already poor, access to medications

might become much more difficult. This could lead to an elevation in mortality, and it has been linked to a greater incidence of avoidable diseases in children below the age of five, like community-acquired pneumonia. As a result, a combination of inadequate antibiotic usage and decreased accessibility can increase selection pressure in favour of AMR while also boosting mortality by an infection that could have been prevented [25••, 41]. The frequent use of biocides leads to the development of cross-resistance [42••].

## Antimicrobial Stewardship Programmes in Paediatrics

Substantial data suggests that antimicrobial stewardship programmes (ASPs) have a significant impact on antimicrobial use, even in children. The ASP is being considered as a reference for preparing and managing to the COVID-19 outbreak. Modifying clinical variables may have a negative impact on the quality of antibiotic prescriptions during pandemic. Revised COVID-19 protocols are constantly updated to reflect current findings, and earlier standards were adjusted to improve infection control. The pandemic does have the propensity to exert a large impact upon antimicrobial usage in paediatric population; paediatric ASP surveillance and remedies, minimum for the short terms, be essential in preserving the appropriateness of prescriptions [12•].

**Fig. 2** Strategies for maintaining ASP in COVID-19 pandemic [56•, 57]



## Strategies to Minimize Antibiotic Resistance

In low- and middle-income countries (LMICs), identifying bacterial pathogens seems difficult because there were no easily accessible and cost-effective diagnostic or biomarkers that may successfully distinguish between bacterial and viral infections. Due to the risk of COVID-19 spreading, there is expanding recognition of the relevance of antimicrobial stewardship programmes, as well as infection prevention and regulation measures [55]. Figure 2 shows the strategies for maintaining ASP during COVID-19 pandemic.

## Policy Level

In 2021, a policy for reducing AMR was created by the WHO. The purpose of the policy is to better understand how antimicrobial resistance develops and spreads, and also to design antimicrobial programmes, rationalize antimicrobial usage and foster the growth of newer, more effective antimicrobials. Improving infection prevention and control methods, as well as teaching, training, and motivating all parties on the rational use of antimicrobials. According to the WHO, approximately only half of the nations have basic processes and controls in place to ensure that the medications are administered safely [58••]. Adopting and executing national standard treatment recommendations, creating an essential drug list (EDL), and expanding immunisation coverage are all examples of national solutions.

## Organization Level

The most recent edition of WHO's interim guideline on the clinical management of COVID-19 includes antibiotic stewardship principles and specific recommendations. Until the signs and symptoms of infection are evident, antibiotic therapy is not suggested for individuals with mild or moderate infection [53]. According to the guidelines on management of COVID-19 in children (below 18 years) by Ministry of Health and Family Welfare, Government of India, antimicrobials should not be prescribed for treatment or prophylaxis in asymptomatic and mild cases; in moderate to severe cases, it should not be recommended unless there is clinical speculation of a superadded infection; and during septic shock, empirical antimicrobials (according to body weight) are commonly introduced to conceal all likely pathogenic organisms based on clinical assessment, patient immune status, local epidemiological studies and the hospital's antimicrobial policy [54].

## Hospital Level

The principles of ethical prescriptions and optimal use of antimicrobials, as well as effective diagnosis and treatment, and infection reduction and prevention, lead antimicrobial stewardship initiatives. During the COVID-19 outbreak, there are several issues that could affect antimicrobial stewardship activities and drive drug resistance [55]. Boosting clinical competence among health providers who treat COVID-19 patients with tailored training. Second, ensuring that vital health services are available, as well as a constant supply of high-quality and low-cost antimicrobials, such as antiretroviral and tuberculosis drugs, immunisations, COVID-19 testing turnaround time should be shortened, and biocides should be used with extreme caution for environmental and personal disinfection. There should be accurate and low-cost diagnostic assays that discriminate between bacterial and viral respiratory tract illnesses [48]. A procalcitonin-guided (PCT-guided) antimicrobial treatment plan has been shown to be effective in patients with pneumonia and bacteremia during clinical investigations. In order to improve antibiotic stewardship, hospital guidelines should include procalcitonin in their treatment policies [59•]. More recently, a multicenter, randomised controlled trial found that PCT-guided treatment reduced antimicrobial use better than the standard treatment. A subsequent study of the same data revealed that sequential assessments could reliably rule out early-onset sepsis [60•]. These initiatives would help to prevent the spread of drug-resistant illnesses and diseases,

which could trigger a new public health disaster. Even though procalcitonin measurement helps to reduce infections and antimicrobial use there is some inadequacy in identifying community-associated bacterial infections. The recommendations based on PCT should be individualized based on patient comorbidities and also depends on the physician [59•, 60•].

## Antimicrobial Stewardship Programmes During COVID-19

If left uncontrolled, the increased administration of antibiotics in response to COVID-19 will exacerbate the world's already-growing antimicrobial resistance problem. COVID-19 will remain a major issue due to uncertainty about SARS-CoV-2 resistance, the probability of cyclical outbreaks, and the shortage of a vaccine. This shifting environment necessitates the adaptation of antimicrobial stewardship (AMS) tactics.

The increased prevalence of AMR has prompted the creation of proposals to ensure that AMS, that has been one of few ways which has shown the highest success in reducing overuse of antibiotics and mishandling in adults, seems being an enticing alternative in children [56•]. Antibiotic stewardship has been introduced into hospital policies across the globe, with the aim to enhance antimicrobial treatment effectiveness [57].

Antimicrobial indications should be carefully stated, and only people who might be suspected of having a significant bacterial illness should be prescribed antibiotics. Early detection of SARS-CoV-2 using intensive testing could perhaps decrease needless antibiotic prescribing in resource-rich countries. Antiviral or immunomodulatory therapies during early course of infections may help to prevent infection advancement and ICU admissions, as well as lessen healthcare-related consequences and antimicrobial prescribing. Since the vaccine for SARS-CoV-2 is available, the most important AMS strategy for limiting antibiotic usage in the setting of COVID-19 was its prevention through immunisation, as with many other deadly viral diseases [58••, 61••, 62, 63]. Despite the fact that clearing out COVID-19 coinfection with bacterial or fungal infection could enhance antibiotic stewardship, diagnosing co or superinfections among COVID-19 sufferers seems difficult. Intrusive detection methods, including bronchoscopy and radiologic imaging, are limited due to the virus's tremendous infectivity, which can produce aerosols and expose healthcare professionals to the infection. This is exacerbated due to low responsiveness of standard identification tests in pinpointing the pathogen that cause respiratory problems; as a result, the administration of a

wide range of antibiotics may be unavoidable [64–68]. Antimicrobial policies should be stricter, with more awareness campaigns to educate health personnel and the general public about AMR. Biocides are used with caution for individual and environmental disinfection, and biocidal agents with no or minimal selection pressure for antibiotic resistance must be preferred. In order to avoid nosocomial infections in COVID-19 patients, strict infection–control methods should be undertaken [69]. Antimicrobial stewardship programmes are crucial parts of an effective COVID-19 approach, and strategies to enhance effective antimicrobial usage are widely advocated.

### COVID-19 Vaccination in Paediatrics

The juveniles are generally allotted in clinical studies only after proof of a favourable benefit–risk data in adults. Similarly, some of COVID-19 vaccines were first studied on adults (starting at 16 years) and then subsequently broadened to younger ones. In a study which includes 2260 subjects aged 12 to 15 years resulted in the sanction of Comirnaty, which was the first COVID-19 vaccine permitted in Western nations for population less than 16 years. Comirnaty clearance for usage was granted to adolescence (12–15 years) by FDA on May 10, 2021 [64, 65] and thereafter by the European Medicines Agency on May 28, 2021, following favourable appraisal of the relevant safety and efficacy findings for paediatrics [70, 71••, 72, 73]. On July 23, 2021, the European Medicines Agency’s human medicines committee (CHMP) suggested Spikevax authorisation can be extended to children of 12–17 years of age [74•, 75].

In children aged 5 to 11, COVID-19 immunisation plan comprising of two 10 µg doses of BNT162b2 given in 3 weeks’ interval have been proven to be acceptable, highly specific and effective (ClinicalTrials.gov identifier: NCT04816643; BioNTech and Pfizer funding) [76]. Despite many drugs, the dose of vaccine is determined by age of child on the day of vaccination rather than their bodyweight. If a child turns 11 to 12 years old in between the first and second doses, the latter dose of vaccine should be that for children aged 12 up [69, 77•, 78].

Adolescents (12–17 years) had slight to medium systemic and local responses in preauthorization trials of the Pfizer-BioNTech vaccine. In post authorization surveillance, myocarditis was found following vaccination with mRNA vaccines. In a study conducted in the USA, children aged 12–17 years frequently indicated local and systemic responses following vaccination with the Pfizer-BioNTech vaccine, particularly after second dose. A limited percentage of these symptoms are indicative of myocarditis [70]. In India until March 3, 2022, 5,50,25,490 children belonging

to the class 15–18 years received first dose and 2,87,35,449 received second dose of vaccination respectively [71••].

### Conclusion

COVID-19 outbreak has thrown light to inherent flaws in healthcare systems across the world. During COVID-19 outbreak, antibiotic usage in SARS-CoV-2 sufferers outpaced the rate of bacterial coinfections and subsequent illnesses, implying that antibiotics were prescribed inappropriately and excessively. Despite in places where AMS programmes had been in place for a long time, there have been flaws in how antibiotics were used during the crisis. One of the most effective methods to combat AMR is to focus in upgrading healthcare approaches and readiness for pandemics as well as similar infectious disease outbreaks. Improving the clinical competence among health professionals, maintaining access to key health facilities as well as a constant stock of high-quality and low-cost antimicrobials, vaccines, reducing COVID-19 testing turnaround time, use of biocides with prudence would aid in the prevention of drug-resistant illnesses and diseases. To set these protections, all stakeholders such as public health authorities, regulatory agencies, policymakers, scientific community and pharmaceutical companies must work together for better outcomes.

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### Declarations

**Conflict of Interest** The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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