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REVIEW

Role of Pharmacists in Antimicrobial Stewardship During COVID-19 Outbreak: A Scoping Review

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Abstract: Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, pharmacists have been on the front lines of health care, offering vital services. Consequently, the need for pharmacists to support an effective antibiotic stewardship (AMS) program during the COVID-19 outbreak has become increasingly evident. This scoping review was performed to examine related articles in 2020–2022 published in the Scopus, SAGE, and Cochrane databases with the keywords "Pharmacist" and "Antibiotic Stewardship" and "COVID-19". The inclusion criteria were full-text articles written in English. A total of 15 articles were included in this review to describe the role of pharmacists in AMS during the COVID-19 outbreak. In general, pharmacists are responsible for identifying and treating patients during pandemics, ensuring the continued supply and accessibility of medications, promoting health policies, and monitoring antibiotic use for COVID-19 cases and co-infections. At the hospital, as the most significant element for pharmacists on the AMS team, the apparent change is demonstrated in educating patients on telehealth services, clarifying misconceptions about treatments and antibiotic consumption, as well as taking a leadership position to establish local guidelines for the COVID-19 treatment protocol. Pharmacists have an important role in the AMS program, and the COVID-19 pandemic was perceived as a highlight their importance. Therefore, their work with the AMS program needs to be improved as they learn to extend their role in telehealth services, educate and clarify the misconceptions about COVID-19 treatments and other antibiotic consumption in the community, inventory control the COVID-19 drug, antibiotics, and vaccine, as well as take the lead in establishing local guidelines on antibiotic consumption during the pandemic outbreak.

Keywords: pharmacists, antibiotic stewardship, COVID-19

Introduction

The global impact of the Coronavirus Disease 2019 (COVID-19) pandemic has been devastating, and the number of hospitalized patients has overwhelmed healthcare facilities worldwide.[1] It has also put unprecedented pressure on global healthcare systems, culminating in considerable economic disruption and shortages of personal protective equipment (PPE) and medicines, as well as the loss of life.[2,3]

Covid-19 is a virus that causes sickness in numerous organ systems, and respiratory symptoms such as fever and cough are frequently reported, and in severe cases, pneumonia, as well as respiratory failure, might develop.[4] In primary care, antibiotic therapy for respiratory infections is usually empirical, based on clinical judgment rather than microbiological results, and is routinely recommended for community-acquired pneumonia and "chest infection". Consequently, symptoms linked to COVID-19 might elicit antibiotic prescriptions. Azithromycin, ceftriaxone, moxifloxacin, meropenem and piperacillin/tazobactam remained the top five most frequently prescribed antibiotics for COVID-19 patients.[5]

As health practitioners, pharmacists can play a crucial part in the pandemic, interact directly with the public, continue to care for patients with chronic illnesses, work in hospital pharmacies, and offer COVID-19 patients pharmaceutical services. Participate in antibiotic stewardship initiatives as well. The Antimicrobial Stewardship (AMS) program is

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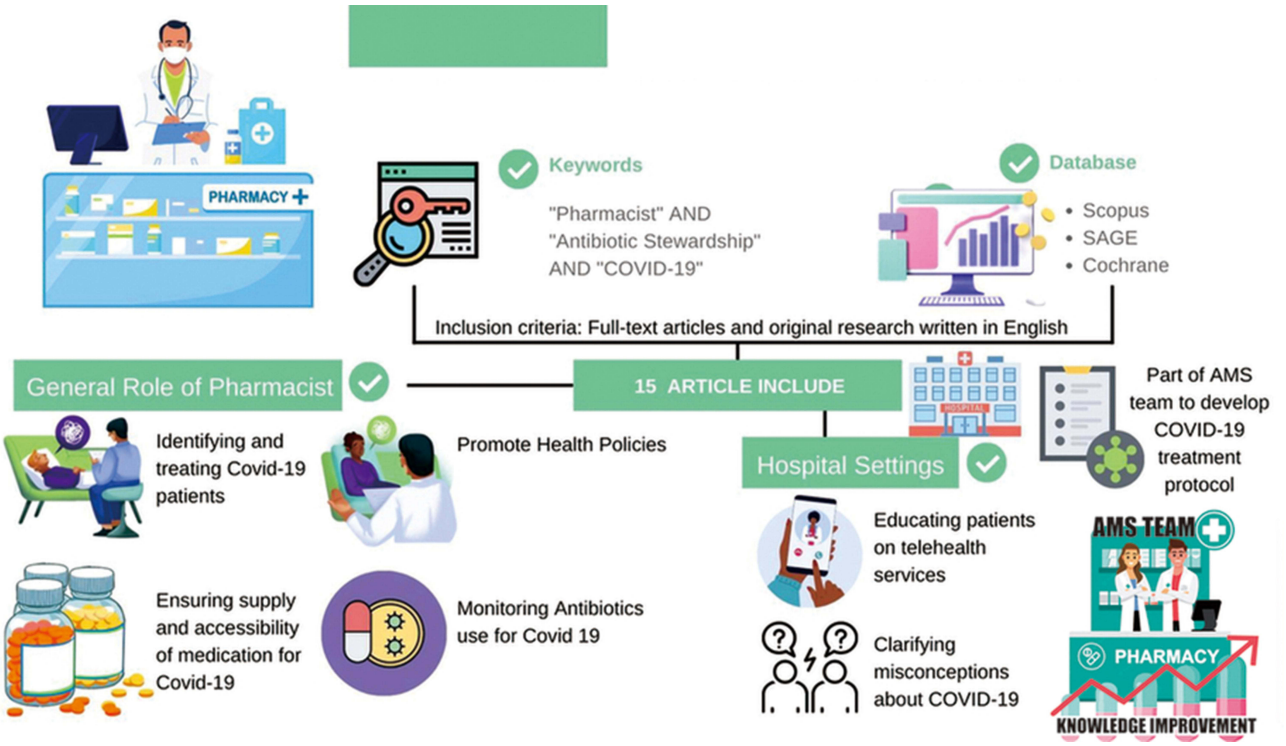
Graphical Abstract



a platform for an organization or healthcare system to promote and watch how antibiotics are used in the future to keep them working.[6] Its major goal is to improve the safety and quality of patient treatment.[7] During the COVID-19 pandemic, this program is critical to optimize treatment while limiting the possible risk associated with antibiotic use for patient and the community. For a variety of reasons, AMS has become a victim of COVID-19,[8] the pandemic's far-reaching changes in clinical service delivery disrupted programs, while other contributing factors include disruptions in global antibiotic supply chains and a tendency to over-treat patients with antibiotics.[9]

Due to severe illness and lengthy hospitalizations, patients with COVID-19 might develop secondary nosocomial infections with bacteria. Antibiotics are widely thought to be misused, presumably due to the difficulties in recognizing concurrent or secondary bacterial illnesses.[10] Empirical and pathogen-directed broad-spectrum antibiotics might be given to patients,[11] therefore, antibiotics must be evaluated in the context of antimicrobial resistance (AMR) when prescribed for a viral illness, even when there is no standard of therapy.

With the urgent need to treat a disease whose course is being scientifically investigated in real-time, the present pandemic has the potential to increase AMR.[12] It has also become a priority because microorganisms that cause resistant infections thrive in hospitals and medical facilities, placing all patients at risk, regardless of their medical condition severity.[13] This is expected to make COVID-19 management more perplexed. Therefore, this scoping review aims to provide an overview of AMS, especially about pharmacist role in the pandemic era including antibiotics use, monitoring, barriers, and ancillary roles to provide improved antimicrobial stewardship.

Methods

Search Strategy and Eligibility Criteria

The selection for the related articles in 2020–2022 was published in Scopus, SAGE, and Cochrane databases with keywords "Pharmacist" AND "Antibiotic Stewardship" AND "COVID-19" to conduct a scoping review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (see Figure 1).[14] We searched for articles on the role of pharmacists

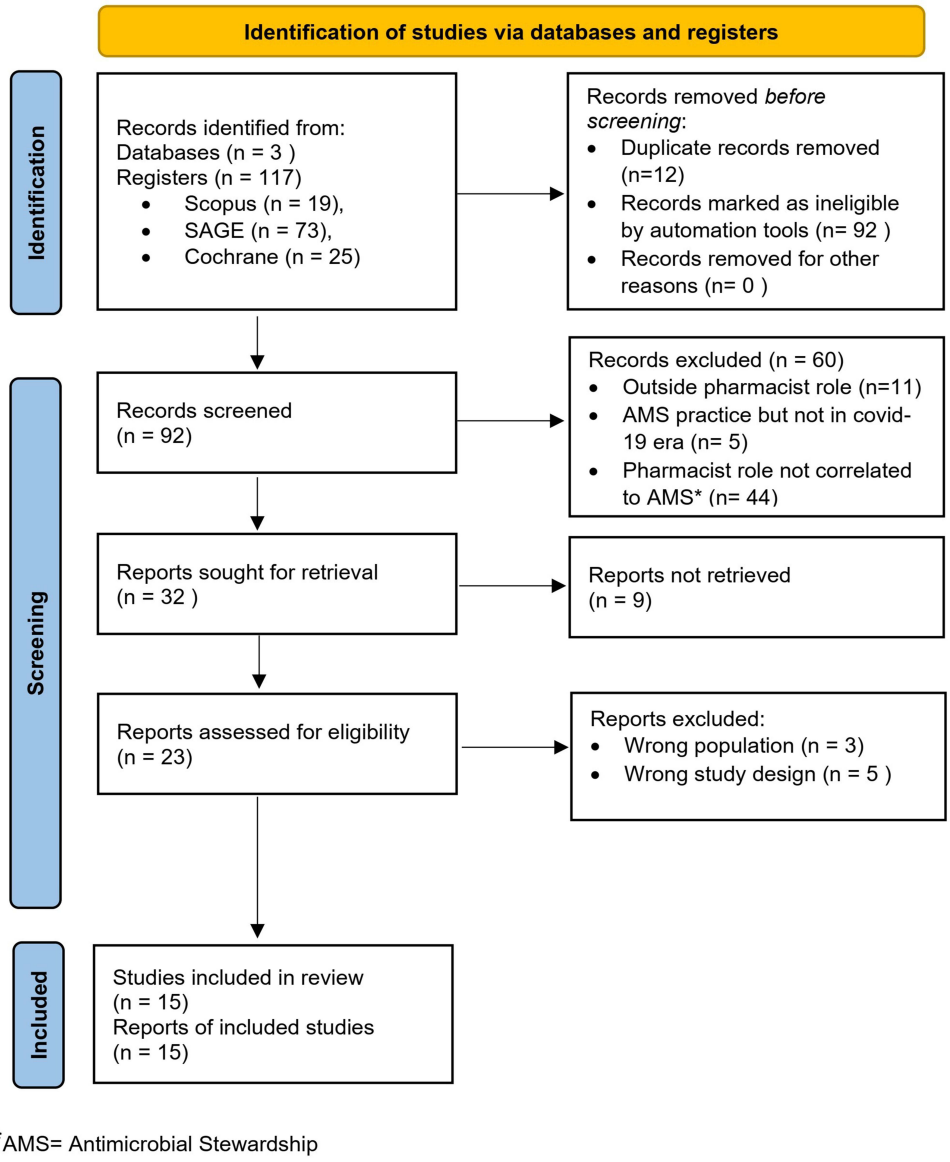


Figure 1 Preferred Reporting Items for Systematic reviews extension for Scoping Reviews (PRISMA-ScR) flow diagram.
Notes: Adapted from: Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71.[14] Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/legalcode).

in antimicrobial stewardship during the COVID-19 outbreak started in October 2021, and the latest search was on May, 2022. After duplicate publications were removed, all titles with abstracts were checked separately and irrelevant articles were removed according to the inclusion and exclusion criteria (Table 1). Discrepancies about the criteria of any article were resolved through discussion, then the full papers were read to compare their relevance to the topic.

Table 1 Inclusion and Exclusion Criteria

Included	Excluded
Full-text available	Review articles
English Language	Handbooks
Associated with AMS in COVID 19 pandemic	Guidelines
Focused on the pharmacist as AMS team	Protocol studies

Abbreviations: AMS, Antimicrobial stewardship; COVID 19, the Coronavirus Disease 2019.

Data Extraction and Analysis

The data were extracted using a form created in Microsoft Excel by three separate authors (IYK, HP, DAEP), while disagreements were worked out through discussion. The study's main themes are summarized in the discussion section. Data on the author, year of publication, region/country, health care sector, and pharmacist role during COVID-19 were collected from included studies to enable greater antimicrobial stewardship in the pandemic era, while descriptive analysis was performed on the features of the included studies. To investigate the existing gaps in knowledge, the source of the article, the publication date, and the topic of AMS in the COVID-19 pandemic were described.

Results

Characteristics of the Studies

The search carried out on 3 databases produced 117 articles but only 92 were non-duplicate citations. After title and abstract screening, 23 papers were screened by full text, while 15 papers were selected for the review, the remaining 8 were ruled out because 3 had the wrong population and 5 had the wrong study design (Figure 1).

All the included articles were published between 2020 and 2022, while most of the 15 selected were conducted in North America,[15–19] Asian,[20–24] and European[25–28] countries. The remaining were conducted in South America,[29] while no relevant studies were available from Africa, Australia, or the Pacific countries. The articles included in this study explain the pharmacists' role in the healthcare sector during the pandemic. The main findings can be categorized into different health care sectors, including hospitals,[16,17,19,20,22,23,25,26,29] clinics,[24] community pharmacy,[18,21] and all pharmacist professional settings.[15,27,28] The key characteristics of all 15 sources included in this review are detailed in the data chart presented in Table 2. Some of the included studies discussed antimicrobial stewardship principles that stressed the need for pharmacists to play an important role during COVID-19, especially in hospitals where they are part of the AMS team and work with other professionals.

Table 2 Results of Scoping Review on the Role of Pharmacist in Antimicrobial Stewardship (AMS) During COVID-19 Outbreak

References	Publication Type	Region	Health Care Sector	Pharmacist Role During COVID-19
Elbeddini et al (2020)[15]	Commentary	Canada	All Professional Setting	Community pharmacists perform the following tasks: delivering medications to patients; educating patients on telehealth services; assessing patients for renewal of chronic medications; performing consultations on minor ailments; clarifying misconceptions about COVID-19 treatments; and contributing to COVID-19 screening. Hospital pharmacists: management of drug shortages for COVID-19 treatments; development of treatment protocols; participation in patient rounds; interpretation of lab results for COVID-19; participant recruitment for clinical trials; exploration of new drugs; medication management advice; antimicrobial stewardship; and control of vaccine stock.
Ashiru-Oredope et al (2022)[27]	Research Article	United Kingdom	All Professional Setting	During pandemics, pharmacists were critical in ensuring ongoing medicine supply and access, supporting public health measures, and assisting in case identification and management.
Marwitz et al (2021)[28]	Commentary	United Kingdom	All Professional Setting	Pharmacists help patients spot false information about medications, vaccinations, COVID-19 pharmacotherapy, and information about public health.
Alnajjar et al (2022)[21]	Original Article	Jordan	All Professional Setting	Community pharmacists educated their patients and counseled the public about the currently available therapeutic options for managing COVID-19 symptoms Hospital pharmacists explored new drug therapies or uses; participated in the antimicrobial stewardship programs; and monitored antibiotic uses for COVID-19 cases and co-infections.
Goff et al (2020)[18]	Original Article	United States of America	Community Pharmacy	During the COVID-19 pandemic, pharmacists from Florida and all over the world set up an online platform (IDStewardship) to share reliable information.

(*Continued*)

Table 2 (Continued).

References	Publication Type	Region	Health Care Sector	Pharmacist Role During COVID-19
Al-Quteimat et al (2022)[24]	Original Article	Uni Emirat Arab	Clinic	Pharmacist interventions to improve communication and medication use in admitted adult patients with COVID-19, optimizing medication use in patients with COVID-19 through prevention, identification, and resolution of existing or potential drug-related problems.
Martins et al (2020)[29]	Current Opinion	Brazil	Hospital	Pharmacists manage drug shortages for COVID treatments, redesign workflow, and review drug formularies and protocols to improve patient and healthcare professional (HCP) safety during the pandemic.
Liu et al (2021)[20]	Original Article	China	Hospital	Clinical pharmacists were responsible for all the clinical wards and antimicrobial education (lectures, online teaching, appraisals) to help physicians, surgeons, nurses, and pharmacists understand and master the rational use of antimicrobials, including the indications, dosage, cautions, and common adverse drug events for COVID-19 treatment.
Jones et al (2021)[16]	Commentary	Georgia	Hospital	Pharmacists are responsible for combining the times when medications are given, improving pharmacotherapy, and keeping track of therapeutic drugs using SARS-CoV-2 PCR surveillance software.
Schmid et al (2022)[25]	Original Article	Germany	Hospital	Hospital pharmacists have responsibility for the indication for and selection of therapy, optimization of dosing, drug interactions, side effects, and other pharmacokinetic, pharmacodynamic, and pharmacoeconomic issues during pandemics.
Al-Qamariat et al (2021)[22]	Original Article	Saudi Arabia	Hospital	Pharmacists are involved in handling infectious disease management during the COVID-19 pandemic.
Ng et al (2021)[23]	Original Article	Singapore	Hospital	Pharmacists maintained the review rate of antibiotic use and provided daily prospective review and feedback on piperacillin-tazobactam, carbapenem, and ciprofloxacin use. They work closely with a team of five infectious diseases physicians who take turns performing PRF on complex cases.
Ashiru-Oredope et al (2021)[26]	Original Article	United Kingdom	Hospital	Pharmacists undertook additional responsibility for managing drug shortages (antimicrobial and non-antimicrobial), managing the supply of medication to patients with COVID-19, and providing PPE advice in extension to routine responsibilities (the provision of infection prevention and round-ward activities) during the COVID-19 pandemic.
Goldstein et al (2020)[17]	Article Navigation	United States of America	Hospital	The pharmacist's role is to control antimicrobial use based on minimal guidance for selecting appropriate treatment versus non-antimicrobial treatment.
Collins et al (2020)[19]	Article Navigation	United States of America	Hospital	Pharmacists intervened to address a wide scope of medication-related issues, giving advice on regimen simplification, timing and dosing adjustments, antimicrobial therapy, and COVID-19 treatment adjustments.

Abbreviations: COVID 19, the Coronavirus Disease 2019; SARS-CoV-2 PCR, SARS-CoV-2 P Polymerase Chain Reaction; PRF, prospective review and feedback; PPE, personal protective equipment.

Components Identification

This scoping review question focuses on the role of pharmacists in antimicrobial stewardship (AMS) or model frameworks during COVID-19. Every community pharmacist can contribute to antimicrobial stewardship. One of the essential elements should be antimicrobial dispensing according to regulations, either prescription only or according to guidelines where pharmacists have prescribing authority. After synthesizing the data in the 15 studies identified, the findings can be divided into two main components, ie, continental differences and the health care sector.

Continental Differences

Various philosophies shape healthcare services worldwide, and this study glances at some prominent examples, specifically pharmacists' role in antimicrobial stewardship during pandemics. This might help explain why different countries experience healthcare differently, based on the search conducted, 6 articles were obtained from the Americas,

including 5 from the North American region and 1 from South America, hence, these sections are described under the single continent of the Americas. Antibiotic Stewardship in the Americas, which includes the United States, Brazil, and Canada, each has differences and similarities in managing antibiotics. Studies in the United States of America (USA) consider antibiotics in patients with bacterial and non-bacterial infections as well as simplify their use according to time and dose. In addition, pharmacists in the USA also played a role in starting an online platform (IDStewardship) to provide the right information.[17–19]

Antibiotic management is also carried out in Brazil, involving drug shortages management by playing a key role in pandemic emergency response.[29] Meanwhile, pharmacists role in Canada managed shortages by exploring new drugs and management of antimicrobial services.[15] A commentary in Georgia (USA) stated that optimizing telepharmacy to conduct pharmacotherapy and monitoring therapeutic drugs using SARS-Cov 2 PCR surveillance software is an important part of antibiotic stewardship.[16]

Furthermore, a total of five studies were found on antibiotic stewardship in the Asian continent which includes China, Singapore, UAE, Saudi Arabia, and Jordan with each indicating differences and similarities in antibiotic management. In China, clinical pharmacists play a role in the management of drugs in hospitals by monitoring all clinical wards, providing pharmaceutical care, and antimicrobial education in helping doctors, surgeons, nurses, as well as other pharmacists understand and master the rational use of antibiotics.[20] In Singapore, pharmacists are evaluated based on daily prospective prescription and feedback on the use of piperacillin-tazobactam, carbapenem, and ciprofloxacin antibiotics.[23] In Saudi Arabia, pharmacists are involved in the management of infectious diseases and they play a role in improving communication on the use of drugs treated with COVID-19.[22]

Meanwhile, in Jordan, the pharmacist community plays a role in increasing knowledge of transmission, symptoms, and treatment of COVID-19.[21] The United Arab Emirates (UAE) also conducts antibiotic management and hospital pharmacist intervention analysis to improve communication and drug use in hospitalized patients.[24]

Studies in Europe are more predominant in the United Kingdom (UK) than in other European countries regarding the role of pharmacists in AMS during the pandemic. A total of four studies were found in the UK and one in Germany, each describing the role of pharmacists in antibiotic management. In Germany, pharmacists in several communities play a role in optimizing COVID-19 treatment based on indications and therapy selection, dose optimization, drug interactions, side effects, pharmacokinetics, pharmacodynamics, and pharmacoeconomic topics.[25] In the UK between 2021 and 2022, pharmacists have the same role in ensuring drug availability and shortages of antimicrobial as well as non-antimicrobial treatments. In 2022, pharmacists have an additional role with the health care team to actively reject misinformation related to drugs and pharmacotherapy in the future of public health.[18,26–28]

Health Care Sectors

Pharmacy and governments have made significant progress toward improving system results through better medication therapy coordination and the implementation of care plans to promote patient outcomes during COVID-19. A pharmacist is a backbone that strengthens the health care system, while antibiotic stewardship is one of the most important things in health care, and pharmacists play a key role in making sure COVID-19 is handled optimally. In general, pharmacists are responsible for identifying and treating patients during pandemics, facilitating the continuous availability and accessibility of drugs, supporting health policies, participating in antimicrobial stewardship programs, and monitoring antibiotic use for COVID-19 cases co-infections during pandemics.[15,21,27,28] Among the included studies in this scoping review, four studies evaluated all professional settings as healthcare sector during COVID-19,[15,21,26,28] nine studies reported hospital settings,[16,17,19,20,22,23,25,27,29] and each study discussed community and clinical settings.[18,24]

Most of included studies discussed hospital settings as a health care sector in AMS activities during the covid 19 pandemic. Hospitals are the most significant element that demands the crucial responsibilities of pharmacists in AMS management during the pandemic. In-hospital rates of bacterial co-infection with COVID-19 are relatively low, but antibiotic use is high. Consequently, judicious antibiotic use is critical to reduce the emergence of AMR and decrease toxicity from unnecessary antibiotics. Schmid et al reported hospital pharmacists oversee evaluating the necessity and choice of treatment, optimizing dosage, monitoring medication interactions, adverse effects, and other pharmacokinetic, pharmacodynamic, and pharmacoeconomic concerns during pandemics.[25] Other included studies detail how pharmacists

intervened to address a variety of medication-related problems, offering guidance on antimicrobial therapy, regimen simplification, timing and dosage adjustments, and COVID-19 treatment modifications.[19]

The additional responsibilities of pharmacists in hospitals are fascinating. Aside from carrying out pharmaceutical services, pharmacists must also ensure antibiotic stocks for general patients, COVID drug and vaccine stocks including antibiotic treatments.[26,29] According to one of the included studies, pharmacists manage COVID drug shortages, restructure workflow, and evaluate prescription formularies and protocols to promote patient and healthcare professional (HCP) safety during the pandemic.[29]

Pharmacists are also involved in the AMS team in hospitals in applying telehealth services for ensuring rational and appropriate antibiotic use.[16,23] They also assist in COVID-19 drug and vaccine studies to determine best practices within pandemic response efforts using local resources, overcoming misinformation related to COVID-19 drugs and vaccines and taking a lead role in focused protocol creation and curation, as well as helping to steward access to potential novel or investigational therapeutic agents.[17,19,20,22,25] Liu et al reported that clinical pharmacists were in control of all clinical wards and antimicrobial education, including lectures, online instruction, and appraisals, to assist doctors, surgeons, nurses, and pharmacists in comprehending and mastering the rational use of antibiotics, including the indications, dosage, warnings, and common adverse drug events for COVID-19 treatment.[20]

Discussion

The COVID-19 pandemic has changed the way health care is routinely delivered, with pharmacists being on the front lines every day, providing important health care services.[30] As drug experts, they provide patient care in a range of settings, including hospitals, clinics, community pharmacies, long-term care, physician offices, as well as national and public health.[31] Pharmacists have the unique skills and expertise to contribute tailored advice on appropriate antimicrobial use to the AMS agenda, helping to minimize the development of AMR.[32] Mas-Morey et al[33] found that pharmacists' intervention on antimicrobial prescriptions was effective in enhancing appropriate drug use with an acceptance rate of 83.4%, as well as reducing toxicity, the use of special-vigilance drugs, and overall antimicrobial cost. However, there is still limited published information about the role of pharmacists in AMS during the COVID-19 outbreak.

The potential effect of AMR considerably increased during the COVID-19 outbreak due to the overuse of antimicrobials. According to the meta-analysis, the prevalence of bacterial infection in COVID-19 is greater than 8%, and 64% of patients took antibiotics.[34] Meanwhile, a high increase in antibiotic consumption might strain worldwide supplies and cause pharmaceutical shortages. During a pandemic, pharmacists can repurpose the existing AMS program to act as a support system. They can also take a role in prospective audit and feedback (PAF) as well as a formulary restriction which is two of the most potent mechanisms within the AMS program. When resources are limited, PAF can be used to evaluate which patients are most likely to benefit from diagnostic testing or to assess the appropriate usage of COVID-19-targeted drugs and concomitant antibiotic treatment,[35] also, pharmacists might apply PAF to aid with medication toxicity monitoring.[36]

Localized guideline development is also an additional core activity; hence, numerous AMS programs currently have local use guidelines, and their expertise in guideline formulation, dissemination, and compliance monitoring can be applied to COVID-19-focused pandemic relief operations. This is one area where, according to anecdotal evidence, several AMS programs have provided considerable help throughout the pandemic.[37] Pharmacists, as one of the main parts of AMS, are in charge of creating and editing COVID-19-specific therapy guidelines. These guidelines include new therapeutic agents, comments on current investigations, and choices for clinical trials.

During the COVID-19 outbreak, pharmacists provide essential frontline care to patients in hospitals, clinics, community pharmacies, long-term care, nursing homes, physician offices, and public health. One of the most important strategies to reduce and mitigate the progression of the pandemic is social distance measures. This is where telemedicine can help and provide support to the healthcare system, especially in the areas of public health, prevention, and clinical practices.[38] To make the AMS program work for this situation, pharmacists are encouraged to provide virtual care delivery services. This made it possible for people to talk to pharmacists one-on-one without having to meet in person.

These services range from prescription management and reconciliation to education on healthy lifestyle interventions and test interpretation.[39]

Educating both patients and other healthcare teams is also a key aspect of AMS programs, during the COVID-19 pandemic, a concomitant infodemic has led to unsupported claims of pharmacotherapeutic superiority and efficacy of antibiotics.[40] It contributed to the incorrect use of antibiotics and exacerbated AMR. Pharmacists have a role in combating instances of drug misinformation and educating other healthcare teams on how to select antibiotics based on their pharmacological effects.[31] They can also assist patients in identifying false information about the use of antibiotics by verifying and discussing how negative emotional information spreads. Also, pharmacists combat incorrect information with patients by providing factual and understandable explanations.[28] During the pandemic, pharmacists were crucial in ensuring the smooth flow of the pharmaceutical supply chain, especially for antibiotics. Due to decreased production and increased stockpiling by people, businesses, and in some cases even countries, the COVID-19 pandemic resulted in a severe imbalance between the supply and demand of medications. The job of pharmacists has changed from simply restocking prescriptions to acting as a therapeutic substitute for doctors, which has contributed to maintaining continuity of care during the epidemic.[41]

Parente & Morton (2018)[42] and Garau & Bassetti (2018)[43] outlined specific recommendations for practice, education, and studies related to pharmacists' roles in AMS. The AMS implementation can be strengthened through multidisciplinary team (MDT) collaboration, including pharmacists. Pharmacists' experience in medical leadership is needed to promote communication and coordination in the delivery of AMS-consistent approaches. Furthermore, pharmacists need access to the patient's health record, including diagnostic results and recent updated local formulary information. This will enable better informed clinical decisions about antibiotics in collaboration with patients and the multidisciplinary team, guaranteeing safe prescribing alongside other medications and health problems. Increased public knowledge of the support, guidance and treatment offered by pharmacists will improve the utilization of healthcare resources and investment in medications. Additionally, it will enable the commissioning of investigations on basic diagnostic testing, the use of clinical scores and routes in a community pharmacy context, and their implications for proper antibiotic prescribing rates. There is a need for continuous, high-quality education, and training for pharmacists to keep informed of the most recent antibiotic scientific basis. This will give pharmacists the confidence to take part in decisions about what to prescribe, as well as how to talk to patients, and use antibiotics.

However, there are limitations in this study. First, the number of publications on COVID-19 is increasing tremendously, and some papers of interest that became accessible after the designated search period were not included. Second, despite scoping reviews' intrinsic characteristics, this review did not evaluate the quality of the research.

Conclusion

Our review imply that pharmacists have a responsibility to play prominent roles in antimicrobial stewardship (AMS), as an important multidisciplinary initiative, while the COVID-19 pandemic directly influenced how pharmacists work in the AMS agenda. During the pandemic, pharmacists played a significant role in identifying and treating patients, ensuring the supply and convenience of access to medications, as well as monitoring antibiotic use for COVID-19 cases and co-infections. Moreover, their role extends to giving telehealth services, educating, and clarifying the misconceptions about COVID-19 treatments along with other antibiotic consumption, as well as taking a lead in establishing local guidelines on antibiotic consumption. Pharmacists must be able to adapt to the circumstances and improve their knowledge with the ability to deal with this pandemic. Integrate pharmacists into the AMS team, determining government policies, continuing care and additional roles in inventory control of antibiotics and vaccines will gain significant traction. Further investigations are needed to fully understand the pharmacist's role in AMS during the COVID-19 outbreak, and how it affects patients.

Ethics Statement

This review did not need ethical approval.

Acknowledgment

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation. All authors gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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