ARE WE OVERTREATING COVID-19 PATIENTS WITH ANTIBIOTICS?

ANTIBIOTICS USE FOR TREATING HOSPITALIZED COVID-19 PATIENTS: A SYSTEMATIC REVIEW & META-ANALYSIS

By

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THESIS TITLE:

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LAY ABSTRACT

Bacteria is a major cause of many infectious diseases. Before the discovery of Antibiotics in 1928, hundreds of thousands of people used to die due to infectious diseases caused by bacteria. While Antibiotics are essential to treat bacterial infectious diseases, overuse or misuse can accelerate Antibiotic Resistance, a phenomenon when bacteria change and/or develop the ability to escape the drugs designed to kill them. Self-medication, availability of antibiotics without a prescription, and inappropriate dosing of antibiotics can worsen the situation. During the COVID-19 pandemic, antibiotics were commonly prescribed as part of the treatment regime for COVID-19, even when a clear bacterial infection was not identified. In our Systematic Review and Meta-analysis, we aimed to see the frequency of antibiotic prescriptions to treat hospitalized COVID-19 patients without any bacterial coinfections.

ABSTRACT

Background: Bacteria is a major cause of many infectious diseases, and the treatment for these diseases is antibiotics designed to kill or subdue the growth of the bacteria. However, bacteria evolve, and if an antibiotic prescription is not the right antibiotic for the right patient at the right time with the correct dose and the right route, Antimicrobial Resistance (AMR) may result. During this pandemic, the use of antibiotics to treat hospitalized COVID-19 patients without any bacterial coinfection threatens the effectiveness of antibiotic treatment for current and future bacterial infections.

Methods: A systematic search was conducted of the Embase, Medline, Web of Science, and Cochrane Library databases by generating search terms using the concepts of "COVID-19," "Bacterial Coinfection," "Secondary bacterial infection," and "Antimicrobial resistance" to identify studies that reported the prevalence of antibiotic prescription for the treatment of COVID-19 in hospitalized patients with and without bacterial coinfection. The pooled estimate of the percentage of the total and confirmed appropriate antibiotic prescriptions provided to hospitalized COVID-19 patients was generated using a random effect meta-analysis with inverse variance weighting.

Result: Of 157,623 participants from 29 studies included in our review, 67% (CI 64% to 71%, P<0.00001) were prescribed antibiotics, among which 80% (CI 76% to 83%, P<0.00001) prescriptions were given for the COVID-19 patients without any bacterial coinfections. The use of antibiotics varied during the pre-immunosuppressive period (before 16 June 2020) and post-immunosuppressive period of the pandemic and between the High-Income Countries and Upper and Lower Middle-Income Countries.

Conclusion: This Systematic Review and Meta-analysis finds greater than expected use of antibiotics to treat hospitalized COVID-19 patients without bacterial coinfections, which can worsen AMR globally. Clear and concrete guidelines for the use of antibiotic prescriptions to treat COVID-19 patients, strict monitoring, and compliance with Antimicrobial Stewardship are needed to prevent over-prescription.

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LIST OF ABBREVIATIONS AND SYMBOLS

ABR	Antibiotic Resistance
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	Community-Acquired Pneumonia
COVID-19	Coronavirus Disease of 2019
DDD	Defined Daily Dose
HIC	High-Income Countries
ICU	Intensive Care Unit
LRTI	Lower Respiratory Tract Infections
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
U&LMIC	Upper and Lower Middle-Income Countries
WHO	World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

I, Fazle Rabbi, declare this thesis to be my work, and I am the sole author of this document. No part of this work has been published or submitted for publication or a higher degree at another institution.

To the best of my knowledge, the content of this document does not infringe on anyone's copyright.

My supervisor, Dr. Russell de Souza, and the members of my supervisory committee, Ms. Laura Banfield, have provided guidance and support at all stages of this project. Ms. Mehnaz Munir assisted with full-text review and data abstraction for the project which is necessary for a systematic review. I completed all of the research work.

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CHAPTER I

INTRODUCTION

"The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection, the microbes are educated to resist penicillin, and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicaemia or pneumonia which penicillin cannot save." (Alexander Fleming, 1945)

Antimicrobials – including antibiotics, antivirals, antifungals, and antiparasitics – are medicines used to prevent and treat infections in humans, animals, and plants (WHO, 2021b). Globally, the use of antibiotics has increased remarkably. Browne et al. (2021) reported in their study that in 2000, the global antibiotics consumption rate was 9.8 DDD (Defined Daily Dose) per 1000 per day; in 2018, it reached 14.3 DDD per 1000 per day (Browne et al., 2021). The study was an analysis of 209 surveys conducted between 2000 and 2018, including 284,045 children suffering from lower respiratory tract infections (LRTI).

While Sustainable Development Goal 3.8 (SDG 3.8) urged for *"access to safe, effective, quality and affordable essential medicines and vaccines for all"* (UNStats, 2022), inaccessibility to antibiotics causes many untreated bacterial infections, raising morbidity and mortality for those

diseases (Laxminarayan et al., 2016). Additionally, "suboptimal dosing" and low-grade pharmaceutical quality, including management of drugs, contribute to the development and breeding of AMR (Pisani, 2015).

The ongoing COVID-19 pandemic has also been a significant contributor to the changing landscape of antibiotic use in patient care. Despite infrequent reporting of bacterial coinfections (1.2% to 46.38%) and/or secondary bacterial infections in patients with COVID-19 infection (1.56% to 32.3%) (Wang et al., 2021; Grasselli et al., 2021), antibiotic prescription for these patients remains high (1.3% to 100% prescription prevalence) among patients hospitalized with COVID-19 (Al-Hadidi et al., 2021; Molla et al., 2021).

The unregulated use of these drugs can lead to antimicrobial resistance (AMR), a global health emergency that kills around 700,000 people in a year (WHO, 2019b). The Predictive statistical model by Murray et al. (2022) calculated 4·95 million deaths could be related to bacterial AMR in 2019, and it was the direct cause for 1·27 million deaths in the same year (Murray et al., 2022). The World Health Assembly acknowledged the threat of AMR and endorsed a Global Action Plan in 2015, to "optimize the use of antimicrobial medicines" as one of the five objectives to ensure Antimicrobial Stewardship (AMS) (WHO, 2019a), defined as *"the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance"* (BSAC, 2018, p. 24). AMS is a comprehensive set of actions to *"promote the responsible use of antimicrobials,"* (WHO, 2019a) that is, *"the right antibiotic for the right*

patient at the right time with the right dose and the right route causing the least harm to the patient and the future patients" (BSAC, 2018, p. 25).

Antimicrobial Resistance (AMR), Antibiotic Resistance, and Antimicrobial Stewardship (AMS)

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness, and death (WHO, 2021b). AMR is one of the most significant global health concerns. AMR is common and occurs over time because of genetic changes in organisms (WHO, 2021b). Every time an organism has been exposed to an antibiotic, there is a risk of AMR. Nevertheless, antimicrobials are used because their benefits outweigh the risk of AMR (CDC, 2021); if used in the appropriate dose, the drug kills the microorganism or prevents its growth. However, if the drugs are misused, overused, or used in an inappropriate dose, they will not be effective and contribute to AMR (WHO, 2021b). Resistant microorganisms (e.g., bacteria, viruses, fungi, and parasites) are not killed by antimicrobial drugs; thus, even judicial treatments become futile, infections persist, and the risk of spreading the infection to others increases (BSAC, 2018, p. 13).

Multi-drug resistant bacteria are increasing and, if unchecked, are likely to spread globally. The COVID-19 pandemic has forced the realignment of many global health priorities, which might have contributed to lagging AMS. Ashiru-oredope et al., 2021 listed several factors, such as the

lack of audit, education, and training programs for quality improvement and the additional workload placed on pharmacists that contributed to compromised AMS program activities during COVID-19. Furthermore, the upsurge of Community-Acquired Pneumonia (CAP) due to COVID-19 altered the management of the disease (Ashiru-oredope et al., 2021). Because of these trends, the World Health Organization called attention to AMR as one of the top 10 global health concerns (WHO, 2021b) and warned that it might be an *'invisible pandemic'* (UNnews, 2019; Larson, 2019) *or 'silent pandemic'* (UNnews, 2022). Based on the rising AMR scenario for six pathogens and the United Nations report on world population prospects until 2050, O'Neill (2016) estimated that AMR could contribute to 10 million deaths per year by 2050 if unchecked (O'Neill, 2016; WHO, 2019b). Unregulated antibiotic prescription without clear evidence of bacterial infection to treat patients with respiratory and multiorgan infections in the setting of the COVID-19 pandemic is likely to worsen AMR.

Antibiotic resistance is bacteria's protective mechanism against the effects of an antibiotic. Two standard methods are pumping the antibiotic out of the bacterial cell or producing molecules that can destroy the antibiotic. In the presence of the antibiotic, non-susceptible, i.e., resistant bacteria, can survive or multiply quicker than susceptible bacteria and increase in number. Clinical resistance occurs when a bacterium grows in antibiotic concentrations that are usually adequate to treat an infection, and this leads to a treatment failure.

Antibiotics disrupt essential functions or structures in the bacterial cell, killing the bacterium or slowing down its growth. Depending on its mechanism of action, an antibiotic is

usually classified as either bactericidal or bacteriostatic. A bactericidal antibiotic kills the bacteria. A bacteriostatic antibiotic does not kill the bacteria but subdues its growth, which allows the immune system to clear the infection.

There are two pathways by which bacteria achieve resistance:

- Random changes in the bacterial DNA (mutations)
- Obtaining resistance genes from different bacteria nearby ("horizontal gene transfer")

If either of these resistance mechanisms improves the bacterium's survival, they are carried forward during cell division. They can also be passed along by horizontal transfer through human contact, in food and water, and occasionally by respiratory droplets. Travel and trade greatly increase the speed at which such resistant bacteria may spread.

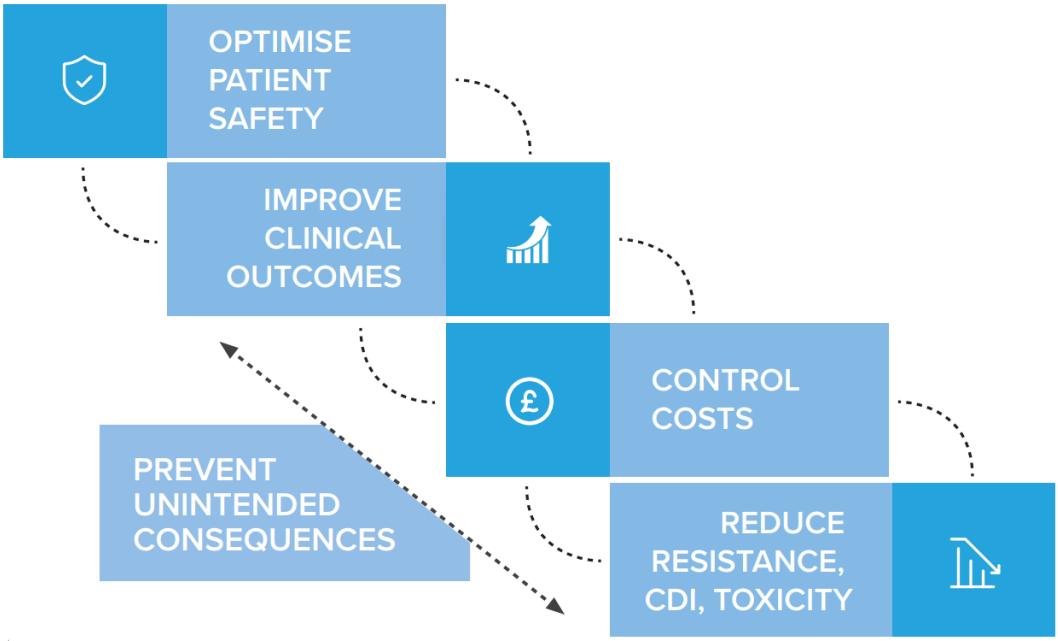

Figure 1: Effectiveness of Antimicrobial Stewardship. Adapted from (BSAC, 2018)

Enhancing the appropriate use of antibiotics is crucial to treating infections effectively, protecting patients from harm caused by disproportionate antibiotic use, and combating antibiotic resistance. AMS programs can help clinicians enhance clinical outcomes and reduce harm by improving antibiotic prescribing.

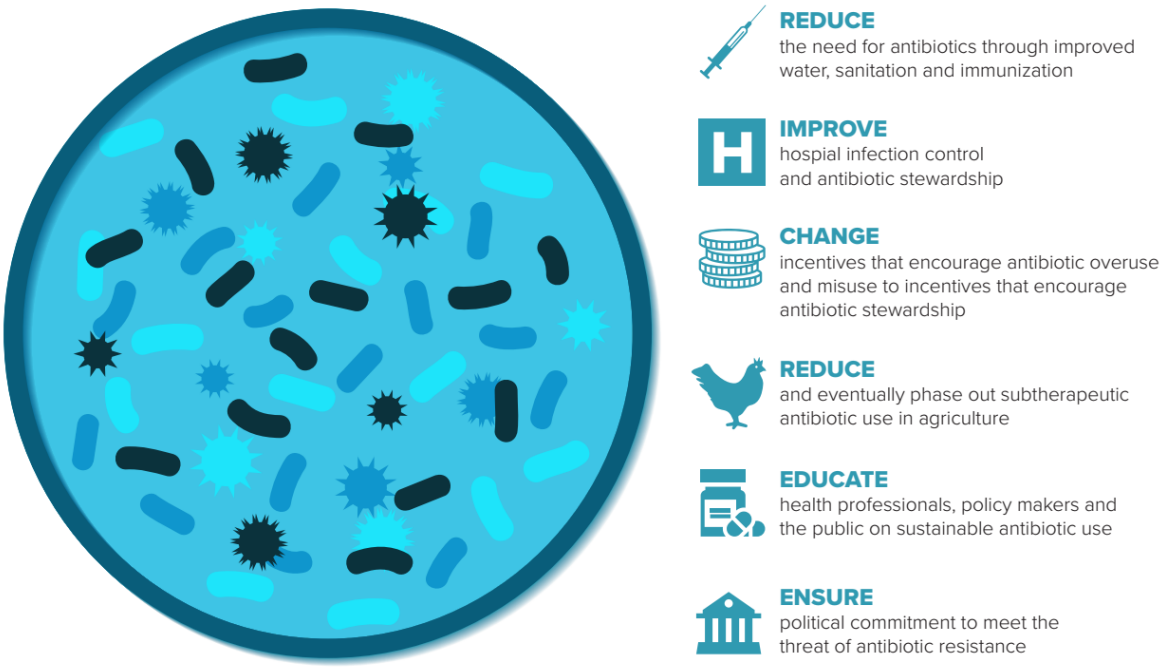

Figure 2: Six core strategies to combat Antimicrobial Resistance. Adapted from (BSAC, 2018)

Correlation between Antibiotics Consumption and Antimicrobial Resistance (AMR)

A systematic review and meta-analysis of 243 studies by Bell et al., 2014 found an association between antibiotic consumption and the subsequent development of bacterial resistance at both the individual and community level, reinforcing the finding that increased antibiotic consumption might not only produce greater resistance at the personal level but might also contribute to the widespread resistance at the community, regional, and national levels, affecting individual patients (Bell et al., 2014). They conducted meta-analyses for different study designs, however, they found similar results for all the designs. Also, antibiotic consumption and positive correlation were higher for the studies that included adults and children. However, the studies from the USA that have cross-sectional design with only children population had a weaker correlation and sometimes a negative association between antibiotic consumption and antibiotic resistance.

The European Surveillance of Antimicrobial Consumption (ESAC) program, analyzing data from 35 countries, demonstrated that antibiotic use was higher in southern European countries than in northern European countries (Goossens et al., 2005; Goossens et al., 2007). The studies found a positive correlation between resistance and antibiotic consumption (The study defined consumption as DDD per 1000 inhabitants per day, that is DID) and observed higher resistance rates in European countries with moderate to high antibiotic consumption. Several ecological studies have shown that increased antibiotic consumption contributes to antibiotic resistance in streptococci (Malhotra-kumar et al., 2007; Goossens et al., 2007).

Pathogens, of which bacteria are one, adapt new resistance mechanisms, transforming into drug-resistant pathogens, leading to AMR (World Health Organization, 2015). The rapid spreading of "superbugs," multi- (non-susceptible to three or more antimicrobial categories) and pan-resistant (non-susceptible to all antimicrobial agents) bacteria, may cause an infection that no existing antimicrobials can treat. This represents one of the most significant global health concerns (World Health Organization, 2015). The WHO has warned that continued misuse of antimicrobial drugs may hasten this process (WHO, 2021b).

Antibiotics usage during the COVID-19 pandemic

The COVID-19 pandemic has been accompanied by a change in antibiotic usage patterns (Rodriguez-Bano et al., 2021; Rezel-Potts et al., 2021; Guisado-Gil et al., 2020). While the overuse and overprescribing of antibiotics had always been a growing global health concern for antimicrobial resistance (Gulliford et al., 2014; Dekker et al., 2015; Rezel-Potts et al., 2021), more liberal and possibly not indicated use during the pandemic may have exacerbated this problem (Rodriguez-Bano et al., 2021; Sulis et al., 2021).

A retrospective study by Ul Mustafa et al. (2021) in five hospitals in Punjab, Pakistan, aimed to investigate the use of antibiotics among hospitalized COVID-19 patients over a two-month span, from August to September 2020, and in 2019 for the corresponding months. The result showed that eight different classes of antibiotics were used widely to treat COVID-19 patients

without any culture tests. There was increased consumption of antibiotics during the COVID-19 pandemic compared to the pre-pandemic period. Azithromycin consumption increased from 11.5 daily defined doses (DDDs) to 17.0 DDDs per 100 occupied bed-days from 2019 to 2020, and the consumption of ceftriaxone increased from 20.2 DDDs to 25.1 per 100 occupied bed-days from 2019 to 2020 (Ul Mustafa et al., 2021). The study showed non-indication-based applications of antibiotics among hospitalized COVID-19 patients in Pakistan.

Al-Hadidi et al. (2021) systematically reviewed 141 studies from 28 countries to document the antibiotic consumption rate among hospitalized COVID-19 patients during the pandemic (November 1, 2019, and December 19, 2020). They found a pooled antibiotic consumption rate of 58.7%, ranging from 1.3% to 100% across countries where most of the studies were from the worst affected countries by the pandemic: China (55), followed by the USA (18), Italy (10), UK (5), Spain (5), Brazil (4), Iran (4), and India (3). Two articles were included from Germany, Belgium, South Korea, Japan, Netherlands, and Saudi Arabia, and one from France, Ireland, Switzerland, Bhutan, Colombia, Niger, Oman, Morocco, Qatar, Singapore, Philippines, Taiwan, and Uganda. Only 9.9% (14/141) of studies reported lower than 50% antibiotic use. The systematic review also reported a comparatively lower antibiotic usage rate among pregnant women (34.5%) and in children (57%) than adults with comorbidities (75%). However, there were no reports on bacterial coinfection in 75% of the articles, suggesting that many antibiotics were used empirically (Al-Hadidi et al., 2021).

Grau et al. (2021) reported that the global antimicrobial consumption rate increased in general hospital wards and Intensive Care Units (ICU) during the pandemic but was only statistically significant in the ICU (Grau et al., 2021). Castro-Lopes et al., 2021 concluded that the COVID-19 pandemic has increased antimicrobial consumption, showing an increased prescription rate during the pandemic over pre-pandemic reference periods in 2020 and 2011-2019. They calculated DDD/100 patient-days for different groups for the first three months of the COVID-19 pandemic (March, April, and May 2020) as a quarterly value and compared with for each year in 2011–2019, using their annual percentage changes to estimate 95% confidence intervals. (Castro-Lopes et al., 2021).

Antibiotics usage during the COVID-19 pandemic and the risk of Antimicrobial Resistance

Experts have a growing concern that excessive use of antibiotics during the pandemic may increase the risk of antimicrobial resistance (Hsu, 2020). WHO and other expert advisory groups suggested not to initiate antibiotic therapy for suspected, probable or confirmed mild COVID-19 (WHO, 2022; NIH, 2022). For moderate COVID-19, no antibiotics should be prescribed unless there was a clear clinical presentation of a bacterial infection or in critically ill patients (WHO, 2022; NIH, 2022; Ginsburg & Klugman, 2020).

The increased use of antibiotics during COVID-19 was mainly in antibiotics that fell under the "Watch" group (see appendix 2), antibiotics that are the main target classes of antibiotic resistance and need close monitoring to ensure timely AMS interventions (Castro-Lopes et al.,

2021). This group includes antibiotics with higher resistance potential and most of the critical priority agents among the highly significant Antimicrobials for Human Medicine and/or antibiotics at relatively high risk of selection of bacterial resistance (Example- Azithromycin, third-generation cephalosporins, and carbapenems). Antibiotics in the Watch group should be prioritized as key targets of stewardship programs and monitoring (WHO, 2019c).

Antimicrobial drug purchase, misuse, and unregulated prescriptions increased throughout the COVID-19 pandemic (Sulis et al., 2021; Rodriguez-Bano et al., 2021; Rawson, Moore, et al., 2020; Garcia-vidal et al., 2020; Bradley J. Langford et al., 2020). Based on the data on the prevalence of coinfections among COVID-19 patients (Bassetti et al., 2020; Bradley J. Langford et al., 2020; Contou et al., 2020), most of these prescriptions are unnecessary.

It is essential to collect data regarding the usage of antibiotics in the setting of COVID-19, assess the contribution of novel prescribing patterns to AMR, and determine the underlying causes to plan strategically according to the new scenario. This systematic review aimed to summarize the frequency of antibiotic use among hospitalized COVID-19 overall, as well as the frequency of antibiotic use in patients with COVID-19 and a These data may contribute to the assessment of the appropriateness of antibiotics use during COVID-19.

Research Question

We used the PICOT worksheet to develop our systematic review's research question. (see Appendix 1 for the detailed pathway for developing the research question)

P	**Patient, Population, or Problem**	How would I describe a group of patients similar to mine?- Hospitalized patients with COVID-19 of any age in any country
I	**Intervention, Prognostic Factor, or Exposure**	Which primary intervention, prognostic factor, or exposure am I considering?- Frequency (or percentage or proportion) of antibiotic prescription
C	**Comparison or Intervention (if appropriate)**	What is the main alternative to compare with the intervention?- Frequency of bacterial coinfection and secondary infection
O	**The outcome you would like to measure or achieve**	What can I hope to accomplish, measure, improve or affect?- Not directly assessed.
T	**Timeframe of the Study**	What is the period for the study?- COVID-19 pandemic (e.g., December 2019 – February 2022)

Table 1: PICOT table. Adapted from (McMasterUniversity, n.d.)

In hospitalized COVID-19 patients of any age in any country, admitted to any service with any length of stay, what is 1) the frequency of antibiotic prescription with no other documented indication (Other than COVID-19 symptom alleviation); and 2) the frequency of bacterial coinfection and secondary bacterial infection?

Objectives of the Systematic Review

General Objective:

- To understand the impact of the COVID-19 pandemic on AMR

Specific Objectives:

- To summarize the percentage of hospitalized patients with COVID-19 without bacterial coinfections who are prescribed antibiotics.
- To compare the prescription patterns of antibiotics in the setting of COVID-19 between High-Income Countries (HICs) and Upper and Lower Middle-Income Countries (U&LMICs).
- To compare the prescription pattern before and after the immunosuppressive period (before and after the announcement of dexamethasone as the treatment for COVID-19).

CHAPTER II

METHODS

We worked with a health sciences librarian to develop a search strategy for OVID Medline, EMBASE, Web of Science, and Cochrane Library. Search terms were generated using the MeSH-major search builder, which generates keywords related to the concepts of: "COVID-19," "SARS-COV-2," "Bacterial secondary infection," and "bacterial coinfection," "Antibiotic prescription," "Antimicrobial resistance," "Antibiotic resistance." We also used Canadian Agency for Drugs and Technologies in Health (CADTH) COVID-19 search strings-generated search vocabularies for searching COVID-9 related literatures in our search strategy for OVID Medline and EMBASE databases. After finalizing the search terms, we conducted our final search on 5th March 2022.

We used ".ti = title, .ab = abstract, .kw = author-provided keyword exact, .kf = word in author provided" in Medline and used ".mp= multipurpose" in Embase for Textword searching. We conducted a text search for "ALL=All Fields" for the Web of Science. We combined all the search terms within a concept with the "OR" Boolean operator and then used the "AND" Boolean operator to combine the concepts.

The detail of the search terms is shown in **Table 2** below.

	Concepts			
Databases	**COVID-19/SARS-COV-2**	**Hospitalization /Inpatients**	**Antibiotics/Antimicrobials**	**ield Codes**
OVID Medline	"COVID-19," "SARS-COV-2"	"Hospitalization," "adolescent, hospitalized/ or child, hospitalized/ or inpatients/," "inpatient*," "in-patient*," "hospital*," "Intensive Care Units," "intensive care," "icu," "picu"	"Anti-Bacterial Agents," "antibiotic*," "antibiotic*," "antimicrobial*," "antimicrobial*," "antibiotic resistan*," "antibiotic resistan*," "antimicrobial resistan*," "antimicrobial resistan*," "Drug Resistance, Microbial/ or Drug Resistance, Multiple, Bacterial/ or Drug Resistance, Bacterial/," "drug resistance*," "Drug Prescriptions"	mp or ti, .ab, .kw, .kf

OVID EMBASE	"COVID-19," "SARS-COV-2"	"Hospitalization," "adolescent, hospitalized/ or child, hospitalized/ or inpatients/," "inpatient*," "in-patient*," "hospital*," "Intensive Care Units," "intensive care," "icu," "picu"	"Anti-Bacterial Agents," "antibiotic*," "antibiotic*," "antimicrobial*," "antimicrobial*," "antibiotic resistan*," "antibiotic resistan*," "antimicrobial resistan*," "antimicrobial resistan*," "Drug Resistance, Microbial/ or Drug Resistance, Multiple, Bacterial/ or Drug Resistance, Bacterial/," "drug resistance*," "Drug Prescriptions"	mp or ti, .ab, .kw, .kf
CADTH COVID-19 Search strings	"(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-			ti,ab,kf,nm,ot,ox,rx

(Not a database) used for OVID Medline and EMBASE	COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2)," "((new or novel or "19 " or "2019 " or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or "CoV" or HCoV))," ,px,kw.			

	"(longCOVID* or postCOVID* or postcoronavirus* or postSARS*)"			
Web of Science	((((ALL=(COVID-19)) OR ALL=(SARS-COV-2)) OR ALL=(nCoV* or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or Severe Acute Respiratory Syndrome Coronavirus 2)) OR ALL=((new or novel or "19 " or "2019 ") adh2 (corona virus*)))	(((((((ALL=(hospitalization)) OR ALL=(inpatients or hospital patient)) OR ALL=(in-patient*)) OR ALL=(inpatient*)) OR ALL=(intensive care unit)) OR ALL=(intensive care*)) OR ALL=(icu)) OR ALL=(pediatric intensive care unit or picu)	((((((((((ALL=(antibiotics or antibiotic agent)) OR ALL=(antibiotic resistance or anti-biotics)) OR ALL=(antibiotic* or antibiotic sensitivity)) OR ALL=(anti-biotic*)) OR ALL=(antimicrobial or antiinfective agent)) OR ALL=(antifungal agent or anti-microbial)) OR ALL=(antimicrobial drug resistance)) OR ALL=(multiple drug resistance or multidrug resistance)) OR	LL

	OR ALL=(longCOVID* or postCOVID*)		ALL=(microbial drug resistance)) OR ALL=(drug resistan*)) OR ALL=(drug-resistan*)	
Cochrane Library	"COVID-19," "SARS-COV-2," "Novel Corona virus"	"Hospitalization," "Inpatient," "ICU"	"Antibiotics," "Antimicrobials," "Antibiotic resistance," "Antimicrobial resistance," "Multidrug resistance"	eSH trees for the search keywords/ terms

Table 2: Search terms for the literature search for different databases

All retrieved titles and abstracts were first screened for duplicates, and unique abstracts were screened by a single reviewer, Fazle Rabbi (FR). The full text of all abstracts that passed screening was then reviewed independently by two reviewers, FR and Mehnaz Munir (MM). Articles that described bacterial coinfection or secondary bacterial infection among COVID-19 hospitalized patients and antibiotic use among those patients were included; studies not in humans, not in hospitalized patients, or not reporting antibiotic use were excluded (Detail of inclusion and exclusion criteria are given below). Reference lists of included articles were reviewed. We did not restrict any study design during our database search. Any conflicts on article selection were

resolved by discussion between two reviewers (FR and MM). Both the reviewers extracted data from selected articles and resolved disagreements after discussing them in detail with each other. Where necessary, a senior investigator (RJdS) was consulted to resolve disagreements.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- English language articles on the frequency of secondary bacterial infection or bacterial coinfection among hospitalized COVID-19 patients and the frequency of Antibacterial prescriptions to treat them.
- Reference lists of included articles.

Exclusion Criteria:

- Studies are not on humans.
- Studies not in hospitalized patients or studies on outpatient department patients.
- Studies did not report antibiotic use.
- Case study/report for individual patients
- Opinion, commentary articles
- Randomized Controlled Trial studies
- Studies that focused on nosocomial infections due to mechanical ventilation

Software and Tools used for the Systematic Review and Meta-analysis

We used Covidence, a web-based collaboration software platform, (Covidence, n.d.) to screen titles and abstracts and full-text of articles, and extract data (Extraction 2.0, a data extraction tool developed by Covidence). The Joanna Briggs Institute (JBI) critical appraisal tool for systematic reviews of prevalence studies was used to assess study risk of bias. We used Review Manager 5.4.1 (TheCochraneCollaboration, 2020) to conduct the Meta-analysis.

Data Synthesis, Management, and Analysis

Ideally, we aimed to extract from each study 1) the total # of patients with COVID-19 who were prescribed antibiotics and 2) of those who had confirmed bacterial coinfection/secondary coinfection and who did not. We, therefore, made the following assumptions:

1) Articles that presented data from patients with COVID-19 and those without COVID-19 together, without sufficient detail to separate the groups were excluded. However, if groups were presented separately, and allowed the calculation of our desired data, data from the study were included.
2) For example- Angell 2021 conducted a study with 405 hospitalized patients, whereas 296 were SARS-COV-2 positive. Among those COVID-19 patients, only 50 were coinfected

with bacterial infections (the total number of bacterial coinfections among the 405 patients was 83), and 105 patients received antibiotics (the total number of patients who were given antibiotics was 175) anytime during their hospital stay. However, only 47 (56.63%) patients received antibiotics among those 83 coinfected patients. So, we assumed the same percentage of antibiotics usage among the COVID-19 with bacterial coinfected patients, which is only 28 patients, which means 77 COVID-19 patients got antibiotics without any bacterial coinfection.

3) Estrada 2021 mentioned 1441 among 1481 COVID-19 with bacterial coinfected patients received Antibiotics, whereas the total number of Antibiotic consumers was 12238, which indicates 10797 (12238-1441) COVID-19 patients without any bacterial infection were prescribed antibiotics.

4) Martin 2021 reported that 09 patients among 12 infected with bacteria received antibiotics, whereas 172 hospitalized COVID-19 patients were prescribed antibiotics. So, we calculated that the 163 (172-9) patients who received antibiotics were not infected with bacteria.

5) Vaughn 2020 mentioned that 47 of 59 patients with community-onset bacterial infection among hospitalized COVID-19 patients received antibiotics, whereas a total of antibiotics prescriptions was for 965 patients. So, we calculated that the antibiotic usage among the patients without bacterial infection was 918 (965-47).

6) Wang 2021 randomly selected 100 patients from their study sample, where 98 of them were prescribed antibiotics. In that case, we calculated this study's total number of antibiotic prescriptions from the percentage of the antibiotic prescriptions.

Then we calculated the pooled percentages of antibiotic prescriptions among patients with or without bacterial coinfection for those studies and used this to impute the percentages for studies that did not provide this information. As a sensitivity analysis, we also repeated the calculation using the upper and lower bounds of the 95% CI for each estimate to assess the robustness of this assumption. **(see Table 3)**

Percentage Calculation

We calculated the percentages of antibiotic use among the bacterial coinfected patients from the articles that reported discrete information on antibiotic consumption among the patients with bacterial coinfections and the patients without bacterial coinfection. We calculated the pooled percentage with confidence interval and then assumed the percentage of antibiotic usage among the bacterial coinfected patients for both the lowest and highest confidence intervals. We will use "assumed data" to refer to those articles throughout the thesis report.

We took a similar approach to estimate the number of antibiotic prescriptions among patients without bacterial coinfections.

For the articles reported discrete information-

Antibiotic usage among the patients with bacterial coinfections= 14048

Total number of patients with bacterial coinfections= 14286

% Of Antibiotic usage among the patients with bacterial coinfections= 98.33%

Confidence Interval= 98.11, 98.53

Antibiotic usage among the patients without bacterial coinfections= 50735

Total number of patients without bacterial coinfections= 71903

% Of Antibiotic usage among the patients without bacterial coinfections= 70.56%

Confidence Interval= 70.23, 70.89

We used the Wilson Score Interval method to calculate the confidence interval.

Wilson score interval

$$\hat{p} = \frac{\hat{p} + Z^2/2n}{1+Z^2/n} \pm \frac{Z}{1+Z^2/n}\sqrt{\left(\frac{\hat{p}(1-\hat{p})}{n} + \frac{Z^2}{4n^2}\right)}$$

For the studies that did not report on secondary bacterial infection or have no discrete information on bacterial coinfection or secondary bacterial infection (termed as bacterial infection), we registered them as "bacterial coinfection." **(see Table 4)**

However, we excluded the articles with unrealistic estimations while calculating them with the pooled percentage. For example- we excluded the articles where the Antibiotic prescriptions among patients without bacterial coinfections were higher than the total antibiotic prescriptions (see Table 3 articles #9, #13, #23, #27; and **Figure 6** & **Figure 7**).

#	Study ID	Sample Size	# of Pt wit ABT	% of Patient with Antibiotics	# of patients received antibiotic who have Bacterial Co-infection	# of patients received antibiotic but have no Bacterial Co-infection	# of Pt with Bacterial CI	# of Pt without Bacterial CI	# of patients received antibiotic who have Bacterial Co-infection_Lower CI (pooled)	# of patients received antibiotic who have Bacterial Co-infection_higher CI (pooled)	# of patients received antibiotic but have no Bacterial Co-infection_Lower CI (pooled)	# of patients received antibiotic but have no Bacterial Co-infection_Higher CI (pooled)
1	Angell 2021	296	105	35.47	28	77	50	246	28	28	77	77
2	Asmarawati 2021	218	164	75.2	36	128	43	175	36	36	128	128
3	Baghdadi 2021	64961	49551	76.3	12040	36049	12040	52921	12040	12040	36049	36049
4	Cheng 2020	147	52	35	12	19	12	135	12	12	19	19
5	Coenen 2021	384	228	81	11	182	11	373	11	11	182	182
6	Elabbadi 2021	101	58	57.4	10	48	20	81	10	10	48	48
7	Estrada 2021	13932	12238	87.8	1441	10797	1481	12451	1441	1441	10797	10797
8	Grasselli 2021	774	534	69	229	305	359	415	229	229	305	305
9	Hughes 2021	624	310	49.7		NA	17	607	17	17	426	430
10	ISARIC4CInvestigators 2021	48902	39258	85.2		NA	1942	46960	1905	1913	32980	33290
11	Karaba 2021	1016	717	71	12	674	12	1004	12	12	674	674
12	Karami 2021	925	669	72.32		NA	15	910	15	15	639	645
13	Lehmann 2021	321	222	69		NA	7	314	7	7	221	223
14	Martin 2021	208	172	83	9	163	12	196	9	9	163	163
15	Martinez-Guerra 2021	794	731	92		NA	29	765	28	29	537	542
16	Milas 2021	164	100	61		NA	28	136	27	28	96	96
17	Neto 2021	242	162	67	46	116	46	196	46	46	116	116
18	Nori 2021	152	120	79		NA	61	91	60	60	64	65
19	Papst 2022	988	521	52.7		NA	19	969	19	19	681	687
20	Petty 2021	2205	1386	62.9	127	1259	141	2064	127	127	1259	1259
21	Pink 2021	99	68	68.7		NA	12	87	12	12	61	62
22	SEMI-COVID-19Network 2(	13932	10885	78.13		NA	1519	12413	1490	1497	8718	8800
23	Sharma 2021	1844	611	75		NA	146	1698	143	144	1193	1204
24	Soto 2021	93	76	81.7		NA	37	56	36	36	39	40
25	Stevens 2021	654	557	85.1		NA	49	605	48	48	425	429
26	Townsend 2020	117	95	81		NA	15	102	15	15	72	72
27	VanLaethem 2022	429	171	39		NA	21	408	21	21	287	289
28	Vaughn 2020	1705	965	56.6	47	918	59	1646	47	47	918	918
29	Wang 2021	1396	1368	98%		NA	12	1384	12	12	972	981

Table 3: Calculated data based on the pooled percentage of # of COVID-19 Patients who received antibiotics who have or have no bacterial infection. Green cells are the data we had available from the article. The yellow cells are the data we calculated from the pooled percentage of the data available from the studies reported on that information.

CHAPTER III

RESULTS

A total of 7422 abstracts from four different databases (OVID MEDLINE, EMBASE, Web of Science, and Cochrane Library) were identified and imported for screening. After the removal of duplicates, 5474 unique citations were reviewed, and we selected 125 studies for full-text review.

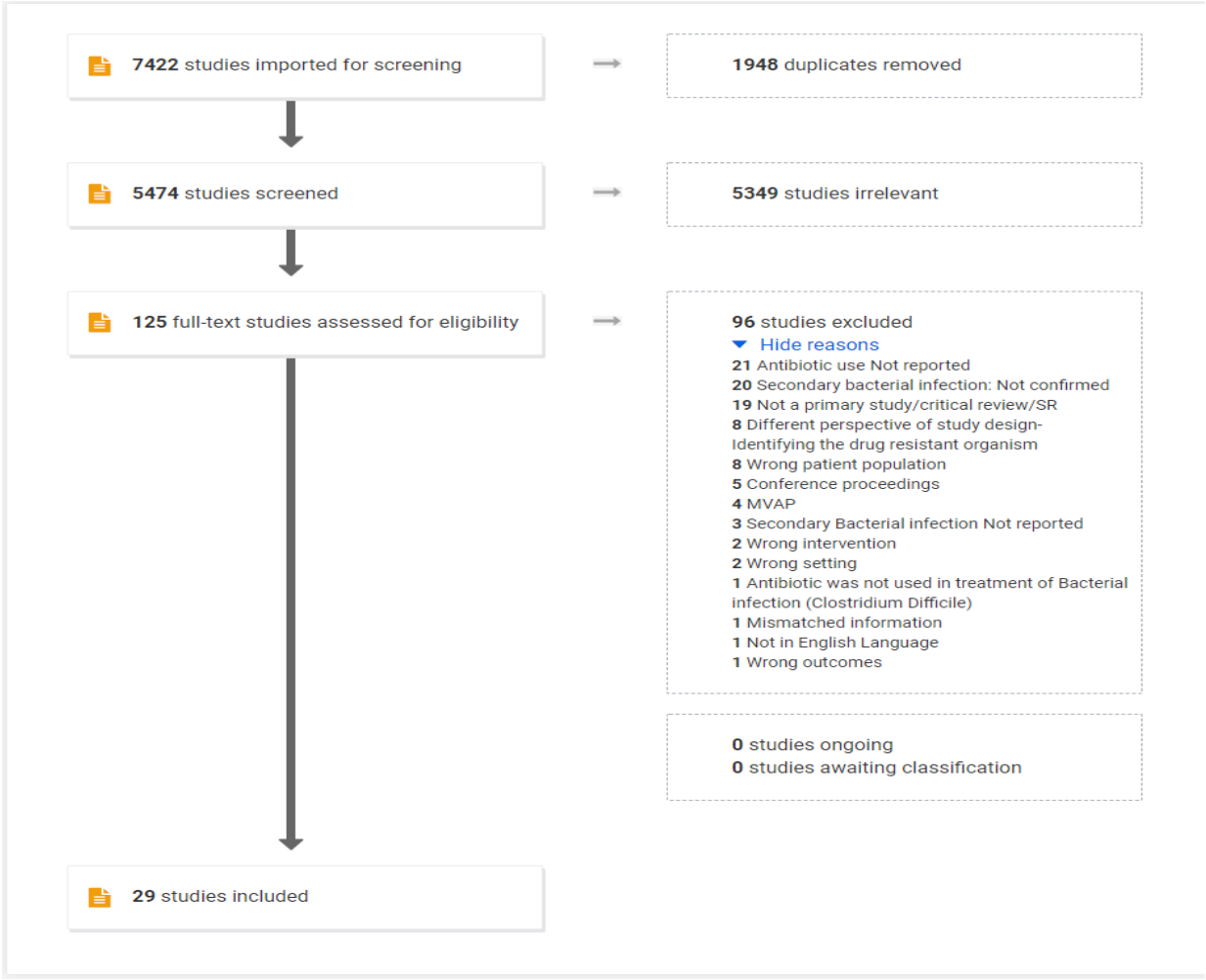

Figure 3: PRISMA flowchart for Systematic Review

Of these, 29 articles were included in this review. The total number of participants contributing data from the selected studies was 157,623, approximately 56% of whom were male (see **Table 4**). **Figure 3** shows the PRISMA flowchart for the study selection process, and **Table 4** depicts the summary for the selected articles.

Only 13 of the 29 (44.23%) identified studies reported discrete information on antibiotic prescription among patients without bacterial infection and/or bacterial coinfections, and only five articles among the included 29 reported separately about the secondary bacterial infection ranging from 1.56% to 32.3%, with an average of 10.3%.

Among the included studies, 93% (27) were cohort studies, and only 7% (#9 and #16) were cross-sectional studies. The studies from Upper and Lower Middle-Income Countries (U&LMICs, using the World Bank Country and Lending Groups (WorldBank, 2022)) were rare, and we only found 4 (14%) studies (only 2% of the total study population) from U&LMICs that met our eligibility criteria; 86% of studies (representing 98% of the study population) were from High-Income Countries (HICs). to We found the highest number of the studies for our review from the USA (10, 34%), followed by the UK (3, 10%), Belgium (2, 7%), Netherlands (2, 7%), Spain (2, 7%), and 1 (3%) study from each of the following countries- France, Germany, Hong Kong, India, Indonesia, Ireland, Italy, Mexico, Peru. One multinational study was conducted in Croatia, Italy, Serbia, and Slovenia.

The timeline for the study period is categorized as the pre-immunosuppressive (1 December 2019 to before 16 June 2020) and post-immunosuppressive (After 17 June but before 30 November 2021) to observe the antibiotic prescription pattern before and after the announcement of dexamethasone as the treatment for COVID-19 (Ledford, 2020). A total of 18 studies (62%) were conducted during the pre-immunosuppressive period and 11 (38%) during the post-immunosuppressive period. We also categorized the period around the beginning of omicron (end of November 2021) because hospitalization with/for COVID had become a common but severe occurrence, creating a different pandemic situation than the pre-omicron. However, we did not find any studies from the end of November 2021 onwards.

Figure 5 shows the percentages of antibiotic prescriptions among the total population. Only four studies reported an antibiotic prescription percentage lower than 50%, and the highest percentage was observed by Wang (2021) at 98%, with CI 97% to 99%. The bacterial coinfection pooled percentage was only 12%, ranging from 1.2% (Wang et al., 2021) to 46.38% (Grasselli et al., 2021), which was available from 157623 participants in 29 studies.

Summary Table for the Selected Articles

#	Study ID	Country of the research	Study design	Study period ended	Sample Size	Age	Age CoT measurement	# of Male	# of Female	% of Patient with Antibiotics	Most common Antibiotic prescribed	% of Most common Antibiotic prescribed	Second Most common Antibiotic prescribed	% of 2nd Most common Antibiotic prescribed	Third Most common Antibiotic prescribed	% of 3rd Most common Antibiotic	# of Pt with Bacterial CI	% of Pt with Bacterial CI
1	Vaughn 2020	USA	Cohort study	1 Dec 2019 to before 16 Jun 2020	1705	64.7	Median	885	820	56.6	Cephalosporin	38.9	Vancomycin	13.8	Doxycycline	10.9	59	3.5
2	Petty 2021	USA	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	2205	64.9	Median	1154	1051	62.9	NA	NA	NA	NA	NA	NA	141	6.4
3	Lehmann 2021	USA	Cohort study	1 Dec 2019 to before 16 Jun 2020	321	60	Mean	155	166	69	NA	NA	NA	NA	NA	NA	7	2.2
4	Nori 2021	USA	Cohort study	1 Dec 2019 to before 16 Jun 2020	152	62	Median	89	63	79	NA	NA	NA	NA	NA	NA	61	40.13
5	Elabbadi 2021	France	Cohort study	1 Dec 2019 to before 16 Jun 2020	101	61	Median	79	22	57.4	NA	NA	NA	NA	NA	NA	20	19.81
6	Asmarawati 202	Indonesia	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	218	52.45	Median	120	98	75.2	Quinolone	60.1	Cephalosporin	28.44	Carbapenem	23.85	43	19.72
7	Sharma 2021	India	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	1844	48	Median	NA	NA	75	NA	NA	NA	NA	NA	NA	146	17.9
8	VanLaethem 20	Belgium	Cohort study	1 Dec 2019 to before 16 Jun 2020	429	64	Median	245	184	39	Penicillin + Beta lactamase inhibitor	89.5	Quinolone	4.1	Macrolide	2.7	21	5
9	Papst 2022	Croatia, Italy, Serbia and Slovenia	Cross sectional study	After 17 Jun 2020 but before 30 Nov 2021	988	NA	Median	NA	NA	52.7	Cephalosporin	NA	Carbapenem	NA	Macrolide	NA	19	1.9
10	Martin 2021	USA	Cohort study	1 Dec 2019 to before 16 Jun 2020	208	69	Median	105	103	83	Cephalosporin	66	Macrolide	57	Beta lactam and Vancomycin	23	12	8
11	Angell 2021	USA	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	296	NA	Mean	NA	NA	35.47	NA	NA	NA	NA	NA	NA	50	16.89
12	Baghdadi 2021	USA	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	64961	18 to >70	Range	34370	30494	76.3	Cephalosporin	48.5	Macrolide	46	Glycopeptides and lipoglycopeptides	22.9	12040	18.5
13	Townsend 2020	Ireland	Cohort study	1 Dec 2019 to before 16 Jun 2020	117	66	Median	74	43	81	Penicillin+Clavulanic acid	NA	Penicillin+tazobactam	NA	Cephalosporin	NA	15	12.82
14	Cheng 2020	Hong Kong	Cohort study	1 Dec 2019 to before 16 Jun 2020	147	36	Median	85	62	35	Cephalosporin	88	Penicillins	88	Tetracyclines	27	12	8.2
15	Milas 2021	Belgium	Cohort study	1 Dec 2019 to before 16 Jun 2020	164	60.5	Median	81	83	61	Penicillin+ Beta lactamase inhibitor	52.4	Macrolide	30	Cephalosporin	28	28	17.1

Summary Table for the Selected Articles (Continued)

#	Study ID	Country of the research	Study design	Study period ended	Sample Size	Age	Age CoT measurement	# of Male	# of Female	% of Patient with Antibiotics	Most common Antibiotic prescribed	% of Most common Antibiotic prescribed	Second Most common Antibiotic prescribed	% of 2nd Most common Antibiotic prescribed	Third Most common Antibiotic prescribed	% of 3rd Most common Antibiotic prescribed	# of Pt with Bacterial CI	% of Pt with Bacterial CI
16	Karaba 2021	USA	Cross sectional study	1 Dec 2019 to before 16 Jun 2020	1016	62	Median	543	473	71	NA	NA	NA	NA	NA	NA	53	5.2
17	SEMI-COVID-1	Spain	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	13932	56.5-77.2	Range	NA	NA	78.13	Beta lactam	72.2	Quinolone	13.4	Oxazolidinones (Linezolid)	2.2	1519	10.9
18	Grasselli 2021	Italy	Cohort study	1 Dec 2019 to before 16 Jun 2020	774	62	Median	597	177	69	Broad Spectrum	44.94	Narrow Spectrum	55.06	Other: NA	NA	359	46.38
19	Karami 2021	Netherlands	Cohort study	1 Dec 2019 to before 16 Jun 2020	925	70	Median	591	334	72.32	Cephalosporin	37.8	Combined	NA	Penicillin	NA	15	1.6
20	Wang 2021	UK	Cohort study	1 Dec 2019 to before 16 Jun 2020	1396	67.4	Mean	903	493	98	Penicillin	NA	Penicillin+Macrolide	NA	Cephalosporin	NA	12	1.2
21	Hughes 2021	UK	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	624	40.2-79.5	Range	NA	NA	49.7	Penicillin	65.81	Cephalosporin	8.71	Quinolone	8.39	17	2.7
22	Estrada 2021	Spain	Cohort study	1 Dec 2019 to before 16 Jun 2020	13932	69	Median	7819	5902	87.8	Beta-lactams	72	Macrolide	60.2	Quinolone	13.3	1481	10.8
23	Soto 2021	Peru	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	93	61.7	Median	66	27	81.7	Macrolide	62.37	Cephalosporin	21.51	NA	NA	37	40.86
24	Pink 2021	Germany	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	99	57	Median	72	27	68.7	Penicillin+ Beta lactamase inhibitor	34.3	Meropenem	NA	NA	NA	12	12.121212
25	Martinez-Guerra 2021	Mexico	Cohort study	1 Dec 2019 to before 16 Jun 2020	794	52	Median	489	305	92	Penicillin	46.6	Cephalosporin	29.1	Macrolide	12.9	29	3.65
26	ISARIC4C Investigators 2021	UK	Cohort study	1 Dec 2019 to before 16 Jun 2020	48902	74	Median	27979	20786	85.2	Beta lactam+ Betalactamase inhibitor	30	Penicillin	10.2	NA	8.9	1942	3.97
27	Coenen 2021	Netherlands	Cohort study	1 Dec 2019 to before 16 Jun 2020	384	61.1	Mean	157	124	81	Cephalosporin	73.25	Quinolone	10.96	Combination	10.52	11	2.86
28	Stevens 2021	USA	Cohort study	After 17 Jun 2020 but before 30 Nov 2021	654	63.6	Mean	365	289	85.1	Cephalosporin	NA	Vancomycin	61.76	Macrolide	NA	49	7.49
29	Neto 2021	USA	Cohort study	1 Dec 2019 to before 16 Jun 2020	242	66	Mean	123	119	67	Cephalosporin	54	Vancomycin	48	Macrolide	47	46	19

Table 4: Summary table for the included articles

Quality Assessment for the Risk of Bias

We used The Joanna Briggs Institute (JBI) Critical Appraisal tools checklist for the prevalence study to assess the quality of the included studies and any risk of bias. **Figure 4** presents the summary of the checklist.

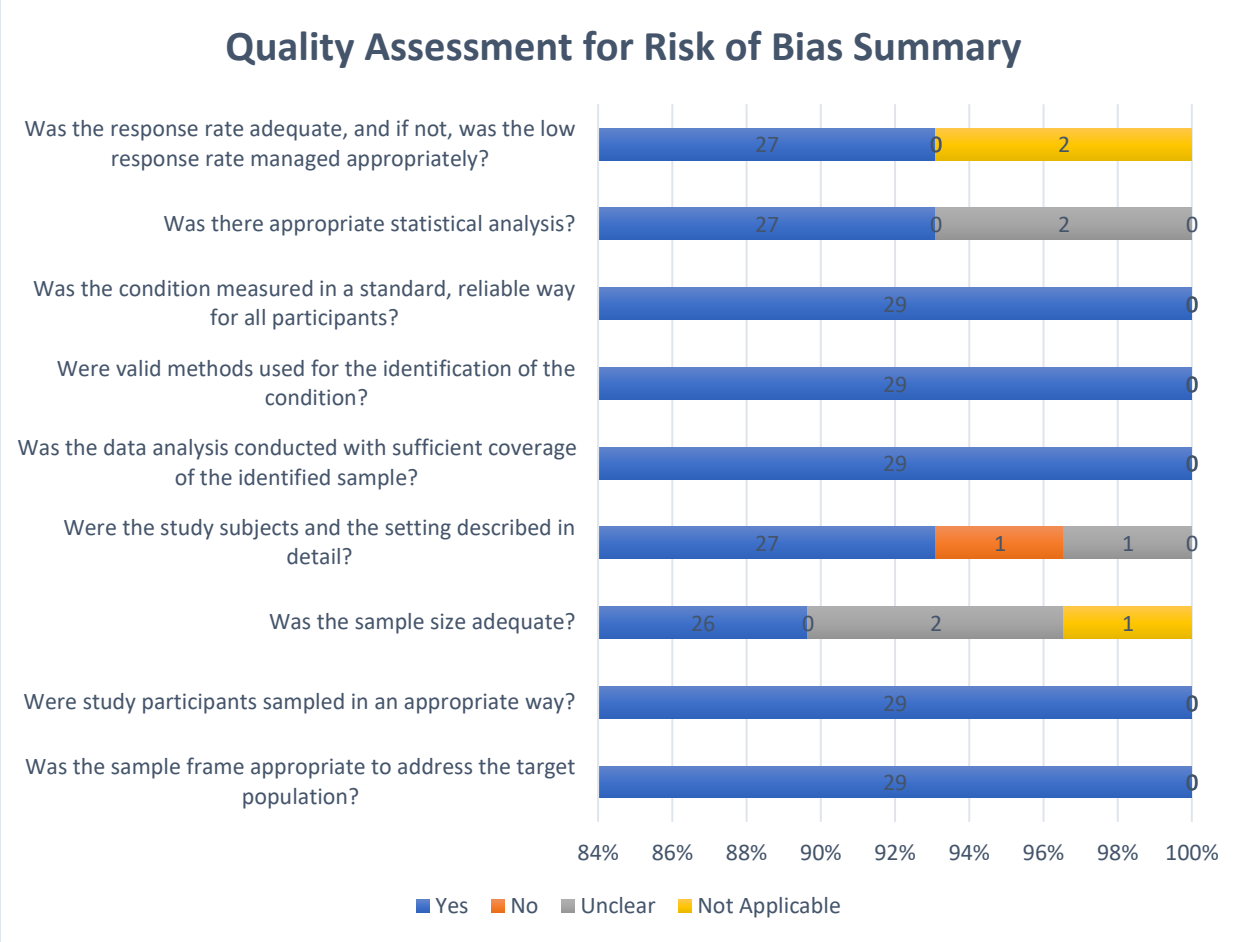

Figure 4: Quality Assessment for the Risk of Bias Summary

100% of the included studies had the proper sample framing and followed the sampling method. Also, all the studies used valid methods to identify the patients' conditions. Data analysis covered sufficient participants for all the studies. For two studies (Elabbadi et al., 2021; Townsend et al., 2020), statistical analysis was unclear as they did not mention any specific method in their

reports. One study (Angell et al., 2021) did not describe the study settings in detail, and it was unclear for another study (Papst et al., 2022). It was unclear for the two studies (Cheng et al., 2020; Pink et al., 2021) for adequate sample size, as they analyzed the data from the hospital register, and there was no sufficient information on the total number of admitted patients during the study period. However, these six studies contributed only 1% (n=1748/157623) of the total population of the review.

Antibiotics Prescription rate among the Hospitalized COVID-19 Patients

The pooled percentage of antibiotic prescriptions was 67% (CI 64% to 71%, P< 0.00001), which was 70% (CI 65% to 75%, P<0.00001) during the pre-immunosuppressive period, and 63% (CI 54% to 72%, P<0.00001) for the post-immunosuppressive period (see **Figure 5**). Although there was a 7% difference in the overall antibiotic prescription rate between before and after the immunosuppressive period, it was not statistically significant (P<0.19).

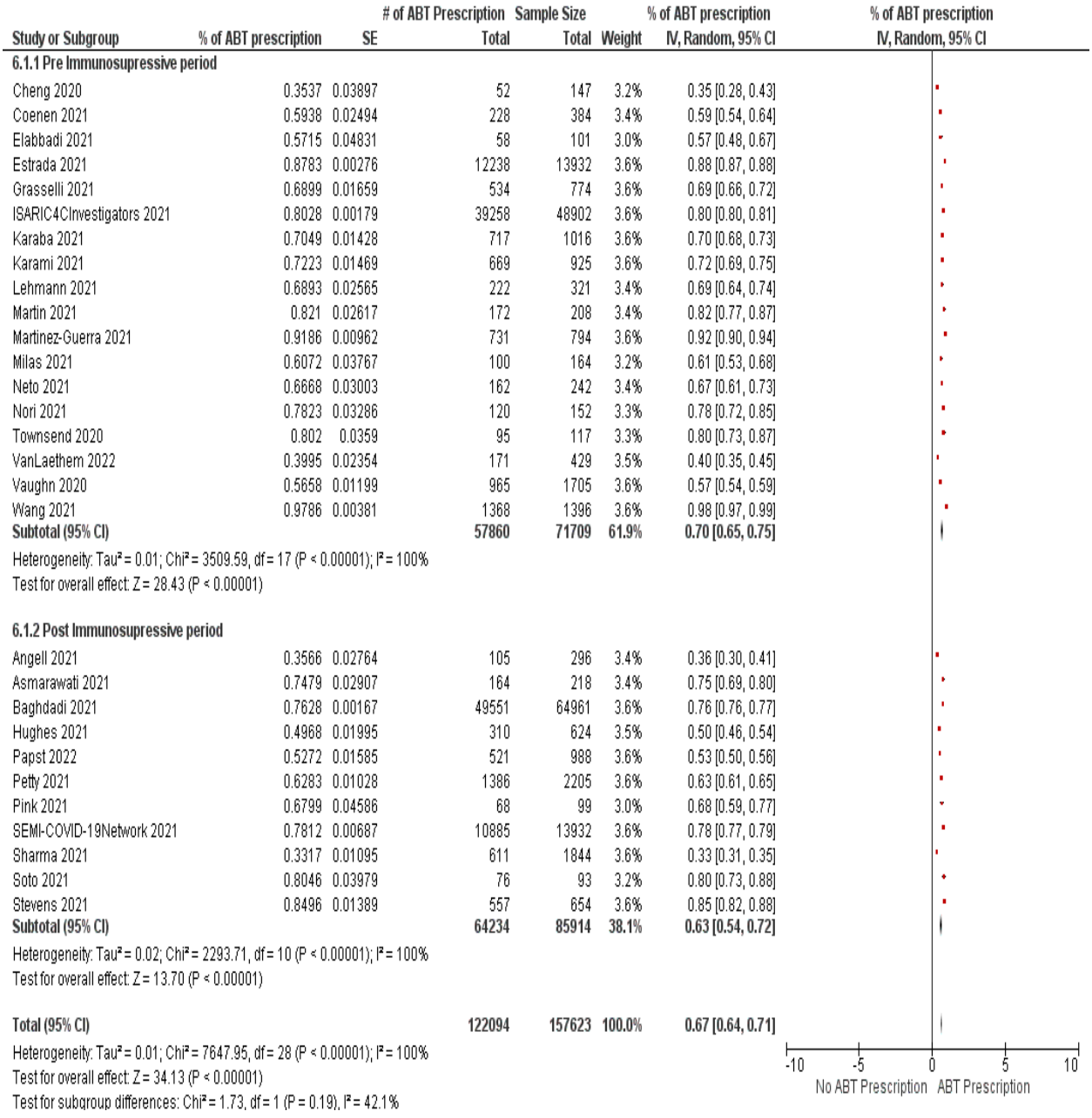

Figure 5: Percentage of Antibiotic prescriptions among the total population

Risk of Receiving Antibiotic Prescription among COVID-19 Patients without Bacterial Coinfections

Of total Antibiotic prescriptions, the percentage of Antibiotic prescriptions among COVID-19 patients without any bacterial coinfection was 81% (CI 75% to 88%, P<0.00001, # of studies=13, antibiotic prescriptions without bacterial coinfections=50735, total antibiotic prescriptions=66332) while calculated only for the articles with available data, 78% (CI 74% to 82%, P<0.00001, # of studies=11, antibiotic prescriptions without bacterial coinfections=44603, total antibiotic prescriptions=53927) while calculated only for the articles with assumed data imputed from the **lowest value of CI** and overall 80% (CI 76% to 83%, P<0.00001, # of studies=24, antibiotic prescriptions without bacterial coinfections=95338, total antibiotic prescriptions=120259) while calculated with both the articles with available data and the articles with assumed data imputed from the **lowest value of CI**. (See **Figure 6** is for Lowest value of CI, and **Figure 7** is for Highest value of CI). If used appropriately, the percentage of patients prescribed antibiotics in the absence of a confirmed bacterial co-infection or secondary infection should be 0%, consistent with the definition of good Antimicrobial Stewardship (Llor & Bjerrum, 2014). Thus the values we have obtained are consistent with over prescription. Of total Antibiotic prescriptions, the percentage of Antibiotic prescriptions among COVID-19 patients without any bacterial coinfection was 79% (CI 75% to 83%, P<0.00001; # of studies=11, antibiotic prescriptions without bacterial coinfections=47855, total antibiotic prescriptions=55762) while calculated only for the articles with assumed data imputed from the **highest value of CI** and overall 80% (CI 76% to 83%, P<0.00001; # of studies=24, antibiotic prescriptions without bacterial

coinfections=98590, total antibiotic prescriptions=122094) while calculated with both the articles with available data and the articles with assumed data imputed from the **highest value of CI**.

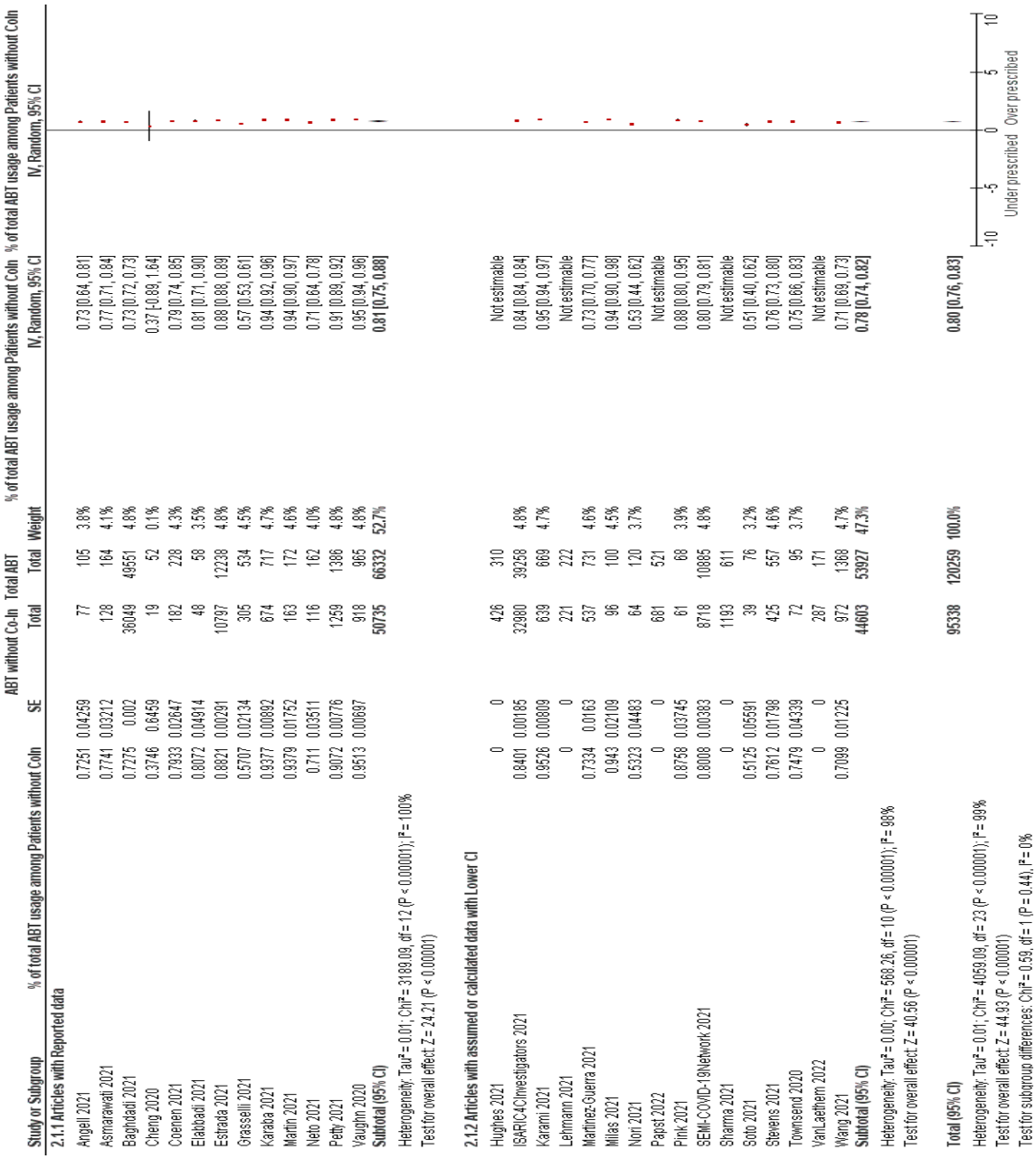

Figure 6: Percentages of Antibiotic prescription among the COVID-19 patients without bacterial coinfections for the articles with available data and the articles with assumed data for lower CI

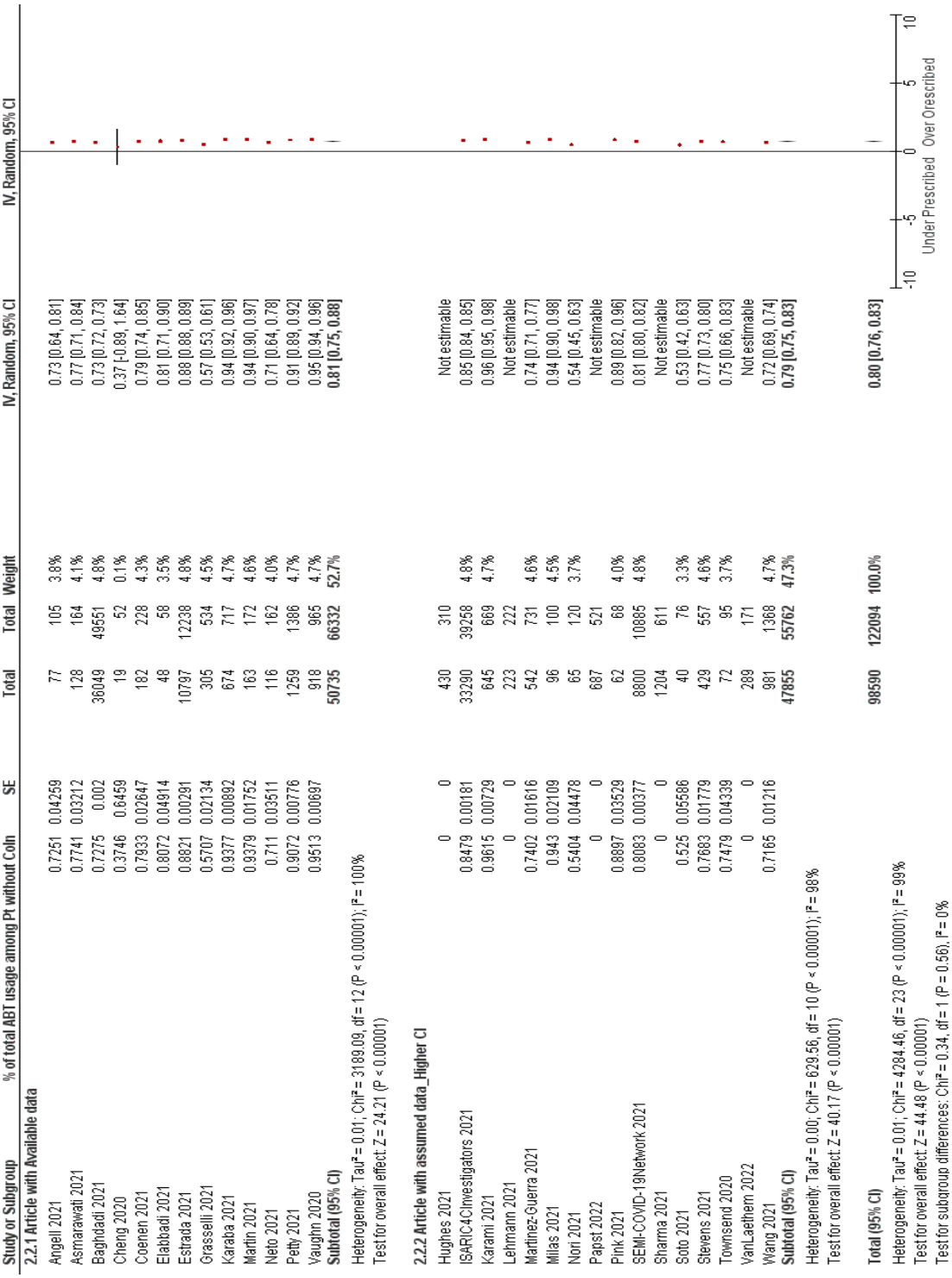

Figure 7: Percentages of Antibiotic prescription among the COVID-19 patients without bacterial coinfections for the articles with available data and the articles with assumed data for higher CI

While comparing the pre-immunosuppressive and post-immunosuppressive periods, we found 4% higher antibiotic prescriptions during the pre-immunosuppressive period. We included the articles where all the data available and the articles with assumed data for both the highest and lowest value of CI. At first, we used the articles with available data and the assumed data imputed from the lowest value of CI. Then we repeated the analysis for the articles with available data and the assumed data imputed from the highest value of CI. The 4% higher antibiotic prescriptions were constant during the pre-immunosuppressive period than the post-immunosuppressive period for both analyses. However, it was not statistically significant (P=0.19 and 0.21) (see **Figure 8** and **Figure 9**), indicating antibiotic prescriptions were not reduced remarkably after the announcement of dexamethasone as the COVID-19 treatment. For the articles with available data and lowest CI data, the Antibiotic prescription rate (of total Antibiotic prescriptions) among the COVID-19 patients without bacterial coinfections was 81% (CI 78% to 85%, P<0.00001; # of studies=16, antibiotic prescriptions without bacterial coinfections=48582, total antibiotic prescriptions=57467) in the pre-immunosuppressive period, whereas it was 77% (CI 72% to 82%, P<0.00001; # of studies=8, antibiotic prescriptions without bacterial coinfections=46756, total antibiotic prescriptions=62792) in the post-immunosuppressive period (see **Figure 8**). The rate was almost similar for the highest CI data and the available data, with 82% (CI78% to 85%, P<0.00001; # of studies=16, antibiotic prescriptions without bacterial coinfections=48913, total antibiotic prescriptions=57467) and 78% (CI 72% to 83%, P<0.00001; # of studies=8, antibiotic prescriptions without bacterial coinfections=49165, total antibiotic prescriptions=64234) in the pre-immunosuppressive period and post-immunosuppressive period respectively (see **Figure 9**).

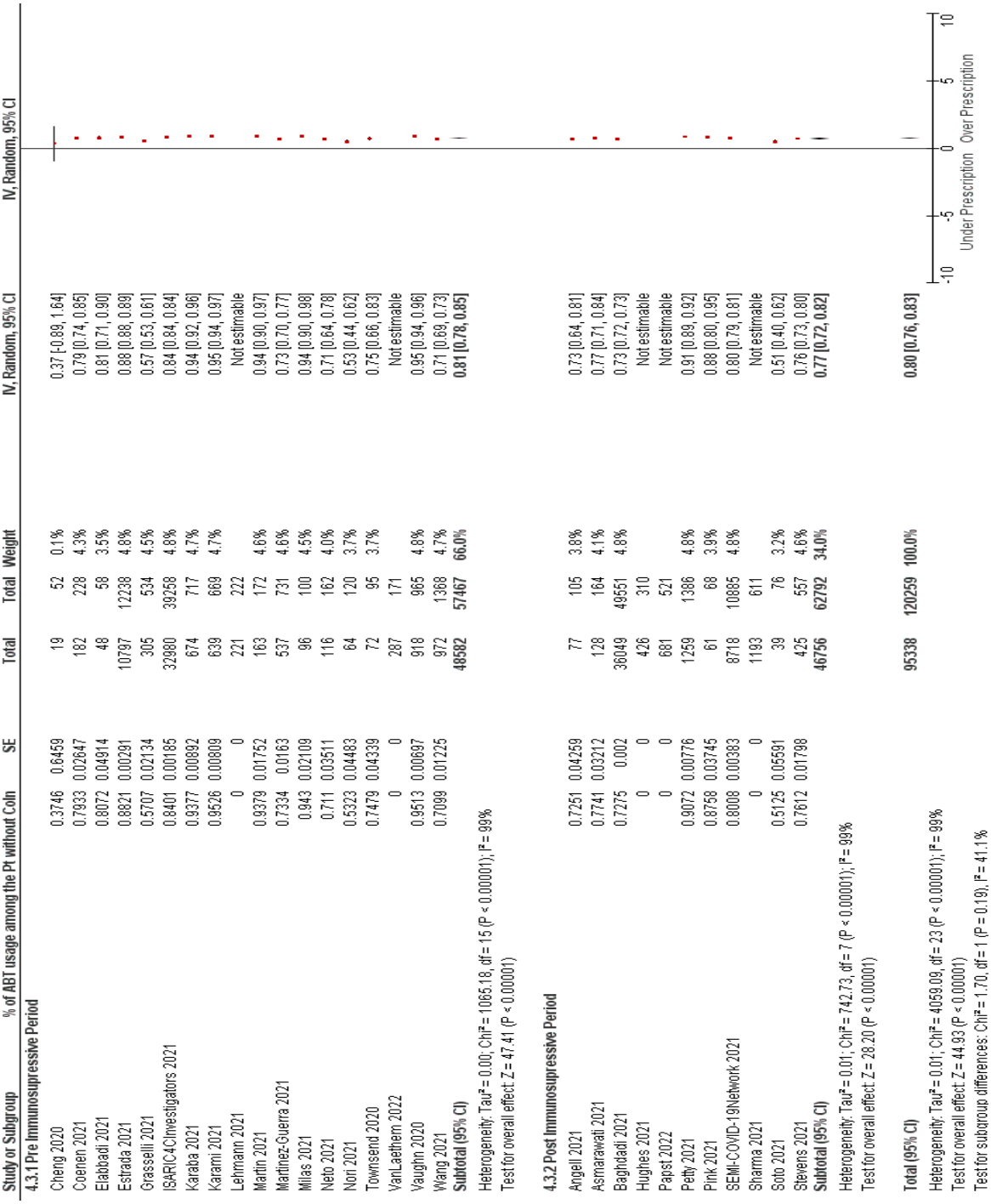

Figure 8: Comparison of Antibiotic prescription percentages among COVID-19 patients without bacterial coinfections between the pre-immunosuppressive period and the post-immunosuppressive period with the articles with available data and the lowest CI data

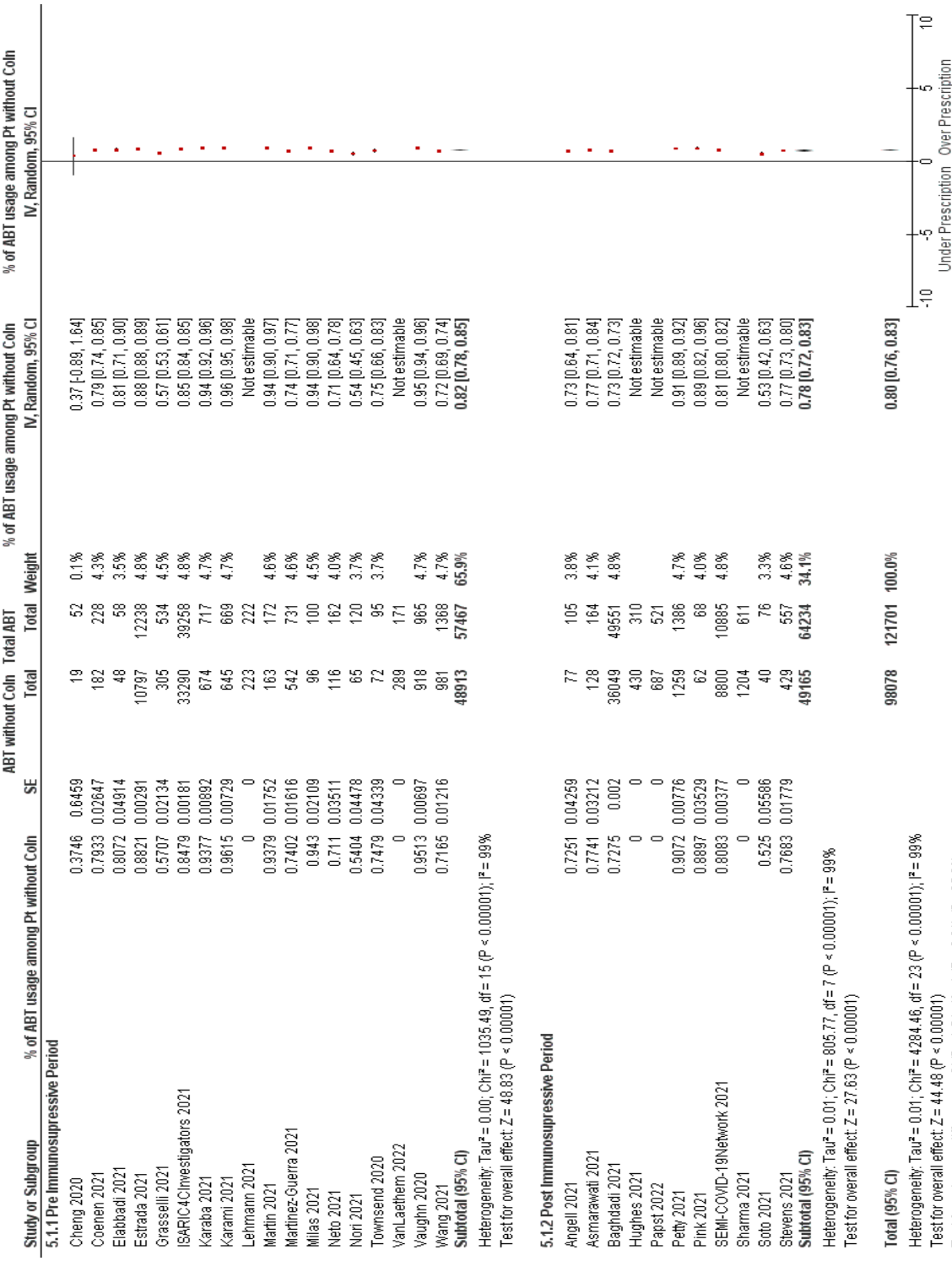

Figure 9: Comparison of Antibiotic prescription percentages among COVID-19 patients without bacterial coinfections between the pre-immunosuppressive period and the post-immunosuppressive period with the articles with available data and the highest CI data

In our meta-analysis, the antibiotic over-prescription rate is remarkably higher in High-income Countries (HICs) than the Upper and Lower Middle-income Countries (U&LMICs). It was the same for the lowest and highest CI data, including the available data. While in HICs, the percentage was 81% (CI 78% to 85%, P<0.00001), it was 69% (CI 59% to 79%, P<0.00001) in U&LMICs (p-value for subgroup differences = 0.03; **Figure 10**). However, U&LMICs comprised only 2% of the study population for our meta-analysis.

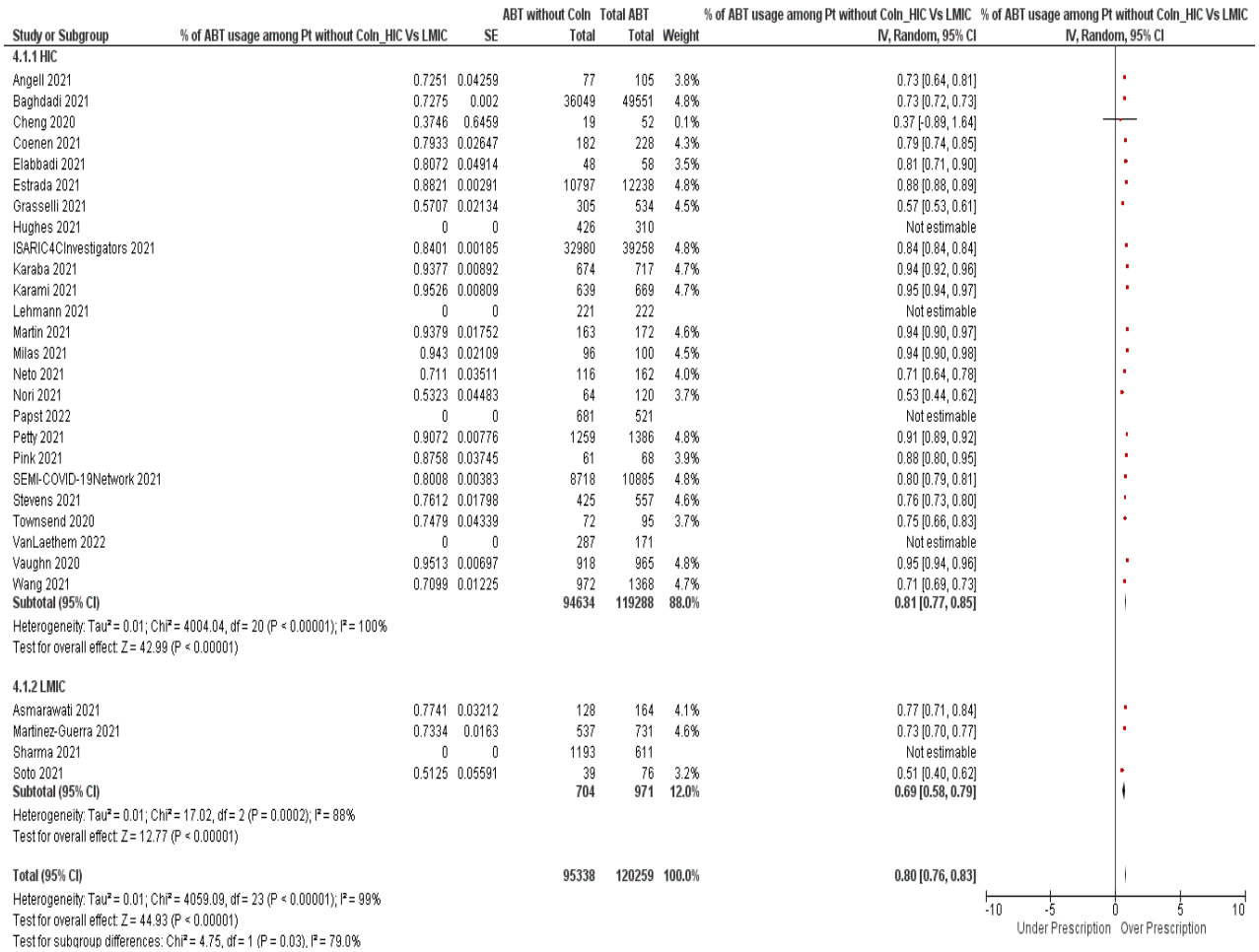

Figure 10: Percentage of over-prescription in HICs and U&LMICs

CHAPTER IV

DISCUSSION

In our Systematic Review and Meta-analysis, we found that more than one-third of the study population were prescribed antibiotics, and four out of five antibiotic prescriptions were given to patients without bacterial infection. The rates were higher in HIC compared with U&LMIC but were robust to several approaches to handling missing data. In contrast, bacterial coinfection was rare among hospitalized COVID-19 patients, and only one out of ten had bacterial coinfection. Critically ill patients were more likely to be affected by bacterial coinfections.

A meta-analysis by Langford et al., 2021 revealed a similar result, with three-quarters of COVID-19 patients being treated with antibiotics, although bacterial coinfections were reported only 6.1% to 8% (B J Langford et al., 2021). In another living rapid review and meta-analysis, Langford et al., 2020 found 3.5% bacterial coinfections, 14.3% secondary bacterial infection, and overall 6.9% bacterial infection among the COVID-19 patients and critically ill patients were mainly affected (B J Langford et al., 2020). However, the antibiotic prescription rate was 71.9% among COVID-19 patients. In our meta-analysis, the study (Grasselli et al., 2021) on hospitalized critical COVID-9 patients reported the highest bacterial coinfection percentage (46.38%). Findings from the Systematic Review study by Abu-Rub et al., 2021 estimated 30.8% bacterial coinfection among the ICU admitted COVID-19 patients, yet 71% antibiotic prescription rate to treat those COVID-19 patients, which was more than double the bacterial infections (Abu-Rub et al., 2021).

In most cases, the patients were empirically given antibiotics during admission without any pathological test, blood, urine, or sputum culture. Multiple studies (B J Langford et al., 2020; Lansbury et al., 2020; Rawson, Zhu, et al., 2020) suggested that the initial reason for prescribing antibiotics was suspected bacterial infection, despite the viral characteristics of the disease. Langford et al., 2020 listed age and mechanical ventilation in ICU as other factors contributing to increased antibiotic prescriptions. Older patients and patients under mechanical ventilation were more likely to receive antibiotics (B J Langford et al., 2021).

At the outset of the COVID-19 pandemic, very little was known about the virus, and there were few options for effective treatments to relieve symptoms. Extreme hospital patient load during the pandemic skewed hospital admission rate might be why antibiotics were prescribed without a confirmed bacterial infection, because of limited knowledge and confusion among clinicians regarding the novel disease, especially at the onset of the pandemic. Abelenda-Alonso & Carratala, 2020 supported the lack of information, emergency preparedness, and testing facilities as the immediate result of increased antibiotic prescription. They also reported that the timeline from March to May of 2020 was the period of the most antibiotics usage (Abelenda-alonso & Carratalà, 2020).

Although we did not do any time-series analysis in our review for the increased usage of antibiotics during the pandemic, compared to the pre-pandemic period, several studies reported increased antibiotic prescriptions during the pandemic, especially at the beginning of it, compared

with the pre-pandemic period (Al-azzam et al., 2021; Andrews et al., 2021; Grau et al., 2021). Al-Azzam et al., 2021 reported on the increased use of specific antibiotics such as third-generation Cephalosporin and Azithromycin during the pandemic's beginning (Al-azzam et al., 2021). We also found that Cephalosporin was the most used antibiotic to treat hospitalized COVID-19 patients. Macrolides were the second and third most commonly prescribed antibiotics. In a time-series analysis examining antibiotic purchasing patterns, Khouja et at., 2022 reported that the global antimicrobial consumption rate increased by 11.2% ($P<0.001$), and the antibiotic consumption rate increased by 6.9% (Khouja et al., 2022) in 2020, over previous years from 2015 to2019. The same study reported that from 2015 to 2019, antibiotic consumption had been steadily decreasing.

Khouja et at., 2022 also reported higher consumption of antibiotics in developed countries than the developing countries in their time-series study from 2015 to 2020, and this higher consumption was consistent. It might be for the accessibility of drugs. Our Systematic review and meta-analysis found a higher antibiotic prescriptions rate in HICs than the U&LMICs. However, it was expected that HICs would be more compliant with judicial antibiotic prescription due to the wide and evident implication of the Antimicrobial Stewardship (AMS) program in those High-income settings (Cox et al., 2017; Kpokiri et al., 2020). Besides, the availability of blood, urine, or sputum culture tests was supposed to be present in high-resource settings, which should also positively impact judicial antibiotic prescriptions. However, the underlying factor for higher consumption of antibiotics in HICs could be the negative impact of COVID-19 on the AMS programs. A study conducted in the UK by Ashiru-oredope et al. (2021) reported a significant negative impact of COVID-19 on the ongoing national AMS program (Ashiru-oredope et al.,

2021). In our review, we found a very minimal population from U&LMICs countries. Although, a study by Molla et al., 2021 reported a 100% antibiotic prescriptions rate in a dedicated COVID-19 ward in Dhaka Medical College Hospitals in Bangladesh (Molla et al., 2021).

Our review also found differences in antibiotic prescription rates between the pre-immunosuppressive period (before the announcement of dexamethasone as the treatment for COVID-19) and post-immunosuppressive period, although the result was not significant (P<0.19). Dexamethasone was the first proven drug that showed positive outcomes in reducing the mortality of COVID-19 patients (Lim et al., 2021). It was a significant breakthrough for COVID-19 treatment, and expected that it would reduce the non-judicial antibiotic prescriptions. However, the research on this issue is rare, and we did not find any studies that explicitly compared the antibiotics usage rate for those periods.

Self-medication for COVID-19 treatment was a critical concern during the pandemic, although self-medicating with antibiotics has always been a contributor to worsening Antimicrobial resistance. An online cross-sectional survey in Dhaka city (Bangladesh) revealed that self-medication during the pandemic of COVID-19 was 88.33%. In contrast, only 179 (29%) sought a doctor's advice before taking medication, and the remaining 447 (71%) study participants took the drugs without any Physicians' concern. Ivermectin (77%) was the most commonly self-prescribed drug, followed by azithromycin (54%) and doxycycline (40%) (Nasir et al., 2020). Due to a lack of a proper monitoring system, it is challenging to track non-prescription drug purchases, especially in Lower and Middle-Income Countries (LMICs). In our current review, we only found

four studies from LMICs, that contributed only 2% of the total study population. Zhang et al., 2021 highlighted "COVID-19 pandemic-induced psychological distress" as one of the significant factors related to increased self-medication. Prophylactic use of antibiotics was also caused by a knowledge gap about antibiotics, inappropriate antibiotic prescription practices, the qualities of the patient-doctor relationship, and demographic factors (Zhang et al., 2021). A comprehensive review by Jirjees et al., 2022 also showed that the prevalence of antibiotic self-prescription rate raised by 25% (from 20.8% to 45.8%) during the COVID-19 pandemic in the Eastern Mediterranean region, and it was associated with fear of COVID-19 infection, quarantine, cost-saving, and easy accessibility (Jirjees et al., 2022).

Findings from our Systematic Review and Meta-analysis suggest that limited testing facilities, as well as a lack of awareness and proper monitoring systems, an overwhelming situation due to skewed patient load and severity during the pandemic, and a lack of experience with such emergencies are vital factors that contributed the overuse of antibiotics. When resources are limited, strict compliance with the AMS can be an effective tool to avoid the misuse of antibiotics. Effective and regular training programs for health workers for emergency preparedness can improve their skills to deal with future health emergencies. Community awareness programs can help improve the general population's health literacy. An effective monitoring system for antibiotic purchases is needed, especially for the U&LMICs, where these crucial bacterial-resistant drugs are easily accessible even from street vendors, without any doctors' prescriptions.

Drug-resistant microorganisms, specifically, multi-drug-resistant bacteria, are likely to spread globally if unchecked. Robust data from U&LMICs is needed to understand the impact of the ongoing pandemic on AMR. In this era of globalization, worsening AMR in U&LMICs, is likely to spread resistant strains at a rapid pace. High-income countries with established mechanisms to control unregulated antibiotic use can support U&LMICs to adapt and introduce these mechanisms. Additionally, a standard data reporting system for inpatient hospital antibiotic use can effectively monitor trends in antibiotic use. Sales reports from pharmaceutical companies can help get the data for outpatient departments and self-medication practices.

The WHO's Antimicrobial Resistance Division on Global Coordination and Partnership is working on research and development of new antibiotics in the pipeline to tackle the AMR issues. However, only six compounds met the WHO innovation criteria, of which only two are effective against at least one multi-drug-resistant gram-negative bacteria (WHO, 2022a). WHO has already warned that though a few new innovative antibiotics are in the pipeline, if the habit of misuse of Antimicrobial drugs is not changed, the new antibiotics will face the same fate (WHO, 2021b).

Our risk of bias analysis showed that the studies (n=6) did not report clearly in different domains and contributed only 1% of the total population of our review. Moreover, the studies that did not clearly report an adequate sample size for analysis were retrospective studies with the data from the hospital register. While we did the subgroup analysis for the studies with a risk of bias

for the overall antibiotic prescription rate among hospitalized COVID-19 patients, we got a significant result (P=0.02) (**Figure 11**). However, for the percentage of antibiotic prescriptions among hospitalized COVID-19 patients without bacterial coinfections of total antibiotic prescriptions, the subgroup analysis for risk of bias was statistically significant (P=0.84) (**Figure 12**).

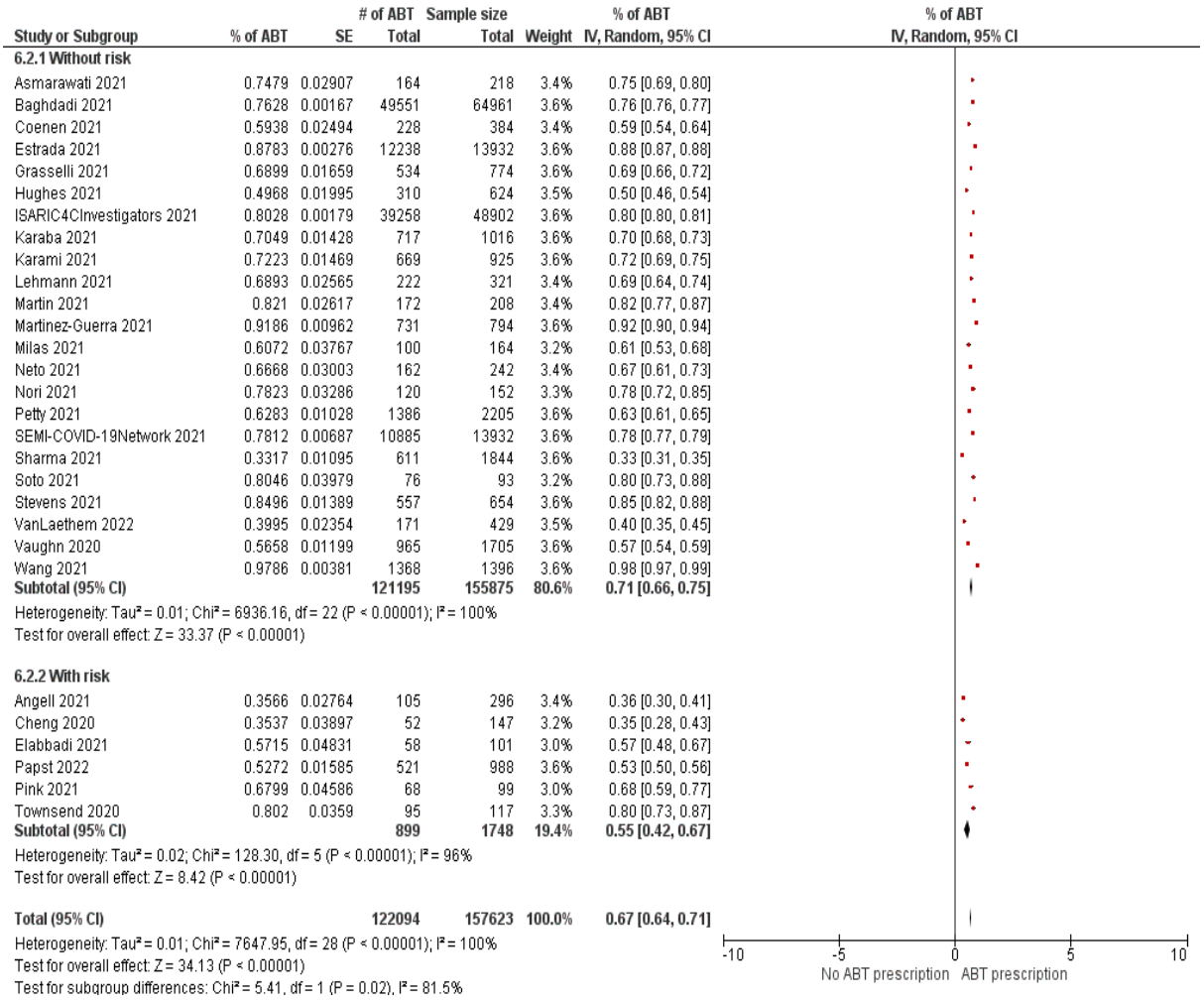

Figure 11: Risk of bias for the overall antibiotic prescriptions. Subgroup analysis for the studies with risk of bias.

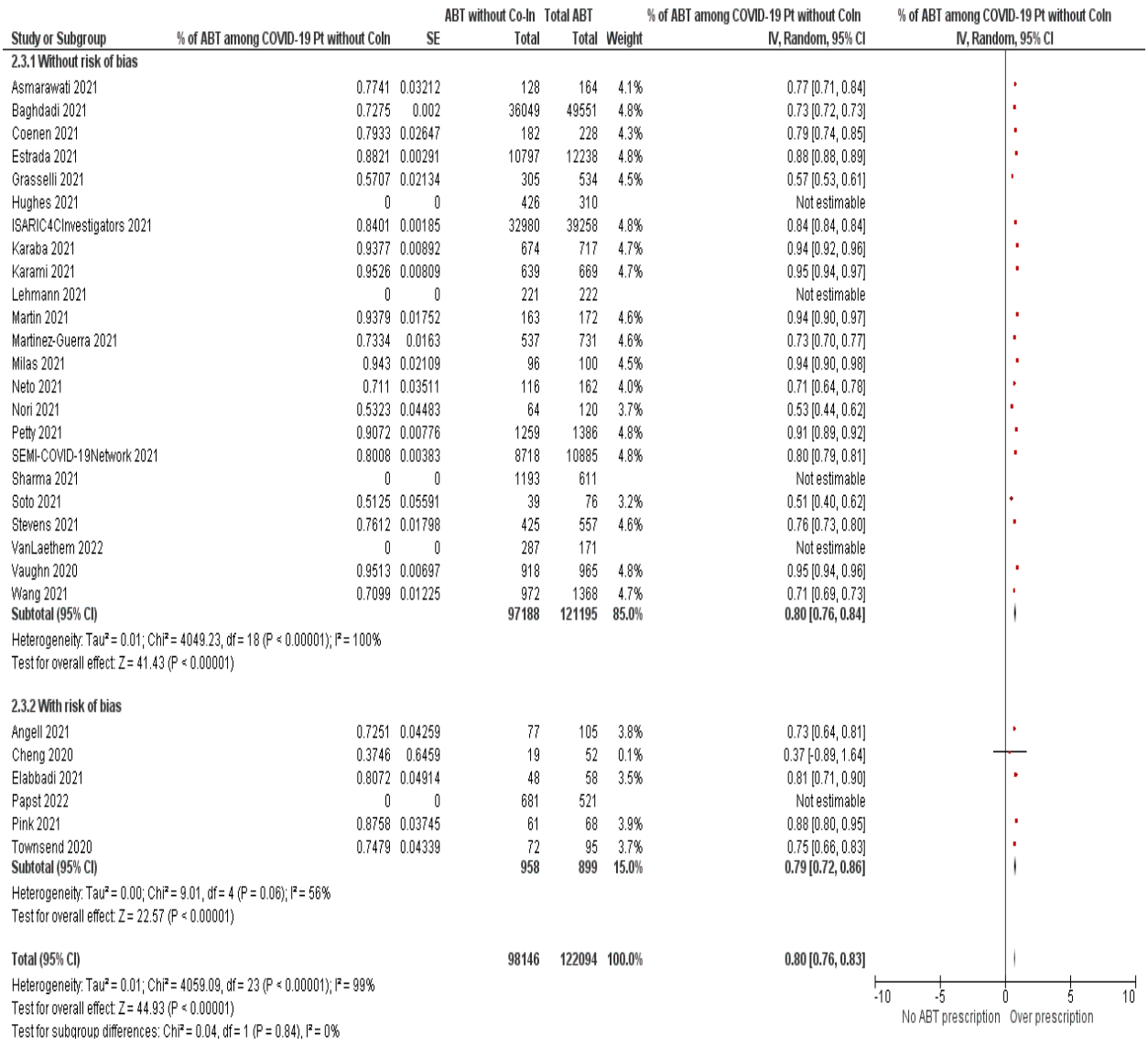

Figure 12: Risk of bias for total antibiotic prescriptions, the percentage of antibiotic prescriptions among the hospitalized COVID-19 patients without bacterial coinfections. Subgroup analysis for the studies with risk of bias.

Strength and Limitation:

Our Systematic Review and Meta-analysis had certain limitations in finding the appropriate data to answer our research question. We aimed to compare bacterial coinfection and antibiotic prescription frequencies among the same population; however, not many studies performed this comparison. Furthermore, few studies specifically presented data comparing antibiotic prescriptions between COVID-19 patients with and without bacterial coinfections. We had to rely on the studies with available data to calculate the percentages for the remaining included articles.

However, we strictly followed a robust literature search strategy with the help of our health science librarian (Information System specialist) to find out the maximum number of relevant articles. We adhered to strict inclusion and exclusion criteria, reviewed full-text articles, and extracted data independently and in duplicate, as per best practices, to ensure high-quality data. We presented the results separately to compare both outcomes for the available and assumed/calculated data (for lower and higher confidence intervals).

CHAPTER V

CONCLUSION

Antimicrobial Resistance (AMR) is one of the most significant global health concerns, threatening the prevention and treatment of infectious diseases caused by microbes. While the world is struggling to eliminate the curse of COVID-19, this "Invisible Pandemic" can be worsened by the misuse or overuse of antibiotics to treat COVID-19 patients without any bacterial infections. While our study portrayed that most antibiotic prescriptions were given to the COVID-19 patients without any bacterial infections, it suggests that the pandemic can be a critical contributor to AMR and worsen the situation globally. Even in the High-Income Countries, where the AMS programs failed to comply with it during the peak pandemic period. Data and research from the U&LMICs are rare; however, it is highly likely to overuse antibiotics in those countries. Additionally, the self-medication practices for those countries during the pandemic can ignite the risk.

At the onset of the 20th century, before the antibiotics era, infectious diseases were one of the major global causes of high morbidity and mortality (STAPLES, 2018). A simple scratch could be fatal; bacterial meningitis was a significant cause of child death with a 90% case fatality rate, and pneumonia and tuberculosis caused thousands of children's death (STAPLES, 2018). In

developed countries, antibiotics increased life expectancy by 20 years (STAPLES, 2018), and it increased from 47 to 77 years in the United States of America (USA) from the pre-antibiotics era before its discovery in 1928 to 2020 (CDC, 2022). However, unnecessary use of antibiotics can lead to antibiotic resistance. If we cannot restrain Antibiotic Resistance, curing the medical conditions caused by bacterial infections will be extremely challenging, and surgical procedures will be difficult due to potential infection due to surgery.

While our research discussed the primary issue of AMR during the COVID-19 pandemic, compared to the graveness of the situation, robust data collection for both HICs and U&LMICs is critical to answering the question of whether we are overtreating the COVID-19 patients with antibiotics. Data on the antibiotic used to treat the COVID-19 patients without bacterial infections and the COVID-19 patients with bacterial coinfections should be collected. Besides, comprehensive research on multi-drug resistant bacteria is crucial to seeing the current AMR status.

CHAPTER VI

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CHAPTER VII

APPENDICES

Appendix 1

DEVELOPING THE SYSTEMATIC REVIEW RESEARCH QUESTION: PICOTS WORKSHEET

Brainstorming

Write down (up to) 5 words that describe the topic of your research. 1. Antimicrobial resistance 2. COVID-19 3. Antibiotic prescription 4. Secondary and Coinfection 5. Hospitalized patients

Describe the problem you are trying to solve in one sentence. Risk of Antimicrobial resistance due to Unregulated antibiotic prescription to hospitalized COVID-19 patients. Does the unregulated use of antibiotics to treat hospitalized COVID-19 patients during the pandemic period worsen the risk of antimicrobial resistance?

Describe your outcome.

Risk of Antimicrobial resistance

Describe your exposure.

Unregulated Antibiotic prescription to treat the hospitalized COVID-19 patients

What databases will you search for the literature?

OVID Medline, PubMed, EMBASE, Web of Science, Cochrane Registry, BIOSIS, SciFinder-N

Refining

Describe your target *Population*:

e.g. "Generally healthy adult men and women aged 18-80 without type 2 diabetes or other serious medical conditions."

Hospitalized COVID-19 patients of any age. Any ward.

Describe your *Intervention/Exposure*:

e.g. "Dietary fructose"

An antibiotic prescription with no indication other than COVID-19 symptoms.

Describe your *Comparison* group:

e.g. "Any other carbohydrate in isocaloric amounts"

n/a – just describing frequency of antibiotic prescription.

Describe your *Outcome*:

e.g. "change in serum triglycerides"

1. Frequency of antibiotic prescription
2. Frequency of bacterial coinfection and secondary infection

Specify the *Timeframe*:

e.g. "3 weeks or longer"

In hospital for any length of stay.

Specify the *study designs*:

e.g. "randomized controlled trials"

observational studies (e.g. case series, prospective/retrospective cohorts or series), possibly randomized trials of other therapies that report antibiotic use

Final PICOT question

e.g. "In adults, aged 18-80, with an average BMI <30 kg/m^2 without type 2 diabetes or other serious medical conditions, does fructose, compared with an equal amount of energy from another carbohydrate, raise serum triglycerides in randomized trials of >3 weeks' duration?"

In hospitalized COVID-19 patients of any age in any country, admitted to any service with any length of stay, what is 1) the frequency of antibiotic prescription with no other documented indication (Other than COVID-19 symptom alleviation); and 2) the frequency of bacterial coinfection and secondary infection?

Appendix 2

WHO Watch group antibiotics- Adapted from (WHO, 2021a)

Watch group antibiotics

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine[1] and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists of Essential Medicines.

[1] Critically Important Antimicrobials for Human Medicine 6th Revision 2018

Antibiotic	Class	ATC code	Category	Listed on EML 2021
Arbekacin	Aminoglycosides	J01GB12	Watch	No
Aspoxicillin	Penicillins	J01CA19	Watch	No
Azithromycin	Macrolides	J01FA10	Watch	Yes
Azlocillin	Penicillins	J01CA09	Watch	No
Bekanamycin	Aminoglycosides	J01GB13	Watch	No
Biapenem	Carbapenems	J01DH05	Watch	No
Carbenicillin	Penicillins	J01CA03	Watch	No
Carindacillin	Penicillins	J01CA05	Watch	No
Cefaclor	Second-generation-cephalosporins	J01DC04	Watch	No
Cefamandole	Second-generation-cephalosporins	J01DC03	Watch	No
Cefbuperazone	Second-generation-cephalosporins	J01DC13	Watch	No
Cefcapene-pivoxil	Third-generation-cephalosporins	J01DD17	Watch	No
Cefdinir	Third-generation-cephalosporins	J01DD15	Watch	No
Cefditoren-pivoxil	Third-generation-cephalosporins	J01DD16	Watch	No

Cefepime	Fourth-generation-cephalosporins	J01DE01	Watch	No
Cefetamet-pivoxil	Third-generation-cephalosporins	J01DD10	Watch	No
Cefixime	Third-generation-cephalosporins	J01DD08	Watch	Yes
Cefmenoxime	Third-generation-cephalosporins	J01DD05	Watch	No
Cefmetazole	Second-generation-cephalosporins	J01DC09	Watch	No
Cefminox	Second-generation-cephalosporins	J01DC12	Watch	No
Cefodizime	Third-generation-cephalosporins	J01DD09	Watch	No
Cefonicid	Second-generation-cephalosporins	J01DC06	Watch	No
Cefoperazone	Third-generation-cephalosporins	J01DD12	Watch	No
Ceforanide	Second-generation-cephalosporins	J01DC11	Watch	No
Cefoselis	Fourth-generation-cephalosporins	to be assigned	Watch	No
Cefotaxime	Third-generation-cephalosporins	J01DD01	Watch	Yes
Cefotetan	Second-generation-cephalosporins	J01DC05	Watch	No
Cefotiam	Second-generation-cephalosporins	J01DC07	Watch	No
Cefoxitin	Second-generation-cephalosporins	J01DC01	Watch	No
Cefozopran	Fourth-generation-cephalosporins	J01DE03	Watch	No
Cefpiramide	Third-generation-cephalosporins	J01DD11	Watch	No
Cefpirome	Fourth-generation-cephalosporins	J01DE02	Watch	No
Cefpodoxime-proxetil	Third-generation-cephalosporins	J01DD13	Watch	No
Cefprozil	Second-generation-cephalosporins	J01DC10	Watch	No

Cefsulodin	Third-generation-cephalosporins	J01DD03	Watch	No
Ceftazidime	Third-generation-cephalosporins	J01DD02	Watch	Yes
Cefteram-pivoxil	Third-generation-cephalosporins	J01DD18	Watch	No
Ceftibuten	Third-generation-cephalosporins	J01DD14	Watch	No
Ceftizoxime	Third-generation-cephalosporins	J01DD07	Watch	No
Ceftriaxone	Third-generation-cephalosporins	J01DD04	Watch	Yes
Cefuroxime	Second-generation-cephalosporins	J01DC02	Watch	Yes
Chlortetracycline	Tetracyclines	J01AA03	Watch	No
Cinoxacin	Quinolones	J01MB06	Watch	No
Ciprofloxacin	Fluoroquinolones	J01MA02	Watch	Yes
Clarithromycin	Macrolides	J01FA09	Watch	Yes
Clofoctol	Phenol derivatives	J01XX03	Watch	No
Clomocycline	Tetracyclines	J01AA11	Watch	No
Delafloxacin	Fluoroquinolones	J01MA23	Watch	No
Demeclocycline	Tetracyclines	J01AA01	Watch	No
Dibekacin	Aminoglycosides	J01GB09	Watch	No
Dirithromycin	Macrolides	J01FA13	Watch	No
Doripenem	Carbapenems	J01DH04	Watch	No
Enoxacin	Fluoroquinolones	J01MA04	Watch	No
Ertapenem	Carbapenems	J01DH03	Watch	No
Erythromycin	Macrolides	J01FA01	Watch	No
Fidaxomicin	Macrolides	A07AA12	Watch	No
Fleroxacin	Fluoroquinolones	J01MA08	Watch	No
Flomoxef	Second-generation-cephalosporins	J01DC14	Watch	No
Flumequine	Quinolones	J01MB07	Watch	No
Flurithromycin	Macrolides	J01FA14	Watch	No
Fosfomycin_oral	Phosphonics	J01XX01	Watch	No
Fusidic-acid	Steroid antibacterials	J01XC01	Watch	No
Garenoxacin	Fluoroquinolones	J01MA19	Watch	No
Gatifloxacin	Fluoroquinolones	J01MA16	Watch	No
Gemifloxacin	Fluoroquinolones	J01MA15	Watch	No
Grepafloxacin	Fluoroquinolones	J01MA11	Watch	No
Imipenem/cilastatin	Carbapenems	J01DH51	Watch	No

Isepamicin	Aminoglycosides	J01GB11	Watch	No
Josamycin	Macrolides	J01FA07	Watch	No
Kanamycin_IV	Aminoglycosides	J01GB04	Watch	No
Kanamycin_oral	Aminoglycosides	A07AA08	Watch	No
Lascufloxacin	Fluoroquinolones	J01MA25	Watch	No
Latamoxef	Third-generation-cephalosporins	J01DD06	Watch	No
Levofloxacin	Fluoroquinolones	J01MA12	Watch	No
Levonadifloxacin	Fluoroquinolones	J01MA24	Watch	No
Lincomycin	Lincosamides	J01FF02	Watch	No
Lomefloxacin	Fluoroquinolones	J01MA07	Watch	No
Loracarbef	Second-generation-cephalosporins	J01DC08	Watch	No
Lymecycline	Tetracyclines	J01AA04	Watch	No
Meropenem	Carbapenems	J01DH02	Watch	Yes
Metacycline	Tetracyclines	J01AA05	Watch	No
Mezlocillin	Penicillins	J01CA10	Watch	No
Micronomicin	Aminoglycosides	to be assigned	Watch	No
Midecamycin	Macrolides	J01FA03	Watch	No
Minocycline_oral	Tetracyclines	J01AA08	Watch	No
Miocamycin	Macrolides	J01FA11	Watch	No
Moxifloxacin	Fluoroquinolones	J01MA14	Watch	No
Nemonoxacin	Quinolones	J01MB08	Watch	No
Neomycin_IV	Aminoglycosides	J01GB05	Watch	No
Neomycin_oral	Aminoglycosides	A07AA01	Watch	No
Netilmicin	Aminoglycosides	J01GB07	Watch	No
Norfloxacin	Fluoroquinolones	J01MA06	Watch	No
Ofloxacin	Fluoroquinolones	J01MA01	Watch	No
Oleandomycin	Macrolides	J01FA05	Watch	No
Oxolinic-acid	Quinolones	J01MB05	Watch	No
Oxytetracycline	Tetracyclines	J01AA06	Watch	No
Panipenem	Carbapenems	J01DH55	Watch	No
Pazufloxacin	Fluoroquinolones	J01MA18	Watch	No
Pefloxacin	Fluoroquinolones	J01MA03	Watch	No
Penimepicycline	Tetracyclines	J01AA10	Watch	No
Pheneticillin	Penicillins	J01CE05	Watch	No
Pipemidic-acid	Quinolones	J01MB04	Watch	No
Piperacillin	Penicillins	J01CA12	Watch	No

Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	J01CR05	Watch	Yes
Piromidic-acid	Quinolones	J01MB03	Watch	No
Pristinamycin	Streptogramins	J01FG01	Watch	No
Prulifloxacin	Fluoroquinolones	J01MA17	Watch	No
Ribostamycin	Aminoglycosides	J01GB10	Watch	No
Rifabutin	Rifamycins	J04AB04	Watch	No
Rifampicin	Rifamycins	J04AB02	Watch	No
Rifamycin_IV	Rifamycins	J04AB03	Watch	No
Rifamycin_oral	Rifamycins	A07AA13	Watch	No
Rifaximin	Rifamycins	A07AA11	Watch	No
Rokitamycin	Macrolides	J01FA12	Watch	No
Rolitetracycline	Tetracyclines	J01AA09	Watch	No
Rosoxacin	Quinolones	J01MB01	Watch	No
Roxithromycin	Macrolides	J01FA06	Watch	No
Rufloxacin	Fluoroquinolones	J01MA10	Watch	No
Sarecycline	Tetracyclines	J01AA14	Watch	No
Sisomicin	Aminoglycosides	J01GB08	Watch	No
Sitafloxacin	Fluoroquinolones	J01MA21	Watch	No
Solithromycin	Macrolides	J01FA16	Watch	No
Sparfloxacin	Fluoroquinolones	J01MA09	Watch	No
Spiramycin	Macrolides	J01FA02	Watch	No
Streptoduocin	Aminoglycosides	J01GA02	Watch	No
Streptomycin_IV	Aminoglycosides	J01GA01	Watch	No
Streptomycin_oral	Aminoglycosides	A07AA04	Watch	No
Sulbenicillin	Penicillins	J01CA16	Watch	No
Tazobactam	Beta-lactamase-inhibitors	J01CG02	Watch	No
Tebipenem	Carbapenems	J01DH06	Watch	No
Teicoplanin	Glycopeptides	J01XA02	Watch	No
Telithromycin	Macrolides	J01FA15	Watch	No
Temafloxacin	Fluoroquinolones	J01MA05	Watch	No
Temocillin	Penicillins	J01CA17	Watch	No
Ticarcillin	Penicillins	J01CA13	Watch	No
Tobramycin	Aminoglycosides	J01GB01	Watch	No
Tosufloxacin	Fluoroquinolones	J01MA22	Watch	No
Troleandomycin	Macrolides	J01FA08	Watch	No
Trovafloxacin	Fluoroquinolones	J01MA13	Watch	No
Vancomycin_IV	Glycopeptides	J01XA01	Watch	Yes
Vancomycin_oral	Glycopeptides	A07AA09	Watch	Yes

The End