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Prevalence of antibiotics prescription amongst patients with and without COVID-19 in low- and middle-income countries: a systematic review and meta-analysis

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ABSTRACT

Antimicrobial resistance (AMR) poses a substantial risk to public health. In low-income and middle-income (LMICs) nations, the impact of AMR is significantly more severe. The absence of data from low-income countries (LMICs) causes this topic to be frequently overlooked. Additionally, the COVID-19 pandemic could make the AMR issue even worse. Earlier guidelines recommended antibiotic use in patients with COVID-19, even in those without bacterial coinfection. This study aims to investigate the proportion of antibiotic prescriptions in LMICs among patients with and without coronavirus disease-2019 (COVID-19), the proportion of inappropriate antibiotics, and multi-antibiotic prescribing. We followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). We retrieved data through online databases, including PubMed, Scopus, and ScienceDirect. Amongst COVID-19 patients, the meta-analytic estimate of antibiotic prescription was 0.80 (95% CI: 0.72–0.88), whereas antibiotic use among patients with non-COVID-19 infections was 0.54 (95% CI: 0.49–0.58). Half of those prescribed antibiotics (0.52, 95% CI: 0.32–0.72) are inappropriate prescriptions. In addition, we found that one-third of antibiotics prescriptions consisted of more than one antibiotic (0.32, 95% CI: 0.21–0.43). In conclusion, antibiotics are highly prescribed across LMICs, and their use is increased in patients with COVID-19. Amongst those prescriptions, inappropriate and multiple use was not uncommon. This study has several limitations, as it included two studies in an ambulatory setting, and some of the studies included in the analysis were conducted on a small scale. Nevertheless, our findings suggest that urgent action to improve prescribing practices is essential.

KEYWORDS
Antibiotic prescription; COVID-19; low-income countries; middle-income countries; antimicrobial resistance

Introduction

Antibiotic or antimicrobial resistance (AMR) poses a significant public health threat [1]. AMR has been estimated as the cause of 700,000 death globally. By 2050, the number was predicted to swell to 10 million, much higher than cancer (8.2 million) [2]. The growth of AMR rates also leads to increased morbidity and economic burden amongst patients, thus, reducing the patient quality of life. Globally, in 2019 there were 192,000 and 47,900 disability-adjusted life years (DALYs) associated and attributed with AMR, respectively [2].

The risk for AMR is attributed to several factors. Those include the high incidence of infectious diseases, low awareness of antibiotics and their risk of resistance, and limited laboratory resources that favor the use of antibiotics empirically [3]. Inappropriate use and prescribing of more than one antibiotic is also reported as a growing concern as a cause of AMR [4].

AMR impacts all countries. Nonetheless, the burden is disproportionately higher in LMICs compared to High-Income Countries (HICs) [5]. AMR is predicted to account for 80% of deaths in LMICs [6]. Partly, the high burden of AMR in LMICs is caused by the high rate of communicable diseases are seen in these countries. LMICs may also have the fewest resources and little information on the prevalence of AMR, thus compounding the AMR problem [3].

A considerable increase of 114% in antibiotics consumption was observed in LMICs between 2000–2015 [7]. It could mean mortality from infectious diseases is decreasing if these antibiotics are used appropriately. However, in LMICs, the driver for inappropriate prescribing of antibiotics is prevalent, leading to frequent antibiotic misuse [8]. Those drivers include a lack of understanding among antibiotic prescribers, insufficient education and supervision given to healthcare professionals, absence of diagnostic tools, and financial incentives for suppliers and prescribers [8].

Approximately 83% of the world's population lives in LMICs [9,10]. With its dense population, the immense burden of infectious disease, limited laboratory resources, and common misuse of antibiotics, LMICs serve as an important reservoir for the occurrence and spread of AMR [6]. Special attention must be

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addressed to the LMICs to halt the spread of AMR. However, the fact that AMR is a critical problem in LMICs is often neglected due to a research gap. In these countries, there is a scarcity of studies about AMR and antibiotic use, and the majority of research focuses more on HICs [2].

The COVID-19 pandemic may further complicate the AMR problem in LMICs. Various antibiotic agents were mentioned in earlier guidelines to treat COVID-19 infection, even in those without bacterial coinfection [11]. The demand of antibiotics is also increasing during the COVID-19 pandemic [12,13].

The increased use of antibiotics during this pandemic could be attributed to an early study from Wuhan, China, that reported half of COVID-19 mortality is associated with a secondary bacterial infection [14]. However, newer research suggested that empirical antibiotic in COVID-19 is unnecessary and bacterial coinfection were only found in 6.9% and 8.1% of COVID-19 patients and critically ill COVID-19 patients, respectively [15].

We conducted a systematic review to assess the proportion of antibiotic prescriptions in LMICs amongst patients with COVID-19 and without COVID-19, inappropriate prescription of antibiotics, and the proportion of prescribing more than one antibiotic in LMICs.

Methods

We Followed Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). The protocol for the systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42022306232.

Eligibility criteria, search strategy, and study selection

We searched online databases, including PubMed, Scopus, and ScienceDirect. The search was limited to literature published between 2012–2022 and to that written in English. The search addressed the following query ((Antibiotic) OR (antimicrobial) OR (antibacterial) AND (((trend) OR (prescription])) OR (use])). Studies will be included if they describe antibiotics prescription in healthcare settings in the LMICs and reported by the number of patients or by the total prescription. Studies were to be excluded if they: (1) done in special populations in which antibiotics use was mainly prophylactic (for example, people with neutropenic fever, rheumatic heart disease, patients who have undergone prophylactic antibiotics including surgical prophylaxis and HIV/AIDS); (2) reported veterinary use of antibiotics; (3) done in the HMICs. The income-based classification of countries into low, lower-middle, upper-middle, or high-income follows the World Bank categorization at the year the study started.

Data extraction and outcomes of interest

We incorporated search results into EndNote 20 software (Clarivate Analytics) and removed the duplicates. Two authors (YAAS and MSU) worked independently on the screening according to the inclusion and exclusion criteria. Any disagreement was resolved by the discussion with the third reviewer (AP). We used a form incorporated into an Excel spreadsheet (Microsoft Corporation) to extract information from all eligible publications.

Eligible studies were reviewed, and the following data were extracted: (1) first author of the study; (2) country in which the study was conducted; (3) diagnosis (reported as COVID-19 and non-COVID-19); (4) data collection method; (5) type of denominator; (6) total of study's participants; (7) number of antibiotic prescriptions; (8) most common antibiotics.

The primary outcome was the proportion of antibiotic prescriptions in LMICs amongst patients with COVID-19 and without COVID-19. In addition, secondary outcomes were inappropriate prescription of antibiotics and the proportion of prescribing more than one antibiotic. The effect measure will be reported as a proportion of antibiotic prescriptions.

Bias assessment

We use the tool Hoy et al [8]. developed to assess publication bias. Two authors (YAAS and MSU) evaluated each study to ensure that the included study carries a minimal risk of bias. Any disagreements will be resolved by a third author (AP). We categorized a summary of the overall bias of individual studies into low, medium, and high risk, according to Hoy *et al* [16].

Data synthesis and statistical analysis

Data were divided into two subgroups according to the diagnosis of the patients as follows: (1) COVID-19 and (2) without COVID-19. To assess the between-study heterogeneity, we performed an I^2 statistic. We conducted Knapp – Hartung adjustment to investigate the sources of heterogeneity. In addition, a leave-one-out sensitivity analysis was performed to know whether the included studies changed the overall result. The proportions of antibiotic prescriptions were then pooled using a random-effects meta-analysis. A Forest plot was provided to illustrate the summary. Statistical analysis was conducted in Stata version 17 (Stata Corp).

Results

Study selection and characteristics

Our search yielded 8,392 unique studies. After screening the abstracts, we reviewed 152 full texts, of which 69 were included in the systematic review (Figure 1).

Nine studies were conducted in low-income countries, 29 in lower-middle-income countries, 28 in upper-middle-income countries, and 1 study was done in 8 countries (low- and lower-middle-income countries). Amongst the included studies, 42 reported the use of antibiotics with patients as the denominator. Twenty-seven studies reported the number of prescriptions as the denominator. In addition, ten studies were done on COVID-19 patients and 59 studies on non-COVID-19 patients. Table 1 summarizes the characteristics of the included studies.

Risk oF bias assessment

The results of the methodological quality of the individual studies are presented in **Appendix 1**. Figure 2 shows the summary of the quality assessment. The majority of the studies were classified as having a low risk of bias (n = 41, 59.42%). Seventeen studies (24.64%) were judged as moderate risk, whilst 11 studies (15.94%) were at high risk of bias. The most significant issue of bias was the representativeness of the national population; most of the studies only selected a few healthcare facilities within one or two provinces.

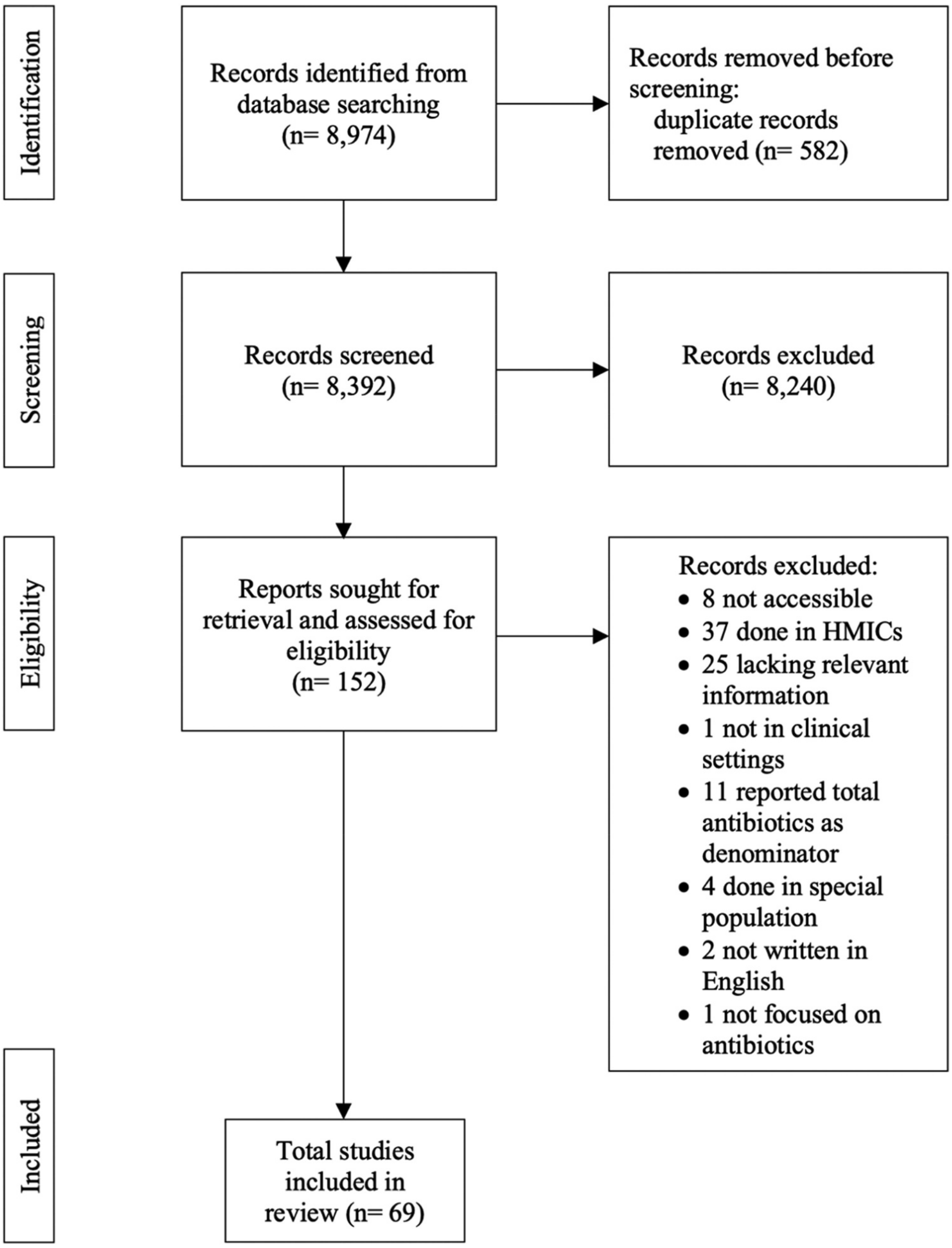

Figure 1. PRISMA flow diagram of the study.

Table 1. Summary of the individual studies.

Study Author	Country	Income	Health Care Level	Diagnosis	Denominator	Total	Antibiotic	Effect Size (95% CI)
Bajis (2014) [17]	Afghanistan	Low	secondary	Non-COVID	Prescription	9678	5417	0.56 (0.55–0.57)
Baltzell (2019) [18]	Malawi	Low	primary	Non-COVID	Patient	9924	5464	0.55 (0.54–0.56)
Bonniface (2021) [19]	Uganda	Low	secondary and tertiary	Non-COVID	Prescription	45160	10402	0.23 (0.23–0.23)
Bunduki (2021) [20]	Malawi	Low	tertiary	Non-COVID	Patient	105	29	0.28 (0.19–0.37)
Chaw (2018) [21]	Gambia	Low	tertiary	Non-COVID	Patient	917	496	0.54 (0.51–0.57)
Mukonzo (2013) [22]	Uganda	Low	primary, secondary, tertiary	Non-COVID	Prescription	23935	9691	0.40 (0.40–0.41)
Worku (2018) [23]	Ethiopia	Low	primary	Non-COVID	Patient	900	504	0.56 (0.53–0.59)
Yebyo (2016) [24]	Ethiopia	Low	primary	Non-COVID	Patient	414	363	0.88 (0.84–0.91)
Yousif (2016) [25]	Sudan	Low	primary	Non-COVID	Prescription	220	120	0.55 (0.48–0.61)
Fink (2019) [26]	8 countries	Low and lower-middle	primary	Non-COVID	Patient	22519	14120	0.63 (0.62–0.63)
Abdulah (2019) [27]	Indonesia	Lower-middle	primary	Non-COVID	Prescription	10118	2373	0.23 (0.23–0.24)
Abubakar (2020) [28]	Nigeria	Lower-middle	secondary	Non-COVID	Patient	321	156	0.49 (0.43–0.54)
Adisa (2015) [29]	Nigeria	Lower-middle	primary	Non-COVID	Prescription	400	220	0.55 (0.50–0.60)
Ahiabu (2015) [30]	Ghana	Lower-middle	primary	Non-COVID	Prescription	1600	306	0.19 (0.17–0.21)
Ahmadi (2017) [31]	Iran	Lower-middle	primary	Non-COVID	Prescription	352399	183600	0.52 (0.52–0.52)
Ahmed (2018) [32]	Bangladesh	Lower-middle	tertiary	Non-COVID	Patient	3570	1395	0.39 (0.37–0.41)
Alkaff (2019) [33]	Indonesia	Lower-middle	primary	Non-COVID	Patient	203	100	0.49 (0.42–0.56)
Andrajati (2016) [34]	Indonesia	Lower-middle	primary	Non-COVID	Prescription	4287	1209	0.28 (0.27–0.30)
Ankrah (2021) [35]	Ghana	Lower-middle	tertiary	Non-COVID	Patient	988	343	0.35 (0.32–0.38)
Ansar (2017) [36]	Pakistan	Lower-middle	tertiary	Non-COVID	Prescription	400	137	0.34 (0.29–0.39)
Atif (2017) [37]	Pakistan	Lower-middle	tertiary	Non-COVID	Prescription	1000	823	0.82 (0.80–0.85)
Bediako-Bowan (2019) [38]	Ghana	Lower-middle	secondary and tertiary	Non-COVID	Patient	540	261	0.48 (0.44–0.53)
Boone (2020) [39]	Bangladesh	Lower-middle	secondary and tertiary	Non-COVID	Patient	448	329	0.73 (0.69–0.78)
Chaudhary (2014) [40]	India	Lower-middle	secondary	Non-COVID	Prescription	100	45	0.45 (0.35–0.55)
Chem (2018) [41]	Cameroon	Lower-middle	primary	Non-COVID	Prescription	30096	11035	0.37 (0.36–0.37)
Dat (2022) [42]	Viet Nam	Lower-middle	secondary and tertiary	Non-COVID	Patient	1747	1112	0.64 (0.61–0.66)
Dodoo (2021) [43]	Ghana	Lower-middle	tertiary	Non-COVID	Patient	300	182	0.61 (0.55–0.66)
Fahimzad (2016) [44]	Iran	Lower-middle	secondary and tertiary	Non-COVID	Patient	858	523	0.61 (0.58–0.64)
Gandra (2018) [45]	India	Lower-middle	secondary and tertiary	Non-COVID	Patient	403	208	0.52 (0.47–0.57)
Jose (2016) [46]	India	Lower-middle	primary	Non-COVID	Patient	552	404	0.73 (0.69–0.77)
Mekuria (2019) [47]	Kenya	Lower-middle	primary	Non-COVID	Prescription	85484	21870	0.26 (0.25–0.26)
Mustafa (2022) [48]	Pakistan	Lower-middle	secondary	COVID-19	Patient	444	377	0.85 (0.81–0.88)
Ndhlovu (2015) [49]	Zambia	Lower-middle	primary and secondary	Non-COVID	Patient	872	470	0.54 (0.51–0.57)
Nepal (2020) [50]	Nepal	Lower-middle	primary and secondary	Non-COVID	Patient	6860	3064	0.45 (0.43–0.46)
Raza (2014) [51]	Pakistan	Lower-middle	primary and secondary	Non-COVID	Prescription	1097	627	0.57 (0.54–0.60)
Safaeian (2015) [52]	Iran	Lower-middle	primary	Non-COVID	Prescription	7439709	3794252	0.51 (0.51–0.51)
Sarwar (2018) [53]	Pakistan	Lower-middle	primary	Non-COVID	Prescription	7200	5869	0.82 (0.81–0.82)

(*Continued*)

Table 1. (Continued).

Study Author	Country	Income	Health Care Level	Diagnosis	Denominator	Total	Antibiotic	Effect Size (95% CI)
Saweri (2017) [54]	Papua New Guinea	Lower-middle	primary	Non-COVID	Prescription	6008	4370	0.73 (0.72–0.74)
Suranadi (2022) [55]	Indonesia	Lower-middle	tertiary	COVID-19	Patient	410	342	0.83 (0.80–0.87)
Thobari (2019) [56]	Indonesia	Lower-middle	primary and secondary	Non-COVID	Patient	1621	551	0.34 (0.32–0.36)
Ababneh (2017) [57]	Jordan	Upper-middle	primary	Non-COVID	Patient	5829	4575	0.78 (0.77–0.80)
Ababneh (2021) [58]	Jordan	Upper-middle	tertiary	Non-COVID	Patient	683	144	0.21 (0.18–0.24)
Aksoy (2021) [59]	Turkey	Upper-middle	primary	Non-COVID	Prescription	1054261396	318941829	0.30 (0.30–0.30)
Alkhaldi (2021) [60]	Jordan	Upper-middle	ambulatory	Non-COVID	Prescription	73701	20133	0.27 (0.27–0.28)
Al-Shatnawi (2021) [61]	Jordan	Upper-middle	tertiary	Non-COVID	Prescription	20494	15883	0.78 (00.77–0.78)
Bozic (2015) [62]	Serbia	Upper-middle	primary	Non-COVID	Patient	1353714	728285	0.54 (0.54–0.54)
Cao (2020) [63]	China	Upper-middle	secondary and tertiary	COVID-19	Patient	199	189	0.95 (0.92–0.98)
Chautrakarn (2020) [64]	Thailand	Upper-middle	tertiary	Non-COVID	Patient	644	279	0.43 (0.39–0.47)
Chen (2020) [65]	China	Upper-middle	secondary	COVID-19	Patient	274	249	0.91 (0.88–0.94)
Choez (2018) [66]	Ecuador	Upper-middle	ambulatory	Non-COVID	Patient	1393	523	0.38 (0.35–0.40)
Ergül (2018) [67]	Turkey	Upper-middle	tertiary	Non-COVID	Patient	113	80	0.71 (0.62–0.80)
Gasson (2018) [68]	South Africa	Upper-middle	primary	Non-COVID	Patient	654	449	0.69 (0.65–0.72)
Greer (2018) [69]	Thailand	Upper-middle	primary	Non-COVID	Patient	83661	81691	0.98 (0.98–0.98)
Guan (2020) [70]	China	Upper-middle	secondary and tertiary	COVID-19	Patient	1099	637	0.58 (0.55–0.61)
He (2020) [71]	China	Upper-middle	secondary	COVID-19	Patient	65	49	0.75 (0.64–0.86)
Kalkan (2021) [72]	Turkey	Upper-middle	tertiary	Non-COVID	Patient	927	748	0.81 (0.78–0.83)
Lima (2017) [73]	Brazil	Upper-middle	primary	Non-COVID	Patient	399	71	0.18 (0.14–0.22)
Liu (2019) [74]	China	Upper-middle	primary	Non-COVID	Prescription	428475	189719	0.44 (0.44–0.44)
Mashalla (2017) [75]	Botswana	Upper-middle	primary	Non-COVID	Prescription	550	235	0.43 (0.39–0.47)
Rahman (2016) [76]	Malaysia	Upper-middle	primary	Non-COVID	Patient	27587	5810	0.21 (0.21–0.22)
Sencan (2022) [77]	Turkey	Upper-middle	secondary and tertiary	COVID-19	Patient	1500	1118	0.75 (0.72–0.77)
Sun (2015) [78]	China	Upper-middle	primary and secondary	Non-COVID	Prescription	8400	979	0.12 (0.11–0.12)
Wang (2014) [79]	China	Upper-middle	primary	Non-COVID	Prescription	10199	6105	0.60 (0.59–0.61)
Wang (2020) [80]	China	Upper-middle	tertiary	COVID-19	Patient	138	89	0.64 (0.56–0.73)
Wang (2020b) [81]	China	Upper-middle	tertiary	COVID-19	Patient	107	85	0.79 (0.71–0.87)
Yang (2020) [82]	China	Upper-middle	secondary	COVID-19	Patient	52	49	0.94 (0.87–1.02)
Yin (2019) [83]	China	Upper-middle	primary	Non-COVID	Prescription	14526	5851	0.40 (0.39–0.41)
Zhan (2019) [84]	China	Upper-middle	primary and secondary	Non-COVID	Prescription	2470	1313	0.53 (0.51–0.55)
Zhang (2017) [85]	China	Upper-middle	primary and secondary	Non-COVID	Patient	9340	3425	0.37 (0.36–0.38)

Antibiotic prescription prevalence

Ten studies (n = 4,288) reported the prevalence of antibiotic prescriptions among COVID-19 patients. All studies were conducted on hospitalized patients. The reported antibiotic prescriptions in COVID-19 patients ranged from 0.58 (95% CI: 0.55–0.61) to 0.95 (95% CI: 0.91–0.98), with the meta-analytic estimate was 0.80 (95% CI: 0.720–0.88; P>Q 0.000; tau^2: 0.017; I^2: 97.85%).

Fifty-nine studies (n = 1,064,378,108) reported antibiotic use amongst patients with non-COVID-19

Table 2. Characteristics of the study reporting inappropriate antibiotic prescription.

Study Author	Country	Income	Health care level	Diagnosis	COVID-19 status	Denominator	Effect Size (95% CI)
Ababneh (2017) [57]	Jordan	UMIC	primary	acute respiratory infection	Non-COVID	Patient	0.59 (0.57–0.60)
Alkhaldi (2021) [60]	Jordan	UMIC	secondary and tertiary	respiratory tract infection	Non-COVID	Prescription	0.30 (0.29–0.31)
Choez (2018) [66]	Ecuador	UMIC	ambulatory	upper respiratory tract infection	Non-COVID	Patient	0.90 (0.88–0.93)
Ergül (2018) [67]	Turkey	UMIC	tertiary	any	Non-COVID	Patient	0.34 (0.23–0.45)
Gasson (2018) [68]	South Africa	UMIC	primary	any	Non-COVID	Patient	0.68 (0.64–0.72)
Sarwar (2018) [53]	Pakistan	LMIC	primary	any	Non-COVID	Prescription	0.16 (0.15–0.17)
Sun (2015) [78]	China	UMIC	primary and secondary	upper respiratory tract infection, common cold	Non-COVID	Prescription	0.89 (0.87–0.91)
Wang (2014) [79]	China	UMIC	primary	any	Non-COVID	Prescription	0.47 (0.45–0.48)
Zhan (2019) [84]	China	UMIC	primary and secondary	any	Non-COVID	Prescription	0.37 (0.34–0.39)

Table 3. Prevalence of multiple antibiotic prescriptions.

Study Author	Country	Income	Health care level	Diagnosis	COVID-19 Status	Denominator	Effect Size (95% CI)
Ababneh (2017) [57]	Jordan	UMIC	primary	acute respiratory infection	Non-COVID	Patient	0.02 (0.01–0.02)
Abubakar (2020) [28]	Nigeria	LMIC	secondary	any	Non-COVID	Patient	0.45 (0.37–0.53)
Ankrah (2021) [35]	Ghana	LMIC	tertiary	any	Non-COVID	Patient	0.77 (0.72–0.81)
Ansar (2017) [36]	Pakistan	LMIC	tertiary	any	Non-COVID	Prescription	0.20 (0.13–0.27)
Atif (2017) [37]	Pakistan	LMIC	tertiary	any	Non-COVID	Prescription	0.35 (0.32–0.38)
Bediako-Bowan (2019) [38]	Ghana	LMIC	secondary and tertiary	any	Non-COVID	Patient	0.82 (0.77–0.86)
Bunduki (2021) [20]	Malawi	LIC	secondary	hospital-acquired infection	Non-COVID	Patient	0.55 (0.36–0.74)
Chautrakarn (2020) [64]	Thailand	UMIC	tertiary	any	Non-COVID	Patient	0.59 (0.53–0.65)
Chem (2018) [41]	Cameroon	LMIC	primary	any	Non-COVID	Prescription	0.05 (0.04–0.05)
Dat (2021) [42]	Viet Nam	LMIC	secondary	any	Non-COVID	Patient	0.42 (0.39–0.45)
Gandra (2018) [45]	India	LMIC	secondary and tertiary	any	Non-COVID	Patient	0.60 (0.53–0.67)
Liu (2019) [74]	China	UMIC	primary	any	Non-COVID	Prescription	0.21 (0.21–0.21)
Mashalla (2017) [75]	Botswana	UMIC	primary		Non-COVID	Prescription	0.19 (0.14–0.24)
Ndhlovu (2015) [49]	Zambia	LMIC	primary and secondary	suspected malaria	Non-COVID	Patient	0.05 (0.03–0.07)
Nepal (2020) [50]	Nepal	LMIC	primary and secondary	any	Non-COVID	Patient	0,09 (0.08–0.10)
Rahman (2016) [76]	Malaysia	UMIC	primary	any	Non-COVID	Patient	0.03 (0.03–0.04)
Sencan (2022) [77]	Turkey	UMIC	secondary and tertiary	COVID-19	COVID-19	Patient	0.37 (0.34–0.40)
Suranadi (2022) [55]	Indonesia	LMIC	tertiary	COVID-19	COVID-19	Patient	0.46 (0.40–0.51)
Thobari (2019) [56]	Indonesia	LMIC	primary and secondary	any	Non-COVID	Patient	0.12 (0.09–0.15)
Yin (2019) [83]	China	UMIC	primary	any	Non-COVID	Prescription	0.18 (0.18–0.19)
Zhang (2017) [85]	China	UMIC	primary and secondary	upper respiratory tract infection	Non-COVID	Patient	0.40 (0.39–0.42)

infection. The use of antibiotics in non-COVID-19 patients ranged from 0.117 (95% CI: 0.110–0.123) to 0.977 (95% CI: 0.975–0.978), and the meta-analytic estimate was 0.540 (95% CI: 0.493–0.588; P>Q 0.000; tau^2: 0.041; I^2: 100.00). Overall, the pooled estimate was 0.540 (95% CI: 0.493–0.588). Two studies were done in an ambulatory setting, in which Alkhaldi et al. reported the prevalence of antibiotic prescription to be 0.27

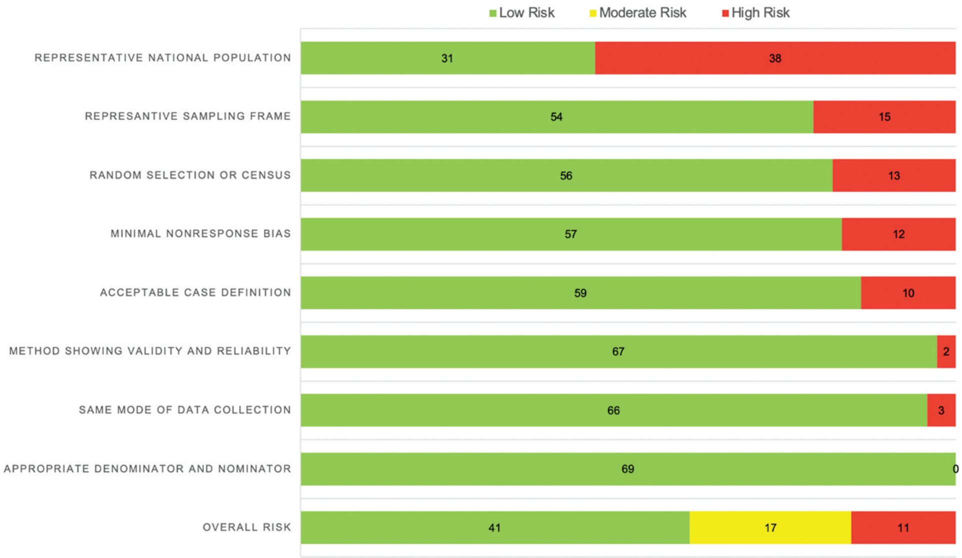

Figure 2. Risk of bias assessment.

(95% CI: 0.27–0.28) and the prevalence of 0.38 (95% CI: 0.35–0.40) was reported by Choez et al. Figure 3 shows a forest plot that summarizes the meta-analysis.

Prevalence of inappropriate antibiotic prescription

If available, we retrieved the proportion of inappropriate antibiotic prescriptions within individual studies. Nine studies reported inappropriate antibiotic prescriptions. Inappropriate prescriptions are defined by included studies as unnecessary use of antibiotics when several criteria are met, such as antibiotic is not indicated, unnecessary use of multiple antibiotics, irrational drug frequency, or inappropriate antibiotic dose. Table 2 showed the characteristics of the study reporting inappropriate antibiotic prescription. The lowest proportion of inappropriate antibiotic prescriptions was 0.16 (95% CI: 0.15–0.17), and the highest was 0.90 (95% CI: 0.88–0.93). Figure 4 showed a pooled effect estimate of 0.52 (95% CI: 0.32–0.72). The study reported the highest inappropriate prescription (0.90, 95% CI: 0.88–0.93) was a study done in an ambulatory setting by Choez et al.

Prevalence of multiple antibiotic prescription

Twenty-one studies reported the use of more than one antibiotic (Table 3). The prevalence of multiple antibiotic prescriptions ranged from 0.02 (95% CI: 0.01–0.02) to 0.82 (95% CI: 0.77–0.86) (Figure 5). The study that reported the highest use of multiple antibiotics was done in tertiary and secondary settings. The most commonly combined antibiotics reported in the study were β-lactam with β-lactamase inhibitor and nitroimidazole [38]. Another study reported cefotaxime/ceftriaxone with metronidazole as the most common combination [37]. One study also observed redundant antibiotic treatments such as dual anaerobic and dual beta-lactam [28].

Discussion

This systematic review summarizes data from 69 studies describing antibiotic prescriptions. Our meta-analysis suggests that antibiotics prescriptions in low-income and middle-income countries were 0.54 (95% CI: 0.49–0.59) of the total patient prescriptions. This means that for every 100 patients or prescriptions, 54 would receive antibiotics, reflecting a high antibiotic use in the LMICs.

COVID-19 pandemics complicate the antibiotic overprescription problem. Our finding showed that in COVID-19 patients, the antibiotic prescription was as high as 0.80 (95%CI: 0.71–0.89) compared to the non-COVID-19 patients with a prevalence value of 0.50 (95%CI: 0.45–0.55). Those numbers are much higher than the World Health Organization indicator, which recommends that antibiotic prescriptions should be lower than 30% of total prescriptions [86]. However, studies on patients with COVID-19 only include those who were hospitalized. This circumstance may cause an overestimate or even underestimate of the actual condition because outpatients were not included in the studies.

One study done in China reported antibiotics usage amongst hospitalized COVID-19 patients with a nosocomial infection [71]. Interestingly, the proportion of antibiotic prescriptions was lower compared to several other studies [48,55,63,65,81,82]. The study that reported the highest prevalence of antibiotic prevalence was a trial of lopinavir-ritonavir in severe COVID-19. It was reported that antibiotic was part of the standard care, alongside supportive therapy.

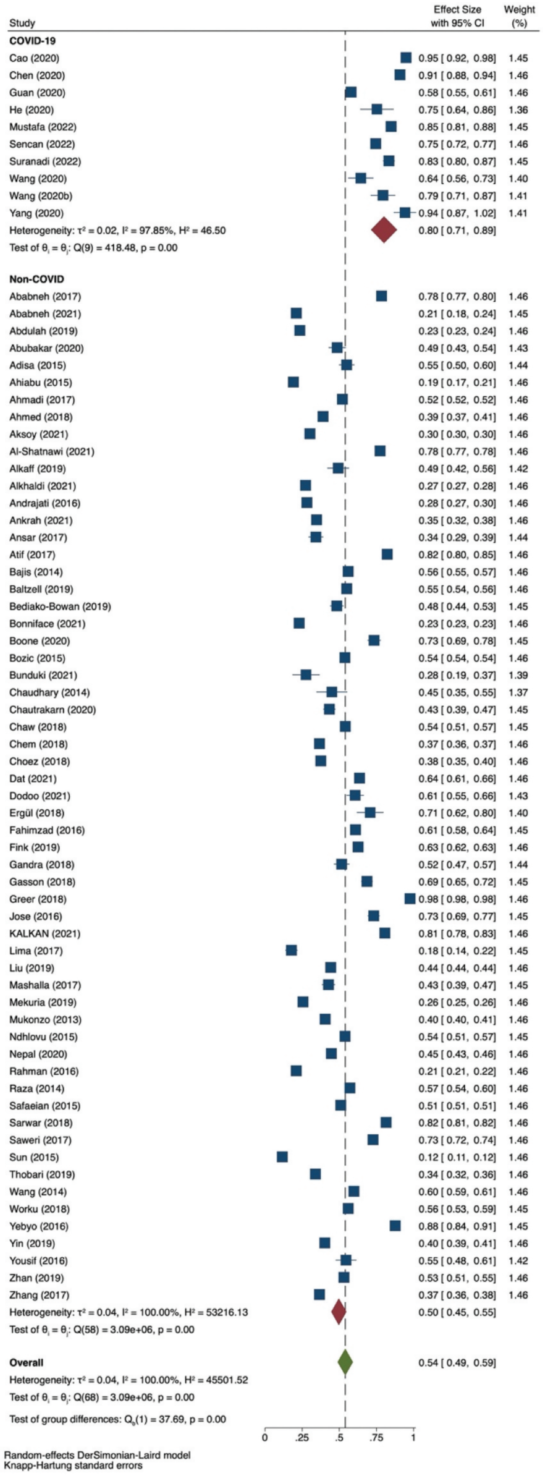

Figure 3. Forest plot for the prevalence of antibiotics prescription.

The high infectious disease burden in the LMICs could be the reason for prevalent antibiotic use. As mentioned before, the prevalent use of antibiotics could be good in LMICs, as it means that access to antibiotics has improved and could decrease the mortality rate of infectious diseases [87]. However, our findings showed a potential concern about the misuse of antibiotics. Half of those prescribed antibiotics (0.52, 95% CI: 0.32–0.72) received an inappropriate antibiotic prescription. Inappropriate antibiotic prescriptions are one of the causes of antimicrobial resistance apart from overuse of antibiotics and the use of multiple antibiotics [4].

The highest circumstances in which antibiotics were inappropriately prescribed were ambulatory settings [66]. Meanwhile, the study reporting the

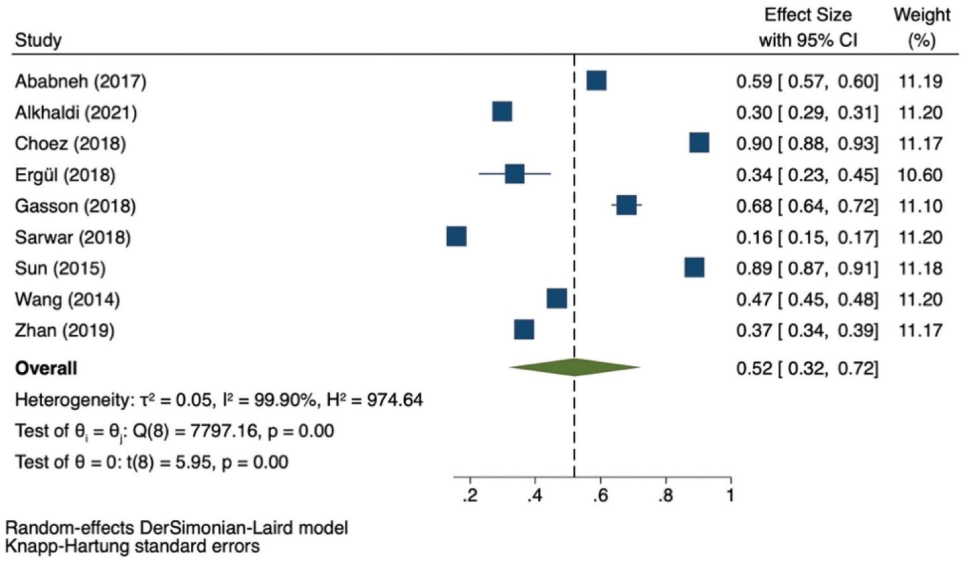

Figure 4. Forest plot for the inappropriate antibiotics prescription.

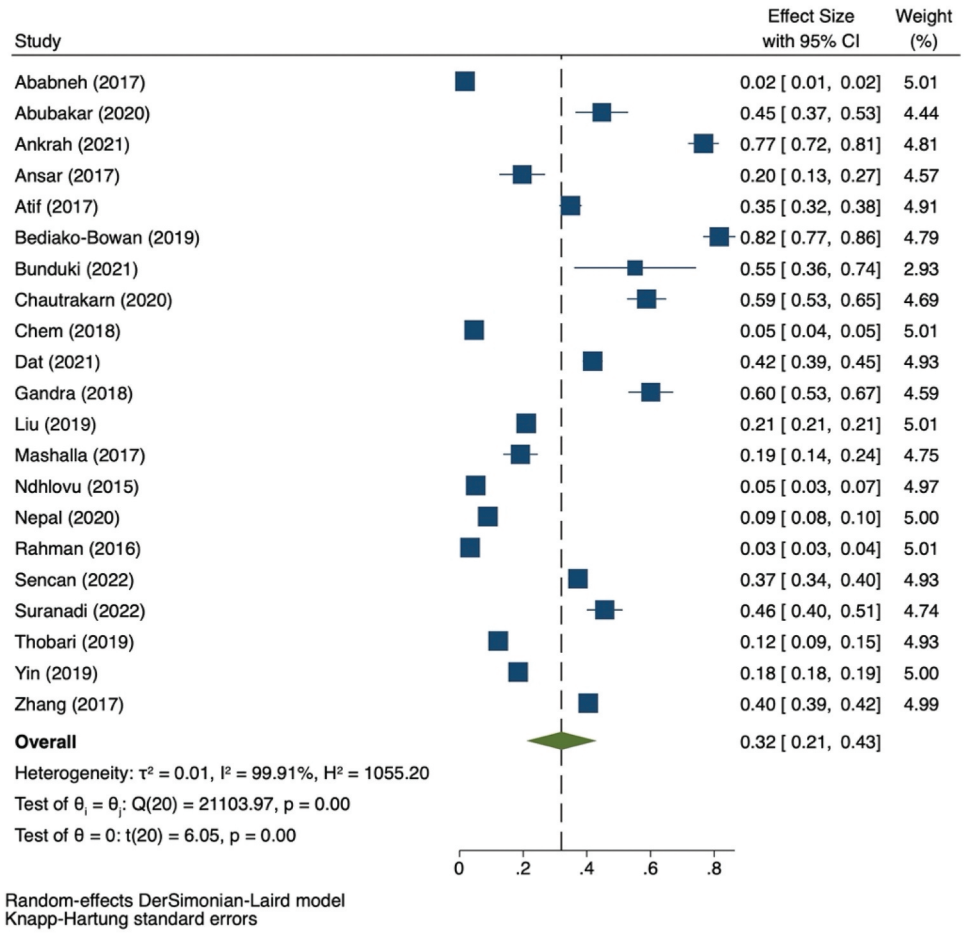

Figure 5. Forest plot for the prevalence of multiple antibiotics prescription.

lowest prevalence of inappropriate antibiotic prescriptions was done in primary health care [53]. Upper respiratory tract infection appeared to be a common diagnosis in both the low or high rate of inappropriate antibiotic prescription. None of the studies reporting inappropriate antibiotic prescriptions were done in COVID-19 patients.

Multiple antibiotic prescriptions were also prevalent based on our findings. We found that one-third of antibiotics prescriptions consisted of more than one antibiotic (0.32, 95% CI: 0.21–0.43). In contrast, World Health Organization recommends that antibiotic prescriptions be lower than two medicines [86]. Multiple antibiotics, if misused, also lead to antibiotic resistance [4].

This study showed a very high level of heterogeneity (I^2 were above 50%). However, our meta-analysis's pooled 95% CI were not showing wide intervals (0.49–0.59; 0.32–0.72; 0.21–0.43; for antibiotic prescription prevalence, inappropriate antibiotic prescription, and multiple antibiotic prescriptions, respectively). Thus, indicating that a similar systematic review study would yield a similar proportion of effect size.

In conclusion, antibiotics prescriptions accounted for half of the drug prescriptions in LMICs, and their use is increased amongst patients with COVID-19. Inappropriate antibiotics prescription accounted for half of the total antibiotic use. In addition, multiple antibiotic use is also common practice in LMICs. The burden of antibiotic use in LMICs corresponds to the decrease in mortality from infectious diseases. However, there is an extent to relying upon antibiotics as their inappropriate and overuse are associated with AMR. Mainly, physicians should use antibiotics appropriately and minimize multiple uses when not indicated.

Our study is not without a limitation. We included studies with a high risk of bias in the analysis, and one research conducted in an ambulatory setting was included in this study. Furthermore, many of the studies were conducted on a small scale. Hence, there is a need for a larger-scale study to accurately capture the prevalence of antibiotic prescription in a country, specifically LMICs. Ideally, the study should also observe the appropriateness of the treatment and the antibiotic agent of choice. Nevertheless, our findings suggest that urgent action to improve prescribing practices is essential.

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Availability of data and material

All data used in this manuscript can be found in the online versions of the studies that were accessed. Our own data synthesis of these manuscripts is available from the author upon a reasonable request.

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