POINT PREVALENCE SURVEYS OF ANTIMICROBIAL USE: A SYSTEMATIC REVIEW AND THE IMPLICATIONS

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Abstract:

Introduction: In view of increasing concerns with antimicrobial resistance (AMR), the World Health Organization (WHO) instituted a Global Action Plan (GAP) to address this.

Area Covered: One of the strategies to achieve the goals of GAP is to conduct regular surveillance of antimicrobial use through point prevalence surveys (PPS). After systematic database screening of 2,893 articles, 60 PPS met the inclusion criteria and consequently were incorporated in this systematic review.

Expert Opinion: This review highlighted that most of the PPS were conducted in upper-middle and high-income countries. Prevalence of antimicrobial use was significantly higher in non-European hospitals compared with European hospitals. The domination of third-generation cephalosporin and fluoroquinolones use across all the regions suggests substantial use of broad-spectrum antimicrobials across countries. Among all identified regions around the world, India was the region where the highest use of antimicrobials was observed. Although PPS is a useful tool to assess the pattern of antimicrobial use and provides a robust baseline, however, a standardize surveillance method is needed. In order to optimize antimicrobial use, more efforts are required to improve the antimicrobial use.

Article Highlights:

- Most of the point prevalence surveys were conducted in upper-middle and high-income countries.
- Prevalence of antimicrobial use was significantly higher in non-European hospitals compared with that European hospitals which can be a serious risk factor for resistance.
- India was the region where the highest use of antimicrobials was seen.
- The most frequently used antibiotics reported were the third-generation cephalosporins
- There were concerns with the lack and use of guidelines to direct antimicrobial use across countries.

Keywords: Point Prevalence Survey, Antimicrobial Prescribing, Review, Antimicrobial Resistance, Guidelines

1. INTRODUTION

Antimicrobials have revolutionized the treatment of infectious diseases, becoming the cornerstone of treatment for infectious diseases to reduce morbidity and mortality [1-5]. However, there is increasing antimicrobial resistance (AMR) as a result of their overuse, which has become a serious problem worldwide [2,4,6,7]. Globally, increasing AMR rates has resulted in the use of more expensive broad-spectrum antibiotics that were earlier reserved for specific conditions [2,3,7,8], along with increasing morbidity, mortality, and costs [9-13]. In view of increasing concerns with AMR and its impact, the World Health Organization (WHO) instituted a Global Action Plan (GAP) in the 68th World Health Assembly in May 2015 [14-16]. In addition, during the United Nations (UN) General Assembly on 21st September 2016, a declaration was made on AMR by the Heads of State, reinforcing the GAP. One of the goals of the GAP is to outline strategies to ensure the quality use of antibiotics thereby reducing inappropriate antibiotic use and associated AMR rates in the future [17,18]. One of the strategies to achieve these goals is to conduct regular surveillance of antimicrobial use through point prevalence surveys (PPS) [19]. As a result, a number of PPS have been conducted in different parts of world to improve future antibiotic use [19]. Point prevalence is the number of individuals with a condition divided by total number of all the individuals in that population in a time interval [20]. Point prevalence surveys (PPS) of antimicrobial use are typically conducted to determine the current in-patient use of antimicrobials to treat infections with the findings used to instigate pertinent quality improvement initiatives within hospitals [21-25].

It has been estimated that total antimicrobial usage, expressed in standard units, increased by 35% between 2000 to 2010, with Brazil, Russia, China, and South Africa alone accounting for 76% of this increase [26]. Moreover, there was an overall increase in the use of broad-spectrum antimicrobials including the carbapenems (45%) [26]. Inappropriate use of antibiotics has always been a challenge, with inappropriate use increasing over time in some countries [2,26]. Irrational empirical antimicrobial prescribing for severe infections in hospitals is currently estimated at between 14.1% to 78.9% of in-patient use [27]. There are also a number of published systematic reviews showing patterns of inappropriate antibiotic use in non-hospitalized patients [28-30]. However, to the best of our knowledge, no systematic review has been conducted to evaluate antimicrobial use surrounding PPS in hospitalized patients, although we are aware of initiatives including the Global PPS which included data from 303 hospitals in 53 countries [25] as well as the recent Pan-European acute care hospital PPS involving 1209 hospitals among 28 countries in the European Union/ European Economic Area (EU/ EEA) [31]. Consequently, we sought to address this by analysing

the burden of antimicrobial use measured through point prevalence surveys to provide direction to all key stakeholders in the future as we are aware that PPS can be used to establish quality initiatives for individual hospitals as well as monitor the effectiveness of any antimicrobial-stewardship (AMS) initiatives to improve future use [32]

2. BODY:

2.1 Search strategy:

All English language papers published in PubMed, EBSCO, Proquest, Cinahl and Scopus between January 2000 and December 2019 were searched. The Medical Subject Heading (MeSH) terms and keywords including "antimicrobial(s)", "antibiotic(s)", "use", "prescribing", "point prevalence", "repeated prevalence", "period prevalence", "survey" & "hospital(s)" were used to identify the relevant literature as well as truncations and Boolean operators ("OR" & "AND"). The titles of published papers and abstracts were subsequently screened in order to identify appropriate surveys reporting antimicrobial use.

2.2. Inclusion and exclusion criteria

Upon removal of duplicities, the full text of papers was retrieved and all original research articles (using an observational or experimental design) were considered for further assessment and inclusion in this systematic review. Potentially relevant articles were reviewed thoroughly in full-text. Original research papers that conducted a point prevalence survey of antimicrobial use in hospital settings were included in this systematic review. After a thorough discussion, the discrepancies in the selected articles were reviewed and possible studies were then reassessed to ascertain whether they met the broad content inclusion criteria of PPS or not. Antimicrobials were defined as antibacterials, antimycotics, and antivirals for systemic use. Antimicrobial use was categorized in children (including neonates and pediatrics) and adults (including surveys for the whole hospital). We included only surveys from acute care hospitals. Surveys conducted in intensive care units (ICU), home-based hospital care (HBHC), long-term care facilities (LTCFs) and nursing homes were excluded. Moreover, review articles, case studies, case series, and personal opinions were also excluded from this systematic review. In addition, studies involving antimicrobial consumption at outpatient clinics and pharmacies as well as those involving agricultural or veterinary use were also excluded. The studies which did not follow the structured standardized survey methodology employed by the European Centre of

Disease Prevention and Control (ECDC), Global PPS or related research methods were also subsequently excluded [33].

2.3 Data extraction and analyses

Extraction and analysis of data were in line with the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA).Core points of these research papers were prearranged including the date of survey, antimicrobial use prevalence, the most common antimicrobials prescribed and indications among children and the adult population throughout different regions of the world. All the relevant data regarding the use of antibiotics as per Anatomical Therapeutic Chemical (ATC) classification of antibiotics were retrieved [34]. In addition, the quantitative data concerning the number of patients administered antibiotics for the prophylaxis or treatment was also extracted.

Studies were classified according to their PPS method and protocol. Countries were classified according to the United Nations Region methodology and World Bank classification by income. For each geographical region, point prevalence surveys of antimicrobial use were pooled to analyze the frequency of use in children and adults for comparative purposes. Most of the time when adults and children were presented together, the proportion of children was typically very small. In this situation, the whole hospital (adults and children) together was documented as adults only. We also compared our findings with those from the recent EU/ EEA and Global PPS studies for these key indicators to add robustness to our findings [25,31].

3. Results:

We identified 2,893 potentially pertinent research papers based on title and abstract. Finally, 60 articles, 17 studies covering children and 43 covering adult populations met the inclusion criteria and were incorporated into this systematic review (Figure 1). The included studies were from Asia (5 children & 13 adults), Africa (1 child, 6 adults), Oceania (1 child & 3 adults), America (1 child & 3 adults), Europe (7 children & 17 adults) and worldwide surveys (2 children & 1 adult). These 60 surveys covered 4,235 health care settings worldwide (508 children & 3,727 adult settings). Most of the PPS were conducted in upper-middle and high-income countries, and most of the studies were published after 2015 in Asian and African countries.

Table 1 and Table 2 summarize the reported number of patients on antimicrobials in different regions of the world as well as key findings by type of healthcare setting split into adults and children. The most frequently used

antibiotics were the third-generation cephalosporins. Respiratory tract infections were typically the most common reason for prescribing antimicrobials. Among all identified regions around the globe, India was the region where the highest use of antimicrobials was seen among in-patients at 98.4% [35]. The prescribing of antimicrobials for prophylaxis was also found to be the highest (71.0%) in this study in India involving neonatal and pediatric patients [35]. The average number of antimicrobials prescribed per admitted patient was found to be highest in Kenya at 3.6 [36]. Table 3 consolidates the prevalence of antimicrobial use among in-patients by region.

3.1 Antimicrobial Use in Children:

Among children, India was the country where the highest use of antimicrobials was seen in two published studies reaching 98.4% [35,37]. Ghana was the second-highest country at 70.6%, China the third (67.8%) and Turkey the fourth-highest country at 54.6% respectively [38-40]. Among 31 hospitals in the USA, the reported use of antimicrobials was 54.4% with gentamicin was most commonly used antibiotic followed by ampicillin and vancomycin [41]. The antimicrobial use rate was 46.0% in a survey conducted in Australia [42]. Among European countries, highest prevalence of antimicrobial use was found in hospitals in the UK followed by Italy. In the 2008 ESAC survey, which was based on pediatric antimicrobial prescribing in 32 hospitals among 21 European countries, the antimicrobial use rate was 32.4% with the most commonly used antibiotics for therapeutic use being the third-generation cephalosporins (18%), aminoglycosides (14%) and extended-spectrum penicillin (10%) [43]. Data from 2 hospitals of Germany and Croatia in 2005 showed antibiotic use at 17.4% among the pediatric population [44], which is also the lowest use compared to other regions of the world.

3.2 Antimicrobial Use in Adults:

Among all the identified regions worldwide, the highest use of antimicrobials among countries and regions was seen in Pakistan (77.6%) which recorded the highest use of ceftriaxone [45]. At the hospital level, China was the second country where the highest use of antimicrobials was seen (75.3%) among all patients admitted onto different wards [46], with the findings already leading to strategies to try and address overuse of antimicrobials [47,48]. Botswana was the third and Nigeria was fourth-highest country at 70.6 % and 69.7% respectively [49,50]. The fifth country with the highest use of antimicrobials was the Congo with an overall 68.0% usage among eleven different hospitals [51]. More than half of the patients were on antimicrobial use in hospital settings of Kenya (54.7% and 67.7%), Hubei province of China (55.6%), Italy (51.1%), and Singapore (51.0%) [22, 36, 52-54]. Among 183 hospitals in the USA, the reported use of antimicrobials was 50% where vancomycin was most commonly used antibiotics

followed by ceftriaxone and piperacillin plus tazobactam to treat different infections [55]. The Global PPS conducted among 335 hospitals across 53 countries found overall antibiotic use at 34.4 % [25]. Antimicrobial use was highest among the African countries taking part at 50.0% of inpatients and lowest in Eastern Europe at 27.4% of patients [25].. Among European countries, the highest prevalence of antimicrobial use was found in Italy (51.1%) [2]. Zarb et al., also found extensive use of antibiotics (34.6%) in a study performed during 2010 across hospital settings among twenty-three European countries [23], while in 2009 from 172 hospitals across twenty-five European countries antibiotic utilization was lower at 29.0% [56]. More recently, Plachouras et al found an average rate of 30.5% among 1209 hospitals in 28 EU/ EEA countries [31]. Among all the identified regions worldwide, antimicrobial use was lowest among patients in a hospital of Norway (16.6%) [57].

4. Discussion:

To date, we believe this is the first systematic review that has fully scrutinized the research articles published on the use of antibiotics in acute care settings using the point prevalence method across countries and regions, building on the Pan-European (ECDC) and Global PPS studies [23,2531,43]. We again found considerable regional variation in antimicrobial prescribing among hospitalized patients (Tables 1 to 3), which could be due to a number of factors. These include differences in underlying infection rates, concerns with an accurate diagnosis, differences in resistance patterns, lack of standard treatment guidelines (STGs) within facilities and their use to guide rational prescribing, differences in the monitoring of antibiotic use especially against agreed guidelines, lack of infection and control procedures, overcrowding on wards, as well as extending prophylactic use of antibiotics with concerns with air and hygiene quality in operating theatres and hygiene on the wards [3,25,50,91-98]. This systematic review exposed the fact that most PPS studies of antimicrobial use are principally conducted among European countries. There have only been a limited number of PPS studies undertaken to date in Africa to date despite the high burden of infectious diseases; however, this is beginning to change with recent studies in for instance Ghana, Nigeria and Zimbabwe in addition to those listed in Table 1 and the 5 countries taking part in the Global PPS study [25, 99-103]. Despite considerable research papers documenting the trend of antimicrobial use and potential adverse events, PPS studies from Asian countries are also scarcer than seen in Europe (Table 1) including Asian countries taking part in the Global PPS study [25].

The domination of third-generation cephalosporin and fluoroquinolones use among all regions in our study suggests substantial use of broad-spectrum antimicrobials across countries. This mirrors the high use of third-generation

cephalosporin, fluoroquinolones and carbapenam in the Global PPS [25]; however different to the recent EU/ EEA study where penicillins with beta-lactamase inhibitors were the most used antimicrobials [31]. Excessive use broad spectrum antibiotics may reflect high AMR rates and/ or the emergence of multidrug-resistant microbes coupled with a lack of culture and sensitivity analysis facilities and available STGs [17,19,98,100,104-106]. Extensive broad-spectrum antimicrobial prescribing could be explained by regionally high rates of carbapenem-resistant or Gram-negative extended-spectrum beta-lactamase-producing organisms [107-109]. We have seen that among American nations, surveillance programs have identified an increase in carbapenem-resistant Klebsiella species and resistance to extended-spectrum cephalosporins, with a high prevalence of *Klebsiella spp* and ESBL-producing *Escherichia coli* with concerns also seen in Asia [110-114]. Consequently, programmes are needed in hospitals to reduce inappropriate antibiotic prescribing, which fuels rising AMR rates adding to morbidity, mortality and the cost of treatment [9,10,12,13,22,51,85,115,116].

A current concern is that we saw limited regulation of antimicrobial use due either to missing guidelines or, more commonly due to lack of enforcement of current STGs among a number of countries including African countries as well as West and Central Asian countries taking part in the Global PPS [19,25,38,46,50,64,83,98]. There was also limited targeted use of antibiotics particularly in Africa as well as West and Central Asia in the Global PPS (14.6% each) [25]. However, encouragingly we saw higher rates of compliance with local guidelines in other regions in the Global PPS study ranging from 64.1% in Latin America to 85.8% in North America where guidelines were available [25]. In addition, 76.3% of the hospitals in the recent EU/ EEA study reported the availability and use of antimicrobial guidelines [31]. There was also good guideline adherence among hospitals in Ghana and Namibia although below target rates of 95% compliance [100, 117]. This is important since adherence to agreed STGs enhances the quality of antimicrobial prescribing [25,50,118]. The lack of guidelines as well as monitoring of antibiotic prescribing in hospitals may help explain the excessive use of broad-spectrum antimicrobials in this and other studies [19,22,38,44,46,55,59,62,64,73,109,116]. The process of rational antimicrobial prescribing is multifaceted supported by local patterns of antimicrobial susceptibility [4,50, 117-119-123]. In regions where antimicrobial susceptibility information is not available, the selection of antimicrobial is challenging even for experienced health care providers [124,125]. The practical differences in antimicrobial prescribing rates between the various countries and regions could be due to a number of factors including, as mentioned. cultural influences, national guidelines, local or regional policies, local resistance patterns, knowledge on rational antimicrobial use and the availability of antimicrobials in the

market. In addition, the activities of pharmaceutical companies if this is the main source of physician information regarding potential antibiotics to prescribe [122,126-128]. For instance in sub-Saharan Africa, there can high rates of HIV, TB and malaria among admitted patients [24,50], which are not seen in other regions. In addition, the implementation of infection prevention and control policies are typically stricter and monitored with greater instigation of antimicrobial stewardship programmes (ASPs) among European countries [31]. In Pakistan, patients are prone to acquire multidrug-resistant infectious disease and healthcare-associated infections [7,94].

Typically the first step to address concerns with inappropriate prescribing of antibiotics in hospitals is the documentation of current utilization and sensitivity patterns to help develop pertinent local guidelines, and subsequently monitor prescribing against these guidelines [117, 121]. This can be part of instigating ASPs in hospitals to reduce inappropriate prescribing [129-132]. However, this is more challenging in lower-and middle-income countries (LMICs) in view of resource, manpower and cultural issues resulting in variable implementation to date [91-93, 133]. However, interventions to decrease irrational antimicrobial prescribing must be carefully handled so as not to restrict access to antimicrobials for patients with true bacterial disease as this can lead to therapeutic failure [134]. Increasing AMR rates and irrational use of antibiotics can potentially be avoided through clinical pharmacist interventions as part of ASPs within hospitals [1135].Improving the rational use of antibiotics will also help decrease adverse drug reactions (ADRs) with antimicrobials currently the second most common reason for ADRs in the USA [136]. Prior use of antimicrobials is also a threat to the growth of multidrug-resistant microbes [109,137], and this must be carefully handled through multiple interventions in ambulatory care to reduce inappropriate prescribing and dispensing of antibiotics alongside ASPs within hospitals [129-133,138-141]. Comparing trends of antimicrobial prescribing between countries and policies also allows key stakeholder groups to understand the wide range of patterns of antimicrobial use and subsequent concomitant resistance between them to develop appropriate strategies to reduce AMR as part of National Action Plans [4,16,138-140,142,].

We acknowledge our appraisal has limitations. A number of possible confounding and biasing parameters might have hindered this systematic review. The mixture of studies with diverse settings and heterogeneity in patients' characteristics hindered a standard systematic appraisal, and figures might not be representative of existing practices in the countries and the regions studied. Our systematic review was also restricted by the quality of research papers accessible for scrutiny as well as limitations intrinsic in our own techniques. For instance, we opted not to incorporate

unpublished data on PPS, and so some degree publication bias may be reflected in our results. The difference in the quality of different countries' health-care systems and the definitions of infections also had a discernible influence on the systematic review. In addition, data on antimicrobial use ranges was not available in most papers and different papers mentioned the top three antibiotics at different levels of ATC classification as there was no standardized way of reporting prevalence and usage data. Another limitation that was beyond your control was that some PPS used only antibacterial agents some anti-infectives, some included a wider range of antimicrobials including those for TB. Finally, throughout this systematic review, we paid attention only to PPS of antimicrobial use. We acknowledge that PPS is not only a methodology to evaluate patterns of antimicrobial use but also seeking ways to improve future use by increasing documentation of key aspects of antimicrobial use including documenting the rationale for their use, start and stop dates, and any missed doses. Nevertheless, we brought into play a broad series of search terms concerning PPS and consequently we presuppose that the terms should spot those research papers covering PPS. Having said this, we believe the strong points of this review include the inclusive search approach and the quality assessment of PPS methodology. In addition, the ability to compare and contrast findings between different countries and regions to provide a basis for the future especially in countries where there are currently concerns with high inappropriate antibiotic use. Consequently, we are confident in our findings.

5. CONCLUSION

In conclusion, we believe PPS is a useful tool to assess the patterns of antimicrobial use within hospitals and across countries and regions, and provides a robust baseline for developing pertinent quality improvement programmes. This is especially important in regions such as Africa where there has been a paucity of PPS studies compared with Europe. However, we believe a standardized surveillance method is needed building on the Global PPS initiative. Another concern is that the prevalence of antimicrobial use is significantly higher among non-European hospitals compared with European hospitals, which can be a serious risk factor for resistance development. In order to optimize antimicrobial use in the future, more efforts are required especially in LMICs to improve diagnosis and management including the instigation of STGs based on local resistance patterns as well as monitoring prescribing against agreed guidelines and quality indicators. Continued comparisons between countries alongside the evaluation of the impact of different initiatives will help countries to improve their antibiotic utilization and reduce future AMR rates. We will be monitoring this in the future.

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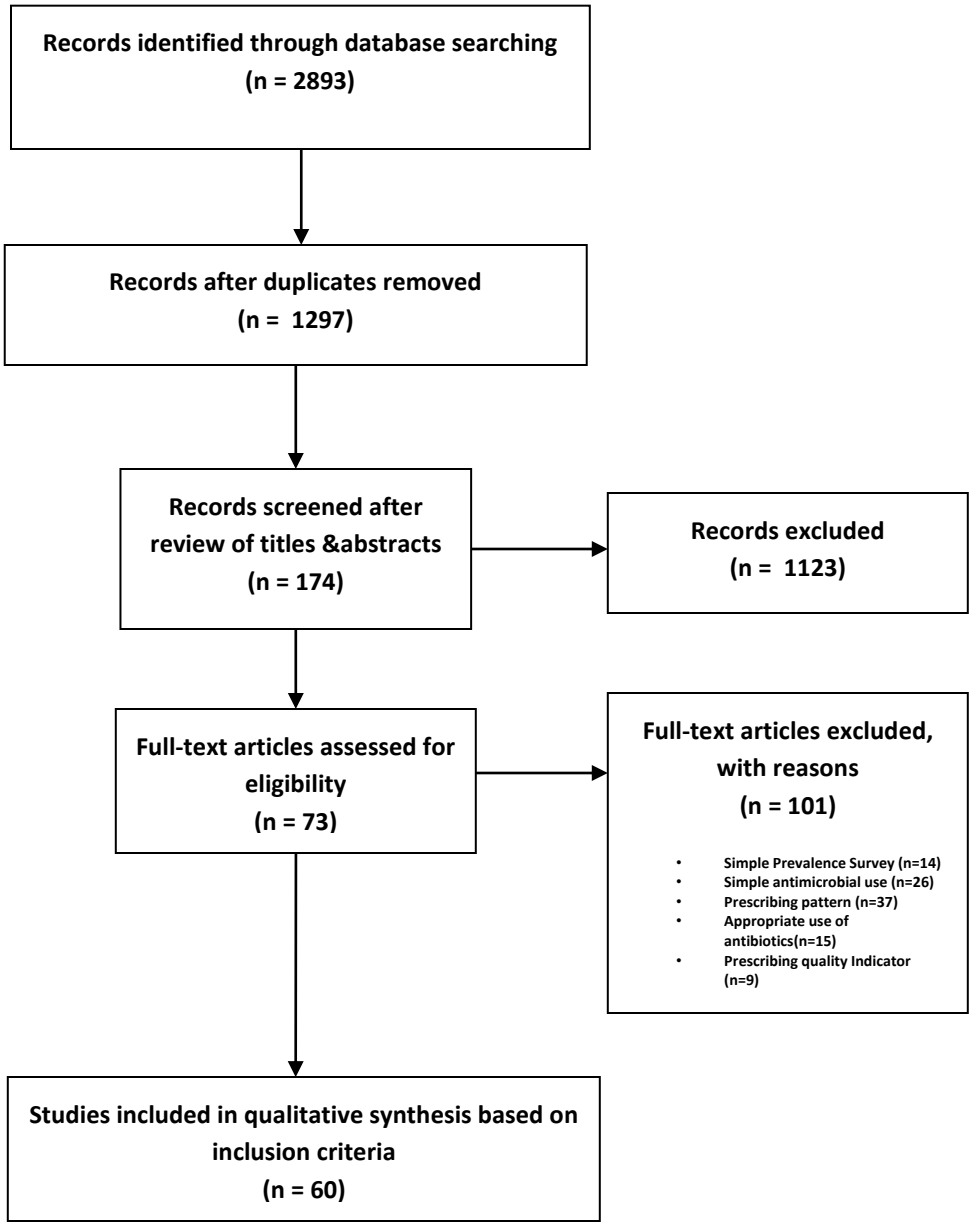

Figure 1: Flow Chart of Study Selection

Table 1: Literature Review of Published Point-Prevalence Surveys (PPS) in Children

Continent and Country	World Bank Classification by income [#]	Author Name & Date	No. of ACH	PPS Method	PPS Protocol	Study Duration	Antimicrobial use rate n (%)	Drug.1 *ATC Code* (%)	Drug.2 *ATC Code* (%)	Drug.3 *ATC Code* (%)	Prophylaxis (%)	Treatment (%)	Antimicrobials (Drugs/Patient)
Asia													
Iran [58]	LM	Soltani et al., 2019	2	Repeated	ARPEC	2011-2012	252 (64.0)	Ceftriaxone *J01DD04* (19.9)	Ampicillin-*J01CA01* (14.3)	Vancomycin-*J01XA01* (13.3)	16.9	82.3	391 (1.55)
China [40]	UM	Zhang et al., 2018	18	Period	GARPEC	December 2016-February 2017	975 (67.8)	Third-generation cephalosporins-*J01DD*	Beta lactum plus beta lactum inhibitors-*J01CR*	-	-	-	1238 (1.27)
India [37]	LM	Gandra et al., 2017	6	Repeated	GARPEC	February 2016-February 2017	419 (61.5)	Ceftriaxone *J01DD04* (18.4)	Co-amoxiclav-*J01CR02* (11.5)	Cefotaxime *J01DD01* (9.6)	18.2	81.8	602 (1.44)
India [35]	LM	Singh et al., 2014	8	One day	ARPEC	November 2012	192 (98.4)	Amikacin-*J01GB06*- J01 (13.5)	Piperacillin plus tazobactam-*J01CR05* (10.4)	Fluconazole-*J02AC01* (8.4)	71.0	29.0	431 (2.2)
Turkey [38]	UM	Ceyhan et al., 2010	12	One day	Own	October 2007	711 (54.6)	Third-generation cephalosporins-*J01DD* (16.6)	Aminoglycosides *J01G* (16.6)	Carbapenems *J01DH* (11.4)	18.7	73.4	1317 (1.85)
Africa													
Ghana [39]	LM	Labi et al., 2018	10	Period	ECDC	September-December 2016	506 (70.6)	Ceftriaxone *J01DD04* (14.9)	Gentamicin-*J01GB03* (13.7)	Cefuroxime *J01DC02 (12.4)*	23.7	71.5	831 (1.6)
America													
USA [41]	H	*Grohskopf et al., 2005*	31	Repeated	PPN/CDC	August 1999 – February 2000	1440 (54.4)	Gentamicin-*J01GB03* (16.9)	Ampicillin-*J01CA01* (14.9)	Vancomycin-*J01XA01* (12.9)	-	-	2647 (1.84)
Oceania													
Australia [42]	H	Osowicki et al., 2014	8	Period	ARPEC	May-July 2012	631 (46.0)	Narrow spectrum penicillins-*J01CE* (18.0)	Beta lactum plus beta lactum inhibitors-*J01CR* (15.0)	Aminoglycoside-*J01GB* (14.0)	37.0	62.0	1174 (1.86)
Eastern Europe													
Russia [59]	UM	Hajdu et al., 2007	1	One day	ECDC	February 2006	183 (38.8)	Third-generation cephalosporins-*J01DD* (14.2)	Second-generation cephalosporins *J01DC* (14.2)	Macrolides *J01FA* (9.5)	13.0	84.0	211 (1.15)
Northern Europe													
UK [60]	H	Gharbi et al., 2016	61	Period	ARPEC	2011-2012	1247 (40.9)	-	-	-	-	24.1	1858 (1.49)
UK [61]	H	Ang et al., 2008	1	Two Days	Own	2008	177 (49.3)	-	-	-	28.4	70.3	-
Latvia [62]	H	Sviestina and Mozgis, 2014	10	One day	ARPEC	November 2012	192 (35.0)	Third-generation cephalosporins *J01DD* (30.7)	Penicillins with extended spectrum *J01CA* (19.8)	Betalactamase sensitive penicillins *J01CE* (13.5)	19.2	80.8	235 (1.22)
Southern Europe													
Italy [63]	H	De Luca et al., 2016	7	One day	ARPEC	October - December 2012	349 (38.9)	Penicillin-*J01C*	Aminoglycoside-*J01GB*	Cephlosporin-*J01DD*	37.0	63.0	543 (1.56)
Germany & Croatia [44]	H	Ufer M et al., 2005	2	Period	Own	2005	104 (17.4)	Cephlosporin *J01D*	Penicillins *J01C*	Aminoglycoside *J01G*	8.0	92.0	-
Multiregional													
21-EC [43]	3 UM; 18 H	Amadeo et al., 2010	32	Period	ECDC	May- June 2008	583 (32.4)	Gentamicin-*J01GB03* (13)	Ceftriaxone *J01DD04* (10.1)	Ampicillin-*J01CA01* (9.3)	26	71	839 (1.45)
41-C [19]	5L; 3 LM; 6 UM;27 H	Versporten et al., 2016	226	Period	ARPEC	October–November 2012	6499 (36.7)	Penicillin *J01C*	Cephlosporin *J01D*	Aminoglycoside *J01G*	32.8	67.2	10196 (1.57)
24-C [64]	2L; 2 LM; 3 UM;17 H	Versporten et al., 2013	73	One day	ARPEC	September 2011	2142 (35.3)	-	-	-	-	-	-

ACH: Acute care Hospitals, **ARPEC:**Antibiotic Resistance and Prescribing in European Children, **ECDC:** European Centre of Disease Control and Prevention, **GARPEC:** Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children, PPN: Pediatric Prevention Network, **L:** Low income, **LM:** Low Middle Income, **UM:** upper Middle Income, **H:** High Income

Table 2: Literature Review of Published Point-Prevalence Surveys (PPS) in Adults

	World Bank Classification by income	Author Name & Date	No. of ACH	PPS Method	PPS Protocol	Study Duration	Antimicrobial use rate	Drug.1-*ATC Code* (%)	Drug.2-*ATC Code* (%)	Drug.3-*ATC Code* (%)	Prophylaxis (%)	Treatment (%)	Antimicrobials (Drugs/Patient)
Eastern Asia													
China [46]	UM	Ren et al., 2016	1313	Period	Own	March-October 2012	592111 (75.3)	-	-	-	39.7	60.3	-
China [22]	UM	Xie et al., 2015	13	One Day	Own	November 2008	6904 (55.6)	Third-generation cephalosporins-*J01DD* (26.3)	Fluoroquinolones-*J01MA* (15.2)	Metronidazole-*J01XD01*(9.3)	26.4	73.6	8682 (1.26)
Japan [65]	H	Morioka et al., 2018	4	One Day	ECDC	July 2016	933 (29.2)	Cephalosporins-*J01D*	Co-trimoxazole-*J01EE*	Antimycotics-*J02*	-	-	1318 (1.4)
Japan [66]	H	Morioka et al., 2016	1	One Day	Own	July 2014	308 (36.6)	Cephalosporins-*J01DD* (33.0%)	Antimycotics-*J02* (14.9%)	Co-trimoxazole-*J01EE* (14.9%)	60.7	37.7	494 (1.6)
Southern Asia													
Pakistan [45]	LM	Saleem et al., 2019	13	Period	Global	October 2017-February 2018	1516 (77.6)	Ceftriaxone-*J01DD04* (35.0)	Metronidazole-*J01XD01*(16.0)	Ciprofloxacin *J01MA02* (6.0)	57.4	40.2	2483 (1.64)
Pakistan [67]	LM	Saleem et al., 2019	1	Repeated	ECDC	March 2018-2019	156 (49.8)	Piperacillin plus tazobactam-*J01CR05* (31.8)	Meropenem-*J01DH02* (7.9)	Ceftriaxone-*J01DD04* (6.2)	15.7	70.2	242 (1.55)
Sri Lanka[68]	LM	Sheng et al., 2019	5	Period	-	June-August 2017	935 (54.6)	Co-amoxiclav-*J01CR02* (33.8)	Third-generation cephalosporins-*J01DD* (23.6)	Metronidazole-*J01XD01*(16.6)	-	-	-
India[69]	LM	Singh et al., 2019	16	Period	Global	Oct-Dec 2017	1005 (57.4)	Ceftriaxone-*J01DD04* (34.0)	Piperacillin plus tazobactam-*J01CR05* (8.0)	Meropenem-*J01DH02* (8.0)	45.9	46.7	1578 (1.57)
India [70]	LM	Nair et al., 2015	1	Repeated	Own	March-August 2014	787 (41.7)	Cefotaxime *J01DD01* (10.2)	Ceftriaxone-*J01DD04* (8.9)	Amikacin- *J01GB06* (7.9)	56.2	44.8	1940 (2.47)
South Eastern Asia													
Singapore [53]	H	Cai et al., 2017	13	Period	ECDC	July 2015 - February 2016	2762 (51.0)	Co-amoxiclav-*J01CR02* (24.6)	Piperacillin plus tazobactam-*J01CR05* (9.2)	Ceftriaxone-*J01DD04* (7.7)	12.8	83.0	3611 (1.31)
Western Asia													
Qatar [71]	H	Hammuda et al., 2013	1	Repeated	ECDC	April - MayS 2012	25 (43.0)	Penicillins plus Beta-lactamase inhibitors-*J01CR* (39.4)	Carbapenems-*J01DH* (15.2)	Fluoroquinolones-*J01MA* (9.1)	6.1	93.9	33 (1.32)
Saudi Arabia [72]	H	Matar et al., 2019	26	Period	Global PPS	May 2016	2182 (46.9)	Ceftriaxone-*J01DD04* (11.7)	Metronidazole-*J01XD01* (9.9)	Cefuroxime *J01DC02* (6.9)	34.6	47.7	3240 (1.48)
Turkey [73]	UM	Usluer et al., 2005	18	One Day	Own	March 2002	2900 (30.6)	Third-generation cephalosporins-*J01DD* (23.7)	Aminoglycosides-*J01G* (17.2)	Flurouinolones-*J01MA* (14.4)	44.2	48.8	-
Africa													
Botswana[70]	UM	Anand Paramadhas et al., 2019	10	Period	MURIA	May-June 2017	711 (70.6)	Cefotaxime *J01DD01* (20.3)	Metronidazole-*J01XD01*(12.8)	Ampicillin-*J01CA01* (9.7)	-	-	982 (1.38)
South Africa[74]	UM	Dlamini et al., 2019	1	Period	MURIA	February-March 2017	193 (37.7)	Broad Spectrum Penicillin- *J01C* (34.1)	Cephlosporin- *J01D* (17.9)	Antituberculosis-*J04A* (12.0)	5.2	89.2	306 (1.59)
Kenya[36]	LM	Momanyi et al. 2019	1	Period	MURIA	April 2017	97 (54.7)	Ceftriaxone-*J01DD04* (39.7)	Benzyl Penicillin-*J01CE08* (29.0)	Metronidazole-*J01XD01*(25.1)	41.4	57.0	357 (3.6)
Kenya**[54]**	LM	Okoth et al., 2018	1	Period	Global PPS	June 2017	182 (67.7)	Third-generation cephalosporins-*J01DD*	Imidazole derivatives- P01, J02	Broad-spectrum penicillins- *J01CA*	51.0	41.0	333 (1.80)

Nigeria [49]	LM	Oduyebo et al., 2017	4	Period	Own	April- June 2015	577 (69.7)	Ceftriaxone-*J01DD04* (18.9)	Metronidazole-*J01XD01* (18.0)	Ciprofloxacin *J01MA02* (9.9)	38.8	51.2	1022 (1.77)
Congo [51]	L	Wambale et al., 2016	11	Period	Own	October 2014	476 (68)	Ampicillin-*J01CA01* (35.0)	Gentamicin-*J01GB03* (13.6)	Amoxicillin-*J01CA04* (13.5)	4.0	96.0	667 (1.40)
Oceania													
Australia [75]	H	Cotta et al., 2014	3	Period	Own	February 2012-February 2013	1125 (32.4)	-	-	-	-	-	1444 (1.28)
Australia [76]	H	Ingram et al., 2011	1	Period	Own	September-October 2010	199 (43.0)	Penicillins plus Beta-lactamase inhibitors-*J01CR* (31)	Fluoroquinolones-*J01MA* (12)	Penicillin-*J01C* (11)	12.0	88.0	262 (1.32)
Australia [77]	H	Ho and Melvani, 2007	1	Repeated	Own	April 2005-April 2006	508 (34)	Penicillin-*J01C* (26.0)	Cephlosporins-*J01D* (20.0)	Metronidazole-*J01XD01* (7.7)	12	88	832 (1.64)
America													
Canada [78]	H	Lee et al., 2015	1	One Day	Own	July 2012	177 (17.3)	Fluoroquinolones-*J01MA*	Third-generation cephalosporins-*J01DD*	1st generation cephalosporins-*J01DB*	10.7	87.0	249 (1.41)
Canada [79]	H	Black et al., 2018	13	Period	ECDC	June-November 2015	458 (30.6)	Metronidazole-*J01XD01* (11.1)	Cefazolin *J01DB04 (10.9)*	Ceftriaxone-*J01DD04* (8.9)	-	-	660 (1.4)
USA [55]	H	Magill et al., 2014	183	One Day	CDC	May-September 2011	5635 (50.0)	Vancomycin-*J01XA01* (14.4)	Ceftriaxone-*J01DD04* (10.8)	Piperacillin plus tazobactam-*J01CR05* (10.3)	18.1	77.5	9865 (1.75)
Northern Europe													
Norway [57]	H	Berild et al., 2002	1	Repeated	Own	1996-1999	1096 (16.6)	Penicillin V and G-*J01CR* (19.1)	Ampicillin-*J01CA01* (16.9)	Dicloxacillin-*J01CF01* (10.9)	5.8	94.2	1370 (1.25)
Scotland [80]	H	Seaton et al., 2007	10	One Day	GAAT	December 2003	1079 (28.3)	Third-generation cephalosporins-*J01DD* (28.3)	Coamoxiclav-*J01CR02* (20.2)	Metronidazole-*J01XD01* (19.2)	-	-	-
Ireland [81]	H	Al-Taani et al., 2018	3	Repeated	Global PPS	2009, 2011, 2015	1239 (34.4)	Penicillins plus β-lactamase inhibitors-*J01CR*	Penicillins with extended spectrum-*J01CA*	Macrolides-*J01FA*	13.0	87.0	1752 (1.41)
Ireland [82]	H	Aldeyab et al., 2012	4	Period	ECDC	May-June 2009	512 (32.0)	Co-amoxiclav-*J01CR02* (21.6)	Piperacillin plus tazobactam-*J01CR05* (11.9)	Metronidazole-*J01XD01* (9.1)	15.9	84.1	713 (1.39)
Western Europe													
France [83]	H	Robert et al., 2012	38	One Day	Own/ ECDC	November 2009	1619 (40.8)	Fluoroquinolones-*J01MA* (23.6)	Penicillins plus Beta-lactamase inhibitors-*J01CR*(22.4)	Third and Fourth-generation cephalosporins-*J010DD, DE* (22.1)	21.2	78.8	N/A
Germany [84]	H	Hansen et al., 2013	132	Period	ECDC	September-October 2011	10,593 (25.5)	Cefuroxime *J01DC02* (14.3%)	Ciprofloxacin *J01MA02* (9.8%)	Ceftriaxone-*J01DD04* (7.5%)	30.0	70.0	-
Austria [85]	H	Lusignani et al., 2016	9	Period	Own/ ECDC	May-June 2012	1425 (33.0)	Amino-penicillin and beta lactamase inhibitors- *J01CR* (20.5%)	Fluroquinolones-*J01MA* (14.8%)	First and Second-generation cephalosporins-*J01DB, J01DC* (12.8%)	N/A	N/A	1792 (1.26)
Netherlands [86]	H	Akhloufi et al., 2015	1	Period	Own	May 2013	337 (33.8)	Fluoroquinolones-*J01MA* (12.1)	Co-amoxiclav-*J01CR02* (11.1)	Meropenem-*J01DH02* (9.1)	34.4	65.6	423 (1.25)
Netherlands [87]	H	Willemsen et al., 2010	19	Repeated	Own	2008-2009	2327 (29.6)	Co-amoxiclav-*J01CR02* (26.3)	Fluoroquinolones-*J01MA* (14.0)	Third and fourth-generation cephalosporins-*J01DD, DE* (7.3)	-	-	2876 (1.24)
Southern Europe													
Italy [52]	H	Antonioli et al., 2016	1	Repeated	ECDC	October 2011-November 2013	63 (51.1)	Fluoroquinolones-*J01MA* (23.0)	Penicillins plus Beta-lactamase inhibitors-*J01CR* (19.2)	Third-generation cephalosporins-*J01DD* (16.6)	-	-	858 (1.35)
Kosovo [88]	UM	Krasniqi et al., 2017	7	Period	ECDC	2013	767 (46.0)	Penicillin *J01C*	Cephalosporins-*J01D*	Aminoglycosides-*J01G*	91.0	9.0	1114 (1.45)

Eastern Europe													
Slovak [89]	H	Stefkovicova et al., 2016	40	Period	ECDC	2012	2575 (30.7)	Fluoroquinolones- *J01MA* (20.9)	Penicillins plus Beta-lactamase inhibitors- *J01CR* 15.7	Extended-spectrum penicillins- *J01CA* (10.1)	28.0	61.3	3205 (1.24)
Multiregional													
53-C [25]	2 L ; 6 LM ; 17 UM ; 28 H	Versporten et al., 2018	335	Period	Global-PPS	January - September 2015	29 891 (34 · 4%)	Penicillins plus Beta-lactamase inhibitors- *J01CR*	Third-generation cephalosporins- *J01DD*	Fluoroquinolones- *J01MA*	25.2	74.8	41 213 (1.38)
23-EC [23]	4 UM; 19 H	Zarb et al., 2012	66	Period	ECDC	May-October 2010	6881 (34.6)	Penicillins plus Beta-lactamase inhibitors- *J01CR* (16.3)	Fluoroquinolones- *J01MA* (13.5)	Second-generation cephalosporins- *J01DC* (9.4)	33.6	66.4	9588 (1.39)
25-EC [56]	4 UM; 21 H	Zarb et al., 2011	172	Period	ECDC	2009	21197 (29.0)	Penicillins/b-lactamase inhibitors (J01CR: 22.1%)	Fluoroquinolones- *J01MA* (9.1)	N/A	19.2	80.8	29665 (1.40)
20-EC [33]	3 UM; 17 H	Ansari et al., 2009	20	Period	STRAMA	April-May 2006	3482 (30.1)	Penicillins plus Beta-lactamase inhibitors- *J01CR* (24.0)	Macrolides- *J01F* (15.2)	Fluoroquinolones- *J01MA* (11.2)	23.3	76.7	4748 (1.36)
5-EC [90]	1 UM; 4 H	Vlahović□ Palčevski et al., 2007	5	One Day	Own	May 2003	1025 (24.8)	Cefazolin *J01DB04*	Ciprofloxacin *J01MA02*	Cefuroxime *J01DC02*	26	64	1218 (1.19)
28-EC [31]	5 UM; 23 H	Plachouras et al., 2018	1209	Period	ECDC	2016-2017	102,093 (32.9)	Amoxicillin and beta-lactamase inhibator (J01CR02)	Piperacillin and beta-lactamase inhibator (J01CR05)	Ceftriaxone (J01CR04)	24.9	70.9	139,609 (1.4)

ACH: Acute care Hospitals, **ARPEC:**Antibiotic Resistance and Prescribing in European Children, **ECDC:** European Centre of Disease Control and Prevention, **L:** Low income, **LM:** Low Middle Income, **UM:** upper Middle Income, **H:** High Income

Table 3: **Antimicrobial use in hospital inpatients, by UN region**

			Country Range	
UN-region	**Prevalence of antimicrobial use (%, country range)**	**Mean AMU prevalence (%)**	**Lower (%)**	**Upper (%)**
East Europe	34.7 (30.7-38.8)	34.7	30.7	38.8
North Europe	33.8 (16.6-49.3)	33.8	16.6	49.3
South Europe	38.3 (17.4-51.1)	38.3	17.4	51.1
West Europe	32.5 (25.5-40.8)	32.5	25.5	40.8
Africa	62.7 (37.7-70.6)	62.7	37.7	70.6
Asia	55.3 (29.2-98.4)	55.3	29.2	98.4
Oceania	38.9 (32.4-46.0)	38.9	32.4	46.0
America	38.1 (17.3-54.4)	38.1	17.3	54.4