JAC-Antimicrobial Resistance

Continuous rise in cephalosporin and fluoroquinolone consumption in Pakistan: a 5 year analysis (2014–18)

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Background: Pakistan was third on the list of the highest antibiotic-consuming countries among low- and middle-income countries in 2015. Studies have suggested that areas with higher consumption of antibiotics are likely to have higher antibiotic resistance rates.

Objectives: With limited surveillance data on consumption and resistance in Pakistan, this study investigated the 5 year trends (April 2014 to March 2019) in consumption of the two highest-sold antibiotic classes, cephalosporins [Anatomical Therapeutic Chemical (ATC) group J01D] and fluoroquinolones (ATC group J01MA).

Methods: IQVIA Pakistan data (retail) on antibiotic sales presented in units were used. These data were standardized and a DDD was assigned to all formulations, based on WHO's ATC/DDD index, and the data expressed as DIDs (DDDs per 1000 inhabitants per day). WHO's AWaRe classification of antimicrobials was used for the analyses, especially of those categorized as 'Watch'.

Results: The findings showed a significant increase in consumption trends for 'Watch' cephalosporins (61.5%) while the use of 'Reserve' cephalosporins doubled during the studied period. In 2018, combined consumption of second- and third-generation cephalosporins (both in the 'Watch' group) was nearly five times higher than that of the first-generation cephalosporins. For fluoroquinolones, the total consumption only showed a major increase for ciprofloxacin, with 127 820 more persons per day. The consumption of cephalosporins and fluoroquinolones in Pakistan increased by 1.86 DIDs in just 5 years.

Conclusions: It is urgent to establish a National Antimicrobial Commission in Pakistan, to critically analyse the pharmaceutical market offerings and implement surveillance systems and antimicrobial stewardship.

Introduction

Evidence has shown an association at an individual patient level between the prescribing of antibiotics in primary healthcare and antimicrobial resistance (AMR) in bacteria at different sites, with the strongest effects in the month after antibiotic consumption, but detectable for up to 12 months.[1] Since 2007, the rates of antibiotic-resistant bacteria-related infections in Europe have continuously increased in comparison with other infections[2] and countries with higher consumption of antibiotics have higher AMR rates.[3] Pakistan is the third highest antibiotic-consuming country among low- and middle-income countries (LMICs) and in 16 years the number of DDDs increased by 65%. The consumption rates were 19.6 DDDs per 1000 inhabitants per day (i.e. 19.6 DIDs) in 2015.[4]

While surveillance data have helped multiple countries realize and intervene in their high consumption of antibiotics,[5] the absence of national surveillance data on consumption and resistance, along with limited laboratory facilities, is a significant hindrance to knowing the correct numbers and designing the best interventions.[6]

The emergence of *Escherichia coli* strains resistant to third-generation cephalosporins and fluoroquinolones is worrying.[7] Similarly, resistance has been developing to extended-spectrum cephalosporins, including third- and fourth-generation cephalosporins in the Asia–Pacific Rim region, since 2009[8] and increasing and worrying exposure to these high-end cephalosporins has been observed in the paediatric population in Pakistan.[9] Multiple studies from Pakistan have shown *E. coli* and *Klebsiella pneumoniae* to be significantly associated with ESBL production, with one

multicentre study showing 46% of *E. coli* and 31.9% of *K. pneumoniae* to be MDR strains.[10,11]

Any suboptimal administration of antibiotics provides an opportunity for the susceptible microorganism to develop survival mechanisms and hence contribute to antibiotic resistance.

The present study was planned to investigate the trends in consumption of cephalosporin and fluoroquinolone antibiotics in Pakistan over 5 years.

Methods

We estimated the national antibiotic consumption of cephalosporins [Anatomic Therapeutic Chemical (ATC) classification J01D group] and fluoroquinolones (ATC J01MA group) using the IQVIA Pakistan data for 5 years (April 2014 to March 2019).

IQVIA data are from retail audits capturing sales directly from distributors to pharmacies, wholesalers and retail pharmacies in small private hospitals. In the case of Pakistan, this database comprises 85% actual sales and 15% projected data for companies not sharing their distributor's data. In each sector, data is collected monthly to record direct sales from the manufacturer's designated distributors. This data is granulated into national, regional, city, brick (a group of pharmacies) and pharmacy/medical-store levels for different distribution channels. IQVIA data on antibiotic sales are presented as brands and presentations, which are further shown as units that represent a unit carton of a certain number or volume of tablets, capsules or liquids. All medicines in the country are available as 'Innovator' or 'Generic' brands, while each brand can have multiple dosage strengths (e.g. 5, 10 or 20 mg in the case of rosuvastatin) called presentations. All units were converted into DDDs using the ATC Classification System and DDD methodology (ATC/DDD, 2019) developed by the WHO Collaborating Centre for Drug Statistics Methodology.[12]

The number of DIDs was calculated using population estimates from the 2017 national census (207 770 000 inhabitants), as all other population numbers between 2013 and 2018 were estimates calculated with growth rate factored in. We used the biggest denominator in order to avoid overestimations in the first years.

In order to classify the different antimicrobials, the WHO AWaRe classification was used, including 'Access', 'Watch' and 'Reserve' antimicrobials.[13] As a reference, the 2019 WHO Essential Medicines List (EML) was used.[14]

Ethics

This study was conducted in accordance with the rules and guidelines applicable to such studies as no formal ethical approval was needed.

Results

Cephalosporins and fluoroquinolones were the highest selling anti-infective medicines in the country. The number of brands and presentations were 667 and 1934, respectively, for cephalosporins and 582 and 1139, respectively, for fluoroquinolones.

Cephalosporin consumption

Over the 5 years studied, the net increase in consumption for the whole class was 0.8608 DIDs (approximately 179 000 more people treated each day in 2018 compared with 2014). The highest increase was observed for third-generation cephalosporins ('Watch' group) as their net increase was 0.8855 DIDs (approximately 184 000 more people treated each day at the end of the study).

The consumption of cephalosporins not included in the EML (0.6558 DIDs) was around 22% of the total consumed in 2018. Combined consumption of second- and third-generation cephalosporins ('Watch' group) was nearly five times higher in 2018 in comparison with the sales of first-generation ('Access' group) cephalosporins (2.4463 and 0.5254 DIDs, respectively).

Thus, the population exposed to 'Watch' group cephalosporins increased from 315 000 inhabitants/day in 2014 to 508 000 inhabitants/day in 2018, while for the 'Reserve' group (fourth generation) an estimated increased consumption from 311 to 623 inhabitants/day meant that the population treated daily with these highly important cephalosporins doubled in 5 years (Figure 1).

The 'Access' cephalosporins deserve special comment. While there was a small increase in consumption of the 'Access' cephalosporins included in the EML, there was a decrease in the consumption of 'Access' cephalosporins not included in the EML. Notwithstanding this, it should be noted that the sales of cephalosporins not included in the EML were 4.5 times higher. In the case of 'Watch' cephalosporins, consumption of those included in the EML was 10 times higher than of those not included in the EML (Table 1).

Fluoroquinolone consumption

Regarding fluoroquinolone antimicrobials, all were considered under the 'Watch' group of the AWaRe classification. The net increase for the whole class during the study period was 0.9990 DIDs (approximately 208 000 more people were treated each day). The increase in total consumption of ciprofloxacin was 0.6152 DIDs, while for all other quinolones it was 0.3838 DIDs. It should be highlighted that the consumption of 'other quinolones' in 2018 (2.5991 DIDs) was higher than that of ciprofloxacin (2.1709 DIDs) (Table 1).

Discussion

The present sales analysis of cephalosporin and fluoroquinolone antibiotics in Pakistan over 5 years showed a combined increase of 1.8598 DIDs, i.e. in 2018, an additional 386 000 patients were receiving one of these antimicrobials each day. These figures are relevant because most of the consumed cephalosporins and all of the fluoroquinolones belonged to the 'Watch' group; thus, special attention should be paid to their indications of use as well as actual treatment patterns.

There could be multiple factors driving the high consumption of cephalosporins and fluoroquinolones observed in Pakistan. Excessive prophylactic usage is probably an important driver of high and potentially inappropriate consumption.[15] The data used for this study showed an enormously high number of presentations of these antimicrobials from multiple manufacturers, generating significant annual revenues. Additionally, it should be taken into account that about 10%–15% of antibiotics are believed to be spurious or falsified in the Pakistan market, with quinolones and cephalosporins as the most common classes, both of which are perceived to be the best-choice antibiotics by physicians and patients.[6]

The underlying question is: 'How many are too many when we are talking about antimicrobials?' The appropriate selection of antimicrobials by prescribers, according to clinical, microbiological and pharmacological aspects, has an extraordinary role in improving the use of antimicrobials[16] but public policies are also undoubtedly effective in promoting more rational use of medicines.[17] The absence of robust surveillance data limits the ability of the regulatory authorities to monitor the registrations, renewals, sales and resistance patterns for high-risk antibiotics. In the case of Pakistan, the weaker healthcare regulations exacerbate the industry's influence on the
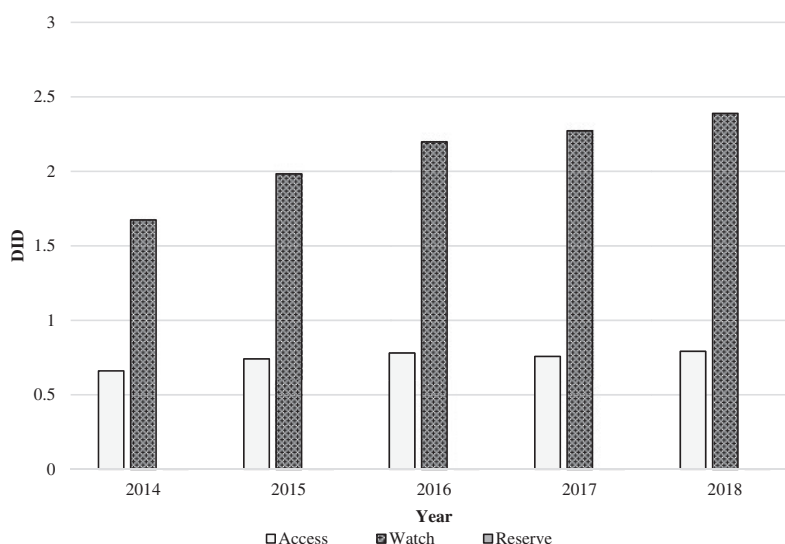
Figure 1. Five-year DID sales trend for 'Access', 'Watch' and 'Reserve' cephalosporins in Pakistan (IQVIA Pakistan data).

Table 1. Evolution of the sales of cephalosporins and fluoroquinolones in Pakistan

Antimicrobials[a]	2014	2015	2016	2017	2018	Net increase
Cephalosporins						
'Access' group						
in EML	0.0913	0.1008	0.0993	0.0988	0.0942	+0.0029
not in EML	0.5064	0.5827	0.4014	0.4134	0.4312	−0.0752
total	0.5977	0.6835	0.5007	0.5122	0.5254	−0.0723
'Watch' group						
in EML	1.3678	1.6432	1.8610	2.0746	2.2247	+0.8569
not in EML	0.1469	0.1868	0.2063	0.1963	0.2216	+0.0747
total	1.5147	1.830	2.0673	2.2709	2.4463	+0.9316
'Reserve' group	0.0015	0.0018	0.0020	0.0025	0.0030	+0.0015
total cephalosporins	2.1139	2.5153	2.5700	2.7856	2.9747	+0.8608
Fluoroquinolones						
ciprofloxacin	1.5557	1.8000	1.9221	2.0543	2.1709	+0.6152
other quinolones						
in EML	1.9183	2.2220	2.3375	2.4148	2.3794	+0.4611
not in EML	0.2970	0.2909	0.2738	0.2567	0.2197	−0.0773
total	2.2153	2.5129	2.6113	2.6715	2.5991	+0.3838
total fluoroquinolones	3.7710	4.3128	4.5334	4.7258	4.7700	+0.9990

Values are DIDs during the study period. Data source: IQVIA Pakistan.
[a]'Access', 'Watch' and 'Reserve' categories according to the AWaRe classification.

prescribers,[6,18] which could be an important factor in what we see as an antibiotic-flooded pharmaceutical market by a higher number of presentations than are reasonably needed, as well as the coexistence of so many brand names containing the same antimicrobial.

While physicians widely acknowledge the weak regulations in the country,[18] antibiotic stewardship programmes (including education, formulary restriction, prior approval programmes, streamlining, antibiotic cycling and automated or computer-assisted prescribing)[19] or increased awareness and control of selling antimicrobials without prescription[20] are necessary for slowing the development of antibiotic resistance.

The threat of antibiotic resistance in a developing country like Pakistan, where the population has limited access to education and healthcare services, is considerable. AMR will remain a major problem in managing various ever-evolving infections unless urgent steps are taken to control the influx of more brands and presentations into an already saturated market for cephalosporins and fluoroquinolones.

Limitations

The present study has some limitations, the most important being that the data used are sales data and do not necessarily reflect actual consumption by patients. Despite this, IQVIA sales data are

considered a proxy for consumption and are exceptionally consistent for time comparisons within the same country, as is the case here. Additionally, IQVIA sales data in Pakistan are not representative of hospital usage for inpatients and also do not include individuals buying over-the-counter antimicrobials for self-medication. Despite this, owing to the lack of any officially validated drug utilization data maintained at the provincial or federal government level, these results can be considered a first approach to the problem.

In conclusion, the increasing use of 'Watch' cephalosporins and fluoroquinolones observed in Pakistan during the last 5 years raises huge concerns regarding its potential role in the growing AMR crisis. Critical analyses of the pharmaceutical market in Pakistan, as well as the promotion of surveillance systems based on drug utilization data at the individual level, are urgent needs in order to try to increase the awareness of society in general and health professionals in particular and, at the same time, try to reduce exposure to these antibiotics that should be reserved for the patients in need of them.

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Transparency declarations

None to declare.

Author contributions

All the authors collaboratively designed the study. F.M. planned the first draft of the manuscript. F.M. did the data collection and analyses under the supervision of A.F. F.M. and A.F. formatted the manuscript according to the journal requirements. All the authors have revised the manuscript and approved it for final submission.

Supplementary data

The Reviewer report is available as Supplementary data at *JAC-AMR* Online.

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