Consumption of oral antibiotic formulations for young children according to the WHO AWaRe groups: an analysis of sales data from 70 middle and high-income countries

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Abstract

Background: The 2017 WHO model list of essential medicines for children grouping of antibiotics (Access, Watch, Reserve: AWaRe) provides an opportunity to review and plan antibiotic access and stewardship at country level.

Methods: Oral antibiotic formulations appropriate for use in young children (defined as child-appropriate formulations, CAFs) were identified from IQVIA-MIDAS® wholesale data, and 2015 antibiotic consumption was estimated for 70 countries with reference to the AWaRe groups. We evaluated Access antibiotic and amoxicillin sales as a percentage of total CAF sales (Access percentage and Amoxicillin-Index), and the Access/Watch ratio (Access/Watch-Index) at country-level.

Findings: The median Access percentage among 70 countries was 76·3% (IQR 62·6-84·2%), confirming the key role of this antibiotic group in treating young children globally. However, in a quarter of countries Watch antibiotics accounted for ≥20% of total consumption. The Amoxicillin-Index was low (median 30·7%, IQR 14·3-47·3%). Finally, the median Access/Watch-Index was 6·0 (IQR 3·1-9·8). CAF antibiotic consumption patterns were highly variable between the 70 countries, without a clear split between high-income and middle-income countries.

Interpretation: A simple combination of metrics based on the AWaRe groups can be informative on individual countries' pattern of antibiotic consumption and stewardship opportunities. These metrics may support countries in developing programmes to improve access to core Access antibiotics, particularly amoxicillin.

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Introduction

Increasing rates of antimicrobial resistance are a threat to global child health. Child mortality due to pneumonia and sepsis are currently not predicted to achieve the Sustainable Development Goals.[1,2] Ensuring appropriate access to antibiotics while avoiding excess use, especially of unnecessarily broad-spectrum agents, is a major challenge in all settings, but particularly so in lower and middle income countries (LMICs).[3,4] Around 90% of all antibiotics are used in the community, and this is potentially where the largest impact for antibiotic access and stewardship may be achieved.[5-7] However, the optimal approach to monitoring antibiotic use in the community remains unclear, especially when detailed data on indication are lacking.[8-10]

Child-appropriate formulations (CAFs) can be defined as oral liquid formulations and solid formulations that are primarily dissolved or dispersed or become liquid upon swallowing.[11] In antibiotic sales or high-level aggregate dispensing data, the volume of CAFs is likely to be directly linked to antibiotic drug use among young children, mostly those below 5 years of age, who find swallowing solid formulations challenging.[12-15] Manipulation, such as crushing, of formulations suitable for adults is not recommended due to increased dosing variability and issues around stability.[16] Inpatient children and neonates treated with antibiotics receive parenteral treatment in 79% and 98% of cases, respectively.[17] Given that hospital consumption of antibiotics accounts for 10% or less of the total and in the light of low use of oral medications among inpatients, utilization of CAFs can be assumed to be broadly representative of community antibiotic use in this age group.

The 2017 revision of the model list of essential medicines for children (EMLc) attempts to mirror the pressure on healthcare systems and clinicians to conserve antibiotics by classifying antibiotics into three groups.[18] Access antibiotics are to be used first or second line for key infections, and high-quality formulations of these should be widely available at low cost. Watch antibiotics are considered to have a higher potential for selecting antibiotic resistance. Finally, Reserve antibiotics should be considered antibiotics of last resort to be used under specialist guidance and with specific monitoring. The explicit recommendation is that this new categorisation should also be used to inform antibiotic stewardship, at a national and global level.[19]

A comprehensive list of common infection syndromes was generated and included in the 2017 EMLc. For each of these syndromes, recommended first and second line antibiotics were defined and included in the Access list. Currently, the EMLc list includes 17 Core Access antibiotics and 9 Watch antibiotics that are classified as Access only for defined indications (Access-Watch).[19,20] In a stewardship context, countries may be able to enhance the use of Access antibiotics without impacting on overall access to adequate antibiotic treatment. In children, who are most frequently treated with antibiotics for respiratory tract infections, amoxicillin as the recommended first line treatment option would be expected to dominate the Access antibiotic prescribing as well as overall antibiotic use.

We aimed to review the current levels of use of CAF for antibiotics, globally. To do this, we summarized 2015 wholesale data on antibiotics sold as CAFs to generate in-depth information on country-specific patterns by describing, amongst all CAFs sold, the percentage of Access group use, amoxicillin use (Amoxicillin-Index), and the relative use of Access and Watch antibiotics (Access/Watch-Index).

Methods

We used data from the IQVIA-Multinational Integrated Data Analysis System (IQVIA-MIDAS®) database to describe global patterns of antibiotic utilization in young children. The IQVIA-MIDAS® is a commercial database, which contains annual pharmacy retail sales data collected throughout the supply chain. In essence, these data include information on the overall volume of antibiotics sold to retail and hospital pharmacies by wholesalers. Importantly, no information is available on individual prescriptions (indication or age of treated patient).[21]

As not all wholesalers contribute in the represented countries, adjustments are made to estimate the likely total sales volume based on knowledge of the market share of participating wholesalers.[21] The exact data collection mechanism and method of adjustment for variable country-level coverage are not publicly available, which limits an assessment of likely data representativeness. Consequently, between-country comparisons should be made with caution.[4] However, IQVIA-MIDAS® and its predecessors have been used for evaluations of global antibiotic consumption patterns.[4,22] Previous analyses were able to document high coverage of at least 80% in most countries, with particularly strong representation of the retail sector. Current information on coverage was not available.[22]

Data on antibiotic sales (defined as products with an associated Anatomic Therapeutic Chemical code J01) from 70 countries for 2015 were considered. Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panama are reported aggregated as Central America in the IQVIA-MIDAS® database. The same is true for Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Guinea, Mali, Senegal and Togo as French West Africa. These regions were not included in our analyses. No country-level data for low-income countries are included in IQVIA-MIDAS®. Therefore only data from high-income and middle-income countries as defined by the World Bank are shown.

Antibiotic consumption was estimated based on the sales volume reported in standard units. Each standard unit is defined by IQVIA-MIDAS® as a single tablet, capsule, ampoule, vial or 5 millilitres of a liquid preparation for oral consumption.[23] To identify antibiotics likely to have been prescribed and dispensed to young children, we classified all recorded oral antibiotic formulations as either child-appropriate and specifically designed for easy use in children or not. CAFs were identified by two senior paediatric specialist pharmacists and independently by two of the authors (YH and JB) (Supplement 1). Parenteral antibiotic formulations were not considered as it is generally not possible to identify vials/ampoules for use in children.

Patterns of antibiotic consumption were described in reference to the 2017 WHO EMLc Access, Watch, Reserve (AWaRe) grouping. Since the EMLc AWaRe grouping of antibiotics excludes some antibiotics, we also included an "Unclassified" group in addition to the Access, Watch and Reserve groups. This group includes (i) antibiotics belonging to a class represented in the EMLc by only one or two specific agents (e.g. narrow-spectrum penicillins: phenoxymethylpenicillin is the only member of this group on the EMLc); (ii) antibiotic classes not represented in the EMLc (e.g. second generation cephalosporins), (iii) fixed combinations of antibiotics excluding beta-lactam/beta-lactam inhibitor combinations and trimethoprim/sulfamethoxazole (regardless of whether any or all components are included in the EMLc).

Only the Core Access antibiotics were considered part of the Access group.[20] We included Access-Watch antibiotics in the Watch group, as most oral Access-Watch antibiotics are to be used as first choice in a limited number of indications (azithromycin – cholera, ciprofloxacin – dysentery, low-risk febrile neutropenia, pyelonephritis).

Three simple metrics to allow for assessment of intra-country patterns and to help identify broad areas of antibiotic use that would most likely benefit from stewardship efforts were considered.

(1) We determined the percentage of use of Access, Watch, Reserve and Unclassified antibiotics for each of the represented countries (Access percentage and AWaRe distribution). This was calculated for each country as the number of CAF standard units of antibiotics in each group/total number of CAF standard units.
(2) We then determined the Amoxicillin-Index (Amox-I). This was calculated as previously described as the number of amoxicillin CAF standard units/total number of CAF standard units.[10]
(3) Finally we calculated the relative use of Access to Watch antibiotics expressed as the ratio of Access to Watch CAF standard units (Access/Watch-Index, AW-I).

The Access percentage and AW-I patterns were described relative to the rounded median of the 70 countries for which data were available. Based on published data suggesting a high percentage of total antibiotic prescribing to young children being accounted for by amoxicillin (see Research in Context), the Amox-I was described relative to the rounded upper quartile.

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The funder had no influence on data analysis or interpretation, writing of the manuscript or on the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Overall, the median volume of CAF antibiotic standard units sold in 2015 per country was 74·5 million (IQR 12·4-210·7 million). The country with the lowest volume of CAF standard units was Luxembourg (1·7 million) and the countries with the highest volume were India (4175·4 million), China (2406·7 million) and Pakistan (1472·6 million).

Percentage use by AWaRe group

There was substantial variation in the percentage of CAF antibiotic use accounted for by Access and Watch groups between the 70 countries (Figure 1). Access group use ranged from 94·4% of total use in Slovenia to 27·0% in Bangladesh, with a median of 76·3% (IQR 62·6-84·2%). For the Watch group, percentage use was highest in Japan (54·0%) and lowest in Slovenia (3·3%). The median percentage of Watch antibiotic use was 12·3% (IQR 8·8-19·8%). Reserve group use of 1% or more was only observed in Egypt (1%). In some countries, a considerable percentage of CAF antibiotics were not AWaRe classified (median 9·7%, IQR 4·7-15·5%), ranging from 0·8% in Russia to 33·6% in Germany.

Access/Watch-Index

The median AW-I was 6·0 (IQR 3·1-9·8), interpretable as 6 standard units of CAF Access antibiotics being consumed for each unit of Watch antibiotics. The lowest AW-I was seen in Bangladesh (0·5) and the highest in Slovenia (28·6). In general, the highest AW-I was observed in countries with the highest proportional use of Access antibiotics, however, some countries with a high percentage of Unclassified use had high AW-I despite comparatively low Access percentages (e.g. Luxembourg: AW-I 7·3, Access percentage 74·4%, Unclassified percentage 15·4% and Egypt: AW-I 7·0, Access percentage 62·6%, Unclassified percentage 27·4%; Figure 2).

There were six countries with an AW-I below one (Bangladesh, China, India, Japan, Kuwait, Vietnam), meaning that less than one standard unit of Access antibiotics was consumed for each standard unit of Watch antibiotics in those countries.

There were 27 countries with both Access percentage and AW-I above the respective medians (Figure S1). The remaining 43 countries either had an Access percentage below the median (≤75%) or an AW-I below the median (≤6). Nine countries (Croatia, Czech Republic, France, Malaysia, Russia, Serbia, Sri Lanka, Tunisia) had an Access percentage >75% but an AW-I ≤6. In these countries most of the non-Access group CAF antibiotics were from the Watch group. Only seven countries (Austria, Egypt, Ireland, Luxembourg, Poland, Romania and the UK) had an Access percentage ≤75% but an AW-I >6. In these countries a high percentage of Unclassified use of at least 15% was observed.

Amoxicillin-Index

Amoxicillin use as a percentage of all CAFs was highly variable (median Amox-I 30·7%, IQR 14·3-47·3%), and was highest in Belgium (69·8%) and lowest in Kuwait (0·1%) (Figure 3).

There were 11 countries with an Amox-I below 10% (Austria, Czech Republic, Egypt, Hungary, India, Kuwait, Saudi Arabia, Slovakia, South Korea, Turkey, Ukraine), indicating that less than 10% of CAF antibiotic use was for amoxicillin.

There were only 13 countries with an Access percentage>75% and with an Amox-I >50% (Argentina, Belgium, Canada, Colombia, France, Lithuania, New Zealand, Peru, Slovenia, South Africa, Thailand, USA and Uruguay; Figure S2). Of note, two of these countries had an AW-I ≤6 (France 4·0, Thailand 5·8). In total, 29 countries had an Access percentage above the median and an Amox-I in the upper quartile. Most of these countries (23/29) also had an AW-I >6.

The total sales volume of CAF standard units, percentage use of Access, Watch, Reserve and EMLc unclassified antibiotic CAFs as well as the Amox-I and AW-I for all countries are listed in Supplement 2 (Tables S1 and S2).

Discussion

Using the IQVIA-MIDAS® database, we first defined and identified child-appropriate oral antibiotic formulations and then assessed their global use against the new 2017 EMLc AWaRe classification. Our analysis confirms the key role of Access antibiotics for young children worldwide. Median percentage of Access antibiotic use was above 76%, and the first quartile was 63% or greater. Therefore only 17 of 70 evaluated countries used less than 63% Access antibiotics. Furthermore, we were able to verify that Access antibiotics are widely used not only in middle-income countries but also in high-income countries. Concerningly, the median percentage of Watch antibiotic use was 12% or more. The third quartile was nearly 20%, meaning that in 17 of 70 countries Watch antibiotic use exceeded 20%. A high level of Watch group use was generally reflected in a low ratio of Access to Watch use, the AW-I. Amoxicillin use, as measured by the Amox-I, was variable with amoxicillin generally accounting for a small fraction of overall prescribing.

As expected, patterns of CAF antibiotic use were found to be highly variable across 70 countries. The three countries with the highest percentage use of Access antibiotics were Slovenia and the Netherlands (high-income), and Brazil (middle-income). Similarly, the three countries with the lowest Access percentage were Japan (high-income), and Bangladesh and China (middle-income). In line with data from hospital antibiotic use, China and India, the two most populous countries, were among the countries with the lowest Access percentage (27·0% and 35·0%), the highest Watch percentage (54·0% and 47·3%) and considerable use of unclassified antibiotics (18·9% and 17·4%).[24,25]

AWaRe unclassified antibiotics, including most fixed combinations of antibiotics, have been identified as being of particular interest for informing stewardship efforts.[26] The Unclassified group may contribute to either narrower-spectrum (beta-lactamase resistant penicillins) or broader-spectrum (second generation cephalosporins) antibiotic use. The exact direction will be determined by country-specific consumption patterns of Unclassified group antibiotics. The limitations of the AWaRe classification in this respect have previously been noted, and further guidance is needed on how unclassified antibiotics can be incorporated into the classification to facilitate stewardship efforts.[20] We were able to confirm that utilization of AWaRe unclassified antibiotics was as high as 33·6% (Germany), and in 25 countries exceeded the use of Watch antibiotics. In these countries, relative utilization of CAF antibiotic groups can be difficult to interpret because reclassification of antibiotics under the AWaRe approach could result in relevant shifts in Access or Watch percentages and AW-I.

Three aspects of community antibiotics use in young children are striking: First, young children have been identified as the highest users of antibiotics, and use has been repeatedly shown to be much higher among younger than among older children.[27-34] This provides some justification for focusing on CAFs given that establishing patterns of antibiotic utilization for the youngest age group would be expected to have the largest impact for antibiotic stewardship and antibiotic access.[2]

Second, at least two-thirds and up to 90% of outpatient antibiotic prescriptions in young children are for respiratory tract infections (RTIs).[28,35-45] These include upper RTIs, mainly otitis media and pharyngitis, in which antibiotic treatment may not necessarily be required in many cases. Equally, when antibiotics are prescribed, most international guidance suggests that narrow-spectrum options such as amoxicillin or phenoxymethylpenicillin should be used.[19,46-49] Of note, data from the ambulatory sector in some LMIC settings suggest that RTIs are a less dominant indication for antibiotic use than in most high-income countries, with undifferentiated fever being a more frequent reason for an antibiotic prescription.[37,50-52] The high use of antibiotics for patients with febrile illness in regions with endemic malaria even when rapid malaria diagnostics are available has recently been noted.[53]

Third and directly related to the importance of RTIs as an indication for community antibiotic prescribing in young children, a limited number of specific antibiotics, all of them Access antibiotics, dominate utilization patterns in children. Amoxicillin alone accounts for up to 70% of overall community antibiotic use among young children in the Netherlands.[10,43,54] Very high levels of amoxicillin use making up 50% or more of all prescriptions have also been described for Canada, France, Madagascar, Nigeria, Norway, Senegal, the US and the UK among children up to 5 years of age.[10,27,28,37,42,55,56] In the US in 2010, amoxicillin was the drug most frequently prescribed to children in the outpatient setting and accounted for more than 18 million prescriptions.[31] In Germany and the UK narrow-spectrum oral penicillins, such as phenoxymethylpenicillin, make up more than 10% of community antibiotic prescribing, and in Denmark these account for over a third of all prescriptions in this age group.[10,29,39,57] In contrast, low amoxicillin use, often below 10%, has been observed in Greece, Italy and South Korea.[27,36,58] In these countries, other Access antibiotics, for example co-amoxicillin, may be used preferentially.

Our analysis has several caveats. IQVIA-MIDAS® provides estimates based on proprietary algorithms. For these reasons, IQVIA-MIDAS® data are known to potentially result in under- or overestimation of antibiotic sales, and this effect may differ by country. Furthermore, extrapolation from antibiotic sales to antibiotic consumption may lead to overestimation of the latter if not all standard units sold are taken by the child.

Similarly, this analysis based on standard units is unusual. The adoption of antibiotic dose units as a measure of antibiotic utilization may be simple to implement and generate easily interpretable data, especially in pediatrics where Defined Daily Doses (DDD) are not easily applicable.[59] An advantage of reporting antibiotic use in this way would be that a conversion into DDD would be possible from the combined information on dispensed packs, pack-sizes and standard units.

However, reporting in standard units can be problematic when dosing regimens and treatment durations are highly variable between countries and between indications Analyses would be biased towards higher Access group use, for example, if Access antibiotics are consistently administered for longer periods or dosed more frequently than Watch antibiotics. Moderate acuity infections treated with oral antibiotics are unlikely to require prolonged treatment or high-frequency dosing regimens.

We attempted to limit our analysis to formulations that would be suitable for administration to young children. The classification of CAFs was based on expert opinion and may need further evaluation. Furthermore, non-CAFs may be used for the treatment of older children or when CAFs are not available, and CAFs may on occasion be used in other patient groups, such as elderly patients or those with a neurological disability. Many liquid formulations and dispersible tablets have a strength that renders them unsuitable for adult dosing, therefore reducing the likelihood of these formulations being used in other patient groups.

While the Access percentage and AW-I may be transferable to analyses considering non-CAFs, it is unclear whether the Amox-I is likely to be as relevant to assessing antibiotic consumption patterns in adults as it is in young children. Some data on antibiotic use amongst children and adults, however, suggest that antibiotic prescriptions for RTIs are as common among adult patients in the community as for children.[33,60-62]

Because of the difficulties in determining which children may be using CAFs in each country and because of the likely influence of antibiotic dosing regimens and durations, we did not standardise antibiotic use according to population as has previously been done in international comparisons.[22] As the focus of our analysis was the identification of broad areas for stewardship intervention at the national level, we primarily evaluated the relative use of different antibiotics under the AWaRe grouping.

Although the proportional use of antibiotics according to AWaRe, the AW-I and the Amox-I have the benefits of being informative, intuitive and simple to calculate, they too have specific limitations. Countries with a high percentage of use of Unclassified antibiotics may consider reclassification of these drugs into the AWaRe groups, for example based on relatedness to currently listed antibiotics. However, they can already use the AW-I to evaluate the general tendency towards greater use of broader-spectrum drugs. The Amox-I begins to address the challenge that the AWaRe grouping does not directly provide information on the spectrum of antibiotics.[20] For example, amoxicillin/clavulanic acid is classified as an Access antibiotic but has been considered broad-spectrum in a quality indicator developed for assessment of community antibiotic use in Europe.[63] However, the Amox-I fails to reflect high levels of use of even more narrow-spectrum agents, such as observed in some Scandinavian countries.

This is, to our knowledge, the first attempt at developing simple metrics of global child community antibiotic use based on the WHO AWaRe classification. We were able to show considerable global variation in the utilization of CAF Access and Watch antibiotics. Interpreting Access percentage, AW-I and Amox-I together can help to identify targets for national antibiotic stewardship efforts, particularly when the percentage of AWaRe unclassified antibiotics is low. In the first instance, countries with low Access percentages could identify opportunities for greater use of these antibiotics for community-based treatment of young children. Countries with moderate or high Access percentages but low Amox-I may prefer to focus on promoting the use of amoxicillin especially for RTIs, as recommended in the AWaRe guidance. A low AW-I may indicate unnecessary use of Watch antibiotics, which could again be specifically targeted. Challenges remain in settings with high percentages of Unclassified antibiotic use, which may need to be reduced or integrated into the AWaRe classification, depending on exact patterns.

Contributor statement

YH, MS and JAB designed the study. IW extracted the data, YH and CJ cleaned the data, YH, CJ, IW and JAB analysed the data and generated the figures. All authors contributed to the interpretation of the results. YH and JAB did the literature search and drafted the first version of the manuscript, which was revised by all authors. All authors contributed to the final version of the manuscript.

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Declaration of interests

JAB's husband is a senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options. All other authors declare no competing interests.

Research in context

Evidence before this study: There is limited reported data on patterns of community antibiotic use among children, and much of it is focused on specific databases in high-income countries. We carried out a systematic review of the literature on Medline® (search strategy (antibacterial OR antibiotic) AND (drug utilization OR practice patterns) AND (date limit 2010 to current) without age or language limitations; search last carried out on Feb, 4th 2018) to identify reports of antibiotic prescribing patterns in paediatric ambulatory care. Studies of antibiotic prescribing only in specific indications, such as community-acquired pneumonia, were excluded. In total, we identified 24 relevant publications from high-income country settings (Canada, Denmark, France, Germany, Greece, Ireland, Italy, Latvia, Netherlands, Norway, Serbia, Spain, South Korea, United Kingdom, United States) and only 6 from lower or middle income countries (Bangladesh, Brazil, Indonesia, Madagascar, Nigeria, Senegal and pooled data from Gambia, Ghana, Kenya, Nigeria and Uganda). No unifying approach in presenting prescribing patterns could be identified across these studies, making studies difficult to compare. Published data confirm, however, that antibiotic use is highest, and generally at least double that of older children, in children up to 5 years of age. When reported, respiratory tract infections, including otitis media and pharyngitis, accounted for more than 60% of antibiotic prescriptions for young children. In line with this, in a number of studies very high levels of amoxicillin use of 50% or more in children up to 5 years of age were identified.

Added value of this study: We first defined child-appropriate oral formulations (CAFs) and then analysed wholesale pharmacy data from a global database to describe global patterns of antibiotic use among young children at country level. We describe the relative use of CAF antibiotics by AWaRe group, including the ratio of Access to Watch group use (Access/Watch-Index) and the percentage of total prescribing accounted for by amoxicillin (Amoxicillin-Index). Joint interpretation of the three metrics will help to identify broad areas for national antibiotic stewardship and guideline development, even when information on indication is not available. Importantly, all three metrics should be interpreted together to obtain a rounded picture of national patterns of antibiotic use. A first analysis of global patterns of CAF antibiotic use demonstrates that (i) very high Access percentages can be observed among both high and middle income countries, (ii) the percentage of use of antibiotics unclassified under the grouping can be considerable and may be a challenge for interpreting patterns, and (iii) the percentage of use accounted for by amoxicillin is highly variable even among countries with high Access percentage.

Implications of all the available evidence: High Access percentages are achieved across countries with highly variable healthcare systems and income classification. Reviewing national Access percentages and aiming to promote Access antibiotic use could be the first step for states wishing to engage in national antibiotic stewardship. Use of Unclassified antibiotics should be reviewed and reduced, or reclassification into the AWaRe groups considered at national level. The AW-I can be used to ensure that the use of Watch relative to Access antibiotics is minimised, and is especially useful when there is residual utilization of Unclassified antibiotics. For children, countries should strongly promote the use of amoxicillin for most common antibiotic treatment indications encountered in community practice.

Figure captions

Figure 1: Percentage antibiotic use of child-appropriate oral formulations according to WHO AWaRe (Access Watch Reserve) group.

Note that only Core Access antibiotics have been included in the Access group.

Figure 2: Country-level Access/Watch-Index and Access percentage (percentage of CAF standard units of antibiotic used accounted for by Access antibiotics) grouped by high-income and middle-income countries

The two vertical lines indicate the rounded AW-I median (6) and the rounded median Access percentage (75%).

Figure 3: Country-level amoxicillin and Access percentages grouped by high-income and middle-income countries.

The amoxicillin percentage (percentage of CAF standard units of antibiotic used accounted for by amoxicillin) corresponds to the Amoxicillin-Index.

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Consumption of oral antibiotic formulations for young children according to the WHO AWaRe groups: an analysis of sales data from 70 middle and high-income countries

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Abstract

Background: The 2017 WHO model list of essential medicines for children grouping of antibiotics (Access, Watch, Reserve: AWaRe) provides an opportunity to review and plan antibiotic access and stewardship at country level.

Methods: Oral antibiotic formulations appropriate for use in young children (defined as child-appropriate formulations, CAFs) were identified from IQVIA-MIDAS® wholesale data, and 2015 antibiotic consumption was estimated for 70 countries with reference to the AWaRe groups. We evaluated Access antibiotic and amoxicillin sales as a percentage of total CAF sales (Access percentage and Amoxicillin-Index), and the Access/Watch ratio (Access/Watch-Index) at country-level.

Findings: The median Access percentage among 70 countries was 76·3% (IQR 62·6-84·2%), confirming the key role of this antibiotic group in treating young children globally. However, in a quarter of countries Watch antibiotics accounted for ≥20% of total consumption. The Amoxicillin-Index was low (median 30·7%, IQR 14·3-47·3%). Finally, the median Access/Watch-Index was 6·0 (IQR 3·1-9·8). CAF antibiotic consumption patterns were highly variable between the 70 countries, without a clear split between high-income and middle-income countries.

Interpretation: A simple combination of metrics based on the AWaRe groups can be informative on individual countries' pattern of antibiotic consumption and stewardship opportunities. These metrics may support countries in developing programmes to improve access to core Access antibiotics, particularly amoxicillin.

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Introduction

Increasing rates of antimicrobial resistance are a threat to global child health. Child mortality due to pneumonia and sepsis are currently not predicted to achieve the Sustainable Development Goals.[1,2] Ensuring appropriate access to antibiotics while avoiding excess use, especially of unnecessarily broad-spectrum agents, is a major challenge in all settings, but particularly so in lower and middle income countries (LMICs).[3,4] Around 90% of all antibiotics are used in the community, and this is potentially where the largest impact for antibiotic access and stewardship may be achieved.[5-7] However, the optimal approach to monitoring antibiotic use in the community remains unclear, especially when detailed data on indication are lacking.[8-10]

Child-appropriate formulations (CAFs) can be defined as oral liquid formulations and solid formulations that are primarily dissolved or dispersed or become liquid upon swallowing.[11] In antibiotic sales or high-level aggregate dispensing data, the volume of CAFs is likely to be directly linked to antibiotic drug use among young children, mostly those below 5 years of age, who find swallowing solid formulations challenging.[12-15] Manipulation, such as crushing, of formulations suitable for adults is not recommended due to increased dosing variability and issues around stability.[16] Inpatient children and neonates treated with antibiotics receive parenteral treatment in 79% and 98% of cases, respectively.[17] Given that hospital consumption of antibiotics accounts for 10% or less of the total and in the light of low use of oral medications among inpatients, utilization of CAFs can be assumed to be broadly representative of community antibiotic use in this age group.

The 2017 revision of the model list of essential medicines for children (EMLc) attempts to mirror the pressure on healthcare systems and clinicians to conserve antibiotics by classifying antibiotics into three groups.[18] Access antibiotics are to be used first or second line for key infections, and high-quality formulations of these should be widely available at low cost. Watch antibiotics are considered to have a higher potential for selecting antibiotic resistance. Finally, Reserve antibiotics should be considered antibiotics of last resort to be used under specialist guidance and with specific monitoring. The explicit recommendation is that this new categorisation should also be used to inform antibiotic stewardship, at a national and global level.[19]

A comprehensive list of common infection syndromes was generated and included in the 2017 EMLc. For each of these syndromes, recommended first and second line antibiotics were defined and included in the Access list. Currently, the EMLc list includes 17 Core Access antibiotics and 9 Watch antibiotics that are classified as Access only for defined indications (Access-Watch).[19,20] In a stewardship context, countries may be able to enhance the use of Access antibiotics without impacting on overall access to adequate antibiotic treatment. In children, who are most frequently treated with antibiotics for respiratory tract infections, amoxicillin as the recommended first line treatment option would be expected to dominate the Access antibiotic prescribing as well as overall antibiotic use.

We aimed to review the current levels of use of CAF for antibiotics, globally. To do this, we summarized 2015 wholesale data on antibiotics sold as CAFs to generate in-depth information on country-specific patterns by describing, amongst all CAFs sold, the percentage of Access group use, amoxicillin use (Amoxicillin-Index), and the relative use of Access and Watch antibiotics (Access/Watch-Index).

Methods

We used data from the IQVIA-Multinational Integrated Data Analysis System (IQVIA-MIDAS®) database to describe global patterns of antibiotic utilization in young children. The IQVIA-MIDAS® is a commercial database, which contains annual pharmacy retail sales data collected throughout the supply chain. In essence, these data include information on the overall volume of antibiotics sold to retail and hospital pharmacies by wholesalers. Importantly, no information is available on individual prescriptions (indication or age of treated patient).[21]

As not all wholesalers contribute in the represented countries, adjustments are made to estimate the likely total sales volume based on knowledge of the market share of participating wholesalers.[21] The exact data collection mechanism and method of adjustment for variable country-level coverage are not publicly available, which limits an assessment of likely data representativeness. Consequently, between-country comparisons should be made with caution.[4] However, IQVIA-MIDAS® and its predecessors have been used for evaluations of global antibiotic consumption patterns.[4,22] Previous analyses were able to document high coverage of at least 80% in most countries, with particularly strong representation of the retail sector. Current information on coverage was not available.[22]

Data on antibiotic sales (defined as products with an associated Anatomic Therapeutic Chemical code J01) from 70 countries for 2015 were considered. Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panama are reported aggregated as Central America in the IQVIA-MIDAS® database. The same is true for Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Guinea, Mali, Senegal and Togo as French West Africa. These regions were not included in our analyses. No country-level data for low-income countries are included in IQVIA-MIDAS®. Therefore only data from high-income and middle-income countries as defined by the World Bank are shown.

Antibiotic consumption was estimated based on the sales volume reported in standard units. Each standard unit is defined by IQVIA-MIDAS® as a single tablet, capsule, ampoule, vial or 5 millilitres of a liquid preparation for oral consumption.[23] To identify antibiotics likely to have been prescribed and dispensed to young children, we classified all recorded oral antibiotic formulations as either child-appropriate and specifically designed for easy use in children or not. CAFs were identified by two senior paediatric specialist pharmacists and independently by two of the authors (YH and JB) (Supplement 1). Parenteral antibiotic formulations were not considered as it is generally not possible to identify vials/ampoules for use in children.

Patterns of antibiotic consumption were described in reference to the 2017 WHO EMLc Access, Watch, Reserve (AWaRe) grouping. Since the EMLc AWaRe grouping of antibiotics excludes some antibiotics, we also included an "Unclassified" group in addition to the Access, Watch and Reserve groups. This group includes (i) antibiotics belonging to a class represented in the EMLc by only one or two specific agents (e.g. narrow-spectrum penicillins: phenoxymethylpenicillin is the only member of this group on the EMLc); (ii) antibiotic classes not represented in the EMLc (e.g. second generation cephalosporins), (iii) fixed combinations of antibiotics excluding beta-lactam/beta-lactam inhibitor combinations and trimethoprim/sulfamethoxazole (regardless of whether any or all components are included in the EMLc).

Only the Core Access antibiotics were considered part of the Access group.[20] We included Access-Watch antibiotics in the Watch group, as most oral Access-Watch antibiotics are to be used as first choice in a limited number of indications (azithromycin – cholera, ciprofloxacin – dysentery, low-risk febrile neutropenia, pyelonephritis).

Three simple metrics to allow for assessment of intra-country patterns and to help identify broad areas of antibiotic use that would most likely benefit from stewardship efforts were considered.

(1) We determined the percentage of use of Access, Watch, Reserve and Unclassified antibiotics for each of the represented countries (Access percentage and AWaRe distribution). This was calculated for each country as the number of CAF standard units of antibiotics in each group/total number of CAF standard units.
(2) We then determined the Amoxicillin-Index (Amox-I). This was calculated as previously described as the number of amoxicillin CAF standard units/total number of CAF standard units.[10]
(3) Finally we calculated the relative use of Access to Watch antibiotics expressed as the ratio of Access to Watch CAF standard units (Access/Watch-Index, AW-I).

The Access percentage and AW-I patterns were described relative to the rounded median of the 70 countries for which data were available. Based on published data suggesting a high percentage of total antibiotic prescribing to young children being accounted for by amoxicillin (see Research in Context), the Amox-I was described relative to the rounded upper quartile.

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The funder had no influence on data analysis or interpretation, writing of the manuscript or on the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Overall, the median volume of CAF antibiotic standard units sold in 2015 per country was 74·5 million (IQR 12·4-210·7 million). The country with the lowest volume of CAF standard units was Luxembourg (1·7 million) and the countries with the highest volume were India (4175·4 million), China (2406·7 million) and Pakistan (1472·6 million).

Percentage use by AWaRe group

There was substantial variation in the percentage of CAF antibiotic use accounted for by Access and Watch groups between the 70 countries (Figure 1). Access group use ranged from 94·4% of total use in Slovenia to 27·0% in Bangladesh, with a median of 76·3% (IQR 62·6-84·2%). For the Watch group, percentage use was highest in Japan (54·0%) and lowest in Slovenia (3·3%). The median percentage of Watch antibiotic use was 12·3% (IQR 8·8-19·8%). Reserve group use of 1% or more was only observed in Egypt (1%). In some countries, a considerable percentage of CAF antibiotics were not AWaRe classified (median 9·7%, IQR 4·7-15·5%), ranging from 0·8% in Russia to 33·6% in Germany.

Access/Watch-Index

The median AW-I was 6·0 (IQR 3·1-9·8), interpretable as 6 standard units of CAF Access antibiotics being consumed for each unit of Watch antibiotics. The lowest AW-I was seen in Bangladesh (0·5) and the highest in Slovenia (28·6). In general, the highest AW-I was observed in countries with the highest proportional use of Access antibiotics, however, some countries with a high percentage of Unclassified use had high AW-I despite comparatively low Access percentages (e.g. Luxembourg: AW-I 7·3, Access percentage 74·4%, Unclassified percentage 15·4% and Egypt: AW-I 7·0, Access percentage 62·6%, Unclassified percentage 27·4%; Figure 2).

There were six countries with an AW-I below one (Bangladesh, China, India, Japan, Kuwait, Vietnam), meaning that less than one standard unit of Access antibiotics was consumed for each standard unit of Watch antibiotics in those countries.

There were 27 countries with both Access percentage and AW-I above the respective medians (Figure S1). The remaining 43 countries either had an Access percentage below the median (≤75%) or an AW-I below the median (≤6). Nine countries (Croatia, Czech Republic, France, Malaysia, Russia, Serbia, Sri Lanka, Tunisia) had an Access percentage >75% but an AW-I ≤6. In these countries most of the non-Access group CAF antibiotics were from the Watch group. Only seven countries (Austria, Egypt, Ireland, Luxembourg, Poland, Romania and the UK) had an Access percentage ≤75% but an AW-I >6. In these countries a high percentage of Unclassified use of at least 15% was observed.

Amoxicillin-Index

Amoxicillin use as a percentage of all CAFs was highly variable (median Amox-I 30·7%, IQR 14·3-47·3%), and was highest in Belgium (69·8%) and lowest in Kuwait (0·1%) (Figure 3).

There were 11 countries with an Amox-I below 10% (Austria, Czech Republic, Egypt, Hungary, India, Kuwait, Saudi Arabia, Slovakia, South Korea, Turkey, Ukraine), indicating that less than 10% of CAF antibiotic use was for amoxicillin.

There were only 13 countries with an Access percentage>75% and with an Amox-I >50% (Argentina, Belgium, Canada, Colombia, France, Lithuania, New Zealand, Peru, Slovenia, South Africa, Thailand, USA and Uruguay; Figure S2). Of note, two of these countries had an AW-I ≤6 (France 4·0, Thailand 5·8). In total, 29 countries had an Access percentage above the median and an Amox-I in the upper quartile. Most of these countries (23/29) also had an AW-I >6.

The total sales volume of CAF standard units, percentage use of Access, Watch, Reserve and EMLc unclassified antibiotic CAFs as well as the Amox-I and AW-I for all countries are listed in Supplement 2 (Tables S1 and S2).

Discussion

Using the IQVIA-MIDAS® database, we first defined and identified child-appropriate oral antibiotic formulations and then assessed their global use against the new 2017 EMLc AWaRe classification. Our analysis confirms the key role of Access antibiotics for young children worldwide. Median percentage of Access antibiotic use was above 76%, and the first quartile was 63% or greater. Therefore only 17 of 70 evaluated countries used less than 63% Access antibiotics. Furthermore, we were able to verify that Access antibiotics are widely used not only in middle-income countries but also in high-income countries. Concerningly, the median percentage of Watch antibiotic use was 12% or more. The third quartile was nearly 20%, meaning that in 17 of 70 countries Watch antibiotic use exceeded 20%. A high level of Watch group use was generally reflected in a low ratio of Access to Watch use, the AW-I. Amoxicillin use, as measured by the Amox-I, was variable with amoxicillin generally accounting for a small fraction of overall prescribing.

As expected, patterns of CAF antibiotic use were found to be highly variable across 70 countries. The three countries with the highest percentage use of Access antibiotics were Slovenia and the Netherlands (high-income), and Brazil (middle-income). Similarly, the three countries with the lowest Access percentage were Japan (high-income), and Bangladesh and China (middle-income). In line with data from hospital antibiotic use, China and India, the two most populous countries, were among the countries with the lowest Access percentage (27·0% and 35·0%), the highest Watch percentage (54·0% and 47·3%) and considerable use of unclassified antibiotics (18·9% and 17·4%).[24,25]

AWaRe unclassified antibiotics, including most fixed combinations of antibiotics, have been identified as being of particular interest for informing stewardship efforts.[26] The Unclassified group may contribute to either narrower-spectrum (beta-lactamase resistant penicillins) or broader-spectrum (second generation cephalosporins) antibiotic use. The exact direction will be determined by country-specific consumption patterns of Unclassified group antibiotics. The limitations of the AWaRe classification in this respect have previously been noted, and further guidance is needed on how unclassified antibiotics can be incorporated into the classification to facilitate stewardship efforts.[20] We were able to confirm that utilization of AWaRe unclassified antibiotics was as high as 33·6% (Germany), and in 25 countries exceeded the use of Watch antibiotics. In these countries, relative utilization of CAF antibiotic groups can be difficult to interpret because reclassification of antibiotics under the AWaRe approach could result in relevant shifts in Access or Watch percentages and AW-I.

Three aspects of community antibiotics use in young children are striking: First, young children have been identified as the highest users of antibiotics, and use has been repeatedly shown to be much higher among younger than among older children.[27-34] This provides some justification for focusing on CAFs given that establishing patterns of antibiotic utilization for the youngest age group would be expected to have the largest impact for antibiotic stewardship and antibiotic access.[2]

Second, at least two-thirds and up to 90% of outpatient antibiotic prescriptions in young children are for respiratory tract infections (RTIs).[28,35-45] These include upper RTIs, mainly otitis media and pharyngitis, in which antibiotic treatment may not necessarily be required in many cases. Equally, when antibiotics are prescribed, most international guidance suggests that narrow-spectrum options such as amoxicillin or phenoxymethylpenicillin should be used.[19,46-49] Of note, data from the ambulatory sector in some LMIC settings suggest that RTIs are a less dominant indication for antibiotic use than in most high-income countries, with undifferentiated fever being a more frequent reason for an antibiotic prescription.[37,50-52] The high use of antibiotics for patients with febrile illness in regions with endemic malaria even when rapid malaria diagnostics are available has recently been noted.[53]

Third and directly related to the importance of RTIs as an indication for community antibiotic prescribing in young children, a limited number of specific antibiotics, all of them Access antibiotics, dominate utilization patterns in children. Amoxicillin alone accounts for up to 70% of overall community antibiotic use among young children in the Netherlands.[10,43,54] Very high levels of amoxicillin use making up 50% or more of all prescriptions have also been described for Canada, France, Madagascar, Nigeria, Norway, Senegal, the US and the UK among children up to 5 years of age.[10,27,28,37,42,55,56] In the US in 2010, amoxicillin was the drug most frequently prescribed to children in the outpatient setting and accounted for more than 18 million prescriptions.[31] In Germany and the UK narrow-spectrum oral penicillins, such as phenoxymethylpenicillin, make up more than 10% of community antibiotic prescribing, and in Denmark these account for over a third of all prescriptions in this age group.[10,29,39,57] In contrast, low amoxicillin use, often below 10%, has been observed in Greece, Italy and South Korea.[27,36,58] In these countries, other Access antibiotics, for example co-amoxicillin, may be used preferentially.

Our analysis has several caveats. IQVIA-MIDAS® provides estimates based on proprietary algorithms. For these reasons, IQVIA-MIDAS® data are known to potentially result in under- or overestimation of antibiotic sales, and this effect may differ by country. Furthermore, extrapolation from antibiotic sales to antibiotic consumption may lead to overestimation of the latter if not all standard units sold are taken by the child.

Similarly, this analysis based on standard units is unusual. The adoption of antibiotic dose units as a measure of antibiotic utilization may be simple to implement and generate easily interpretable data, especially in pediatrics where Defined Daily Doses (DDD) are not easily applicable.[59] An advantage of reporting antibiotic use in this way would be that a conversion into DDD would be possible from the combined information on dispensed packs, pack-sizes and standard units.

However, reporting in standard units can be problematic when dosing regimens and treatment durations are highly variable between countries and between indications Analyses would be biased towards higher Access group use, for example, if Access antibiotics are consistently administered for longer periods or dosed more frequently than Watch antibiotics. Moderate acuity infections treated with oral antibiotics are unlikely to require prolonged treatment or high-frequency dosing regimens.

We attempted to limit our analysis to formulations that would be suitable for administration to young children. The classification of CAFs was based on expert opinion and may need further evaluation. Furthermore, non-CAFs may be used for the treatment of older children or when CAFs are not available, and CAFs may on occasion be used in other patient groups, such as elderly patients or those with a neurological disability. Many liquid formulations and dispersible tablets have a strength that renders them unsuitable for adult dosing, therefore reducing the likelihood of these formulations being used in other patient groups.

While the Access percentage and AW-I may be transferable to analyses considering non-CAFs, it is unclear whether the Amox-I is likely to be as relevant to assessing antibiotic consumption patterns in adults as it is in young children. Some data on antibiotic use amongst children and adults, however, suggest that antibiotic prescriptions for RTIs are as common among adult patients in the community as for children.[33,60-62]

Because of the difficulties in determining which children may be using CAFs in each country and because of the likely influence of antibiotic dosing regimens and durations, we did not standardise antibiotic use according to population as has previously been done in international comparisons.[22] As the focus of our analysis was the identification of broad areas for stewardship intervention at the national level, we primarily evaluated the relative use of different antibiotics under the AWaRe grouping.

Although the proportional use of antibiotics according to AWaRe, the AW-I and the Amox-I have the benefits of being informative, intuitive and simple to calculate, they too have specific limitations. Countries with a high percentage of use of Unclassified antibiotics may consider reclassification of these drugs into the AWaRe groups, for example based on relatedness to currently listed antibiotics. However, they can already use the AW-I to evaluate the general tendency towards greater use of broader-spectrum drugs. The Amox-I begins to address the challenge that the AWaRe grouping does not directly provide information on the spectrum of antibiotics.[20] For example, amoxicillin/clavulanic acid is classified as an Access antibiotic but has been considered broad-spectrum in a quality indicator developed for assessment of community antibiotic use in Europe.[63] However, the Amox-I fails to reflect high levels of use of even more narrow-spectrum agents, such as observed in some Scandinavian countries.

This is, to our knowledge, the first attempt at developing simple metrics of global child community antibiotic use based on the WHO AWaRe classification. We were able to show considerable global variation in the utilization of CAF Access and Watch antibiotics. Interpreting Access percentage, AW-I and Amox-I together can help to identify targets for national antibiotic stewardship efforts, particularly when the percentage of AWaRe unclassified antibiotics is low. In the first instance, countries with low Access percentages could identify opportunities for greater use of these antibiotics for community-based treatment of young children. Countries with moderate or high Access percentages but low Amox-I may prefer to focus on promoting the use of amoxicillin especially for RTIs, as recommended in the AWaRe guidance. A low AW-I may indicate unnecessary use of Watch antibiotics, which could again be specifically targeted. Challenges remain in settings with high percentages of Unclassified antibiotic use, which may need to be reduced or integrated into the AWaRe classification, depending on exact patterns.

Contributor statement

YH, MS and JAB designed the study. IW extracted the data, YH and CJ cleaned the data, YH, CJ, IW and JAB analysed the data and generated the figures. All authors contributed to the interpretation of the results. YH and JAB did the literature search and drafted the first version of the manuscript, which was revised by all authors. All authors contributed to the final version of the manuscript.

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Declaration of interests

JAB's husband is a senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options. All other authors declare no competing interests.

Research in context

Evidence before this study: There is limited reported data on patterns of community antibiotic use among children, and much of it is focused on specific databases in high-income countries. We carried out a systematic review of the literature on Medline® (search strategy (antibacterial OR antibiotic) AND (drug utilization OR practice patterns) AND (date limit 2010 to current) without age or language limitations; search last carried out on Feb, 4th 2018) to identify reports of antibiotic prescribing patterns in paediatric ambulatory care. Studies of antibiotic prescribing only in specific indications, such as community-acquired pneumonia, were excluded. In total, we identified 24 relevant publications from high-income country settings (Canada, Denmark, France, Germany, Greece, Ireland, Italy, Latvia, Netherlands, Norway, Serbia, Spain, South Korea, United Kingdom, United States) and only 6 from lower or middle income countries (Bangladesh, Brazil, Indonesia, Madagascar, Nigeria, Senegal and pooled data from Gambia, Ghana, Kenya, Nigeria and Uganda). No unifying approach in presenting prescribing patterns could be identified across these studies, making studies difficult to compare. Published data confirm, however, that antibiotic use is highest, and generally at least double that of older children, in children up to 5 years of age. When reported, respiratory tract infections, including otitis media and pharyngitis, accounted for more than 60% of antibiotic prescriptions for young children. In line with this, in a number of studies very high levels of amoxicillin use of 50% or more in children up to 5 years of age were identified.

Added value of this study: We first defined child-appropriate oral formulations (CAFs) and then analysed wholesale pharmacy data from a global database to describe global patterns of antibiotic use among young children at country level. We describe the relative use of CAF antibiotics by AWaRe group, including the ratio of Access to Watch group use (Access/Watch-Index) and the percentage of total prescribing accounted for by amoxicillin (Amoxicillin-Index). Joint interpretation of the three metrics will help to identify broad areas for national antibiotic stewardship and guideline development, even when information on indication is not available. Importantly, all three metrics should be interpreted together to obtain a rounded picture of national patterns of antibiotic use. A first analysis of global patterns of CAF antibiotic use demonstrates that (i) very high Access percentages can be observed among both high and middle income countries, (ii) the percentage of use of antibiotics unclassified under the grouping can be considerable and may be a challenge for interpreting patterns, and (iii) the percentage of use accounted for by amoxicillin is highly variable even among countries with high Access percentage.

Implications of all the available evidence: High Access percentages are achieved across countries with highly variable healthcare systems and income classification. Reviewing national Access percentages and aiming to promote Access antibiotic use could be the first step for states wishing to engage in national antibiotic stewardship. Use of Unclassified antibiotics should be reviewed and reduced, or reclassification into the AWaRe groups considered at national level. The AW-I can be used to ensure that the use of Watch relative to Access antibiotics is minimised, and is especially useful when there is residual utilization of Unclassified antibiotics. For children, countries should strongly promote the use of amoxicillin for most common antibiotic treatment indications encountered in community practice.

Figure captions

Figure 1: Percentage antibiotic use of child-appropriate oral formulations according to WHO AWaRe (Access Watch Reserve) group.

Note that only Core Access antibiotics have been included in the Access group.

Figure 2: Country-level Access/Watch-Index and Access percentage (percentage of CAF standard units of antibiotic used accounted for by Access antibiotics) grouped by high-income and middle-income countries

The two vertical lines indicate the rounded AW-I median (6) and the rounded median Access percentage (75%).

Figure 3: Country-level amoxicillin and Access percentages grouped by high-income and middle-income countries.

The amoxicillin percentage (percentage of CAF standard units of antibiotic used accounted for by amoxicillin) corresponds to the Amoxicillin-Index.

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Web-extra material

Table 1: List of oral formulations considered child-appropriate

	Formulation	IMS-MIDAS shorthand
Solid	Oral Solid Ordinary Orally Disintegrating Tablets	AAB (OR DISINTG TAB)
	Oral Solid Ordinary Buccal Tablets	AAE (BUCCAL TABLETS)
	Oral Solid Ordinary Chewable Tablets	AAG (CHEW.TABLETS)
	Oral Solid Ordinary Effervescent Tablets	AAH (EFFERV.TABLETS)
	Oral Solid Ordinary Soluble Tablets	AAK (SOLUBLE TABS.)
	Oral Solid Ordinary Powders	AEA (POWDER ORAL)
	Oral Solid Ordinary Granules	AEB (ORAL GRANULES)
	Oral Solid Ordinary Unit Dose Powders	AEP (U-DOSE POWDERS)
	Oral Solid Retard Unit Dose Powders	BEP (RET DOSE PWDR)
	Oral Solid Retard Other Powders/Granules	BEY (OTH PDR/GRN RT)
Liquid	Oral Liquid Unit Dose Pressurised Aerosols	DEH (EFFERV PDR/GRN)
	Oral Liquid Ordinary Soluble Powders	DEK (SOLUBLE POWDER)
	Oral Liquid Ordinary Unit Dose Powders	DEP (ORAL U-D PWDR)
	Oral Liquid Ordinary Other Powders/Granules	DEY (OTHER PDR/GRN)
	Oral Liquid Ordinary Liquids	DGA (ORAL LIQUID)
	Oral Liquid Ordinary Drops	DGB (DROPS ORAL)
	Oral Liquid Ordinary Dry Suspensions/Syrups/Drops	DGJ (DRY SYRUP/DROP)
	Oral Liquid Ordinary Suspensions	DGK (SUSPENSION)
	Oral Liquid Ordinary Syrups	DGM (SYRUP)
	Oral Liquid Ordinary Unit Dose Liquids	DGN (ORAL U-D LIQ)
	Oral Liquid Retard Soluble Powders	EEK (RET SOLUB PDR.)
	Oral Liquid Retard Unit Dose Powders	EEP (RET U-D PWDR)

Table 2: Percentage use of antibiotics expressed as % of total child-appropriate formulation standard units recorded in IMS country-level wholesale data in 2015 for high-income countries

Country	SU sold (million)	Access %*	Watch %*	Reserve %*	Unclassified %*	Amoxicillin %	AW-I
Australia	85.7	84.3	8.8	0.003	6.9	44.6	9.5
Austria	16.5	72.6	11.5	0.01	15.8	8.1	6.3
Belgium	46.8	87.6	8.9	0.01	3.5	69.8	9.9
Canada	95.1	85.9	8.5	0.006	5.6	66.5	10.1
Chile	30.7	73.1	12.3	0.0	14.6	53.0	5.6
Czech Republic	12.4	75.8	15.4	0.0	8.8	4.5	4.9
Estonia	1.6	65.5	17.9	0.0	16.6	34.9	3.7
Finland	5.5	83.3	4.7	0.0	12.1	37.2	17.8
France	467.4	78.7	19.7	0.008	1.6	54.4	4.0
Germany	121.9	46.8	19.6	0.03	33.6	24.6	2.4
Greece	67.7	69.0	12.2	0.0	18.8	30.2	5.7
Hungary	17.5	62.6	19.5	0.0	17.9	6.9	3.2
Ireland	23.0	71.4	11.0	0.07	17.5	33.8	6.5
Italy	241.4	68.2	27.7	0.008	4.0	22.3	2.5
Japan	255.1	34.4	51.0	0.0	14.6	27.0	0.7
Kuwait	6.4	43.6	49.4	0.0	7.0	0.1	0.9
Latvia	3.2	77.6	12.3	0.0	10.0	46.3	6.3
Lithuania	7.3	78.1	11.3	0.0	10.6	60.1	6.9
Luxembourg	1.6	74.4	10.2	0.0	15.4	50.1	7.2
Netherlands	39.4	92.3	3.4	0.0	4.3	42.5	27.2
New Zealand	28.6	81.0	6.8	0.002	12.2	50.7	11.9
Norway	5.4	85.3	10.0	0.0	4.7	19.7	8.5
Poland	115.3	72.5	12.0	0.0	15.5	21.0	6.1
Portugal	29.9	84.2	6.8	0.004	9.0	29.9	12.3
Puerto Rico	9.9	82.8	10.5	0.005	6.7	41.3	7.9
Saudi Arabia	150.8	56.0	33.0	0.0	11.0	7.8	1.7
Singapore	7.3	72.5	23.7	0.04	3.8	14.3	3.1
Slovakia	12.1	49.5	26.9	0.0	23.6	1.9	1.8
Slovenia	6.1	94.4	3.3	0.0	2.3	53.1	28.9
South Korea	238.4	58.0	29.5	0.0	12.5	0.6	2.0
Spain	213.2	90.4	7.4	0.02	2.2	48.0	12.3
Sweden	8.8	81.9	3.9	0.0	14.2	13.7	21.0
Switzerland	11.8	87.1	9.3	0.01	3.6	34.3	9.4
UK	197.1	73.2	12.1	0.05	14.7	42.5	6.1
Uruguay	7.5	85.8	5.0	0.0	9.1	68.9	17.0
USA	1185.0	86.7	11.9	0.1	1.4	54.5	7.3

*rounding errors may result in the total of Access+Watch+Reserve+Unclassified coming to slightly more or less than 100%

Table 3: Percentage use of antibiotics expressed as % of total child-appropriate formulation standard units recorded in IMS country-level wholesale data in 2015 for middle-income countries

Country	SU sold (million)	Access %*	Watch %*	Reserve %*	Unclassified %*	Amoxicillin %	AW-I
Algeria	583.7	90.2	8.2	0.0	1.6	46.6	11.0
Argentina	124.5	87.4	8.7	0.0	4.0	55.1	10.1
Bangladesh	498.5	29.0	44.4	0.1	26.4	16.5	0.7
Bosnia	7.4	80.8	4.6	0.0	14.6	15.3	17.5
Brazil	499.5	90.5	4.4	0.0	5.1	47.2	20.5
Bulgaria	23.8	62.5	25.6	0.0	11.8	25.2	2.4
China	2406.6	27.0	54.0	0.0	18.9	10.7	0.5
Colombia	85.3	89.6	4.0	0.0	6.3	59.5	22.1
Croatia	11.7	76.7	15.1	0.0	8.2	23.4	5.1
Dominican Republic	7.8	67.4	16.6	0.0	16.0	35.6	4.1
Ecuador	71.8	77.5	6.3	0.0	16.2	31.1	12.3
Egypt	648.6	62.6	9.0	1.0	27.4	7.6	6.9
India	4175.3	35.0	47.3	0.2	17.4	9.6	0.7
Indonesia	247.9	71.6	12.9	0.0	15.5	48.3	5.6
Jordan	25.8	68.0	27.3	0.0	4.7	11.6	2.5
Kazakhstan	50.1	84.6	12.6	0.0	2.9	27.7	6.7
Lebanon	20.9	57.2	34.7	0.0	8.2	11.2	1.6
Malaysia	92.5	77.3	17.4	0.004	5.4	33.9	4.4
Mexico	143.4	69.8	18.1	0.0	12.1	11.7	3.9
Morocco	210.1	89.5	4.1	0.0	6.3	39.8	21.6
Pakistan	1472.6	57.6	24.8	0.05	17.6	19.2	2.3
Peru	80.0	83.5	7.2	0.0	9.3	69.7	11.6
Philippines	165.3	72.6	16.8	0.0002	10.5	29.2	4.3
Romania	77.1	69.5	11.2	0.0	19.3	14.8	6.2
Russia	297.6	79.4	19.8	0.002	0.8	44.9	4.0
Serbia	32.0	83.9	14.1	0.0	2.0	44.4	6.0
South Africa	226.9	85.4	12.2	0.004	2.4	50.4	7.0
Sri Lanka	38.3	80.5	13.9	0.0	5.6	19.1	5.8
Thailand	126.9	78.8	12.1	0.0	9.1	51.4	6.5
Tunisia	113.3	84.0	14.3	0.0	1.7	47.3	5.9
Turkey	776.5	56.6	28.1	0.0001	15.3	2.6	2.1
Ukraine	46.7	61.9	34.2	0.0	3.9	0.4	1.8
Venezuela	103.3	55.9	15.6	0.0	28.5	14.7	3.6
Vietnam	210.6	37.1	43.1	0.0	19.8	11.6	0.9

*rounding errors may result in the total of Access+Watch+Reserve+Unclassified coming to slightly more or less than 100%

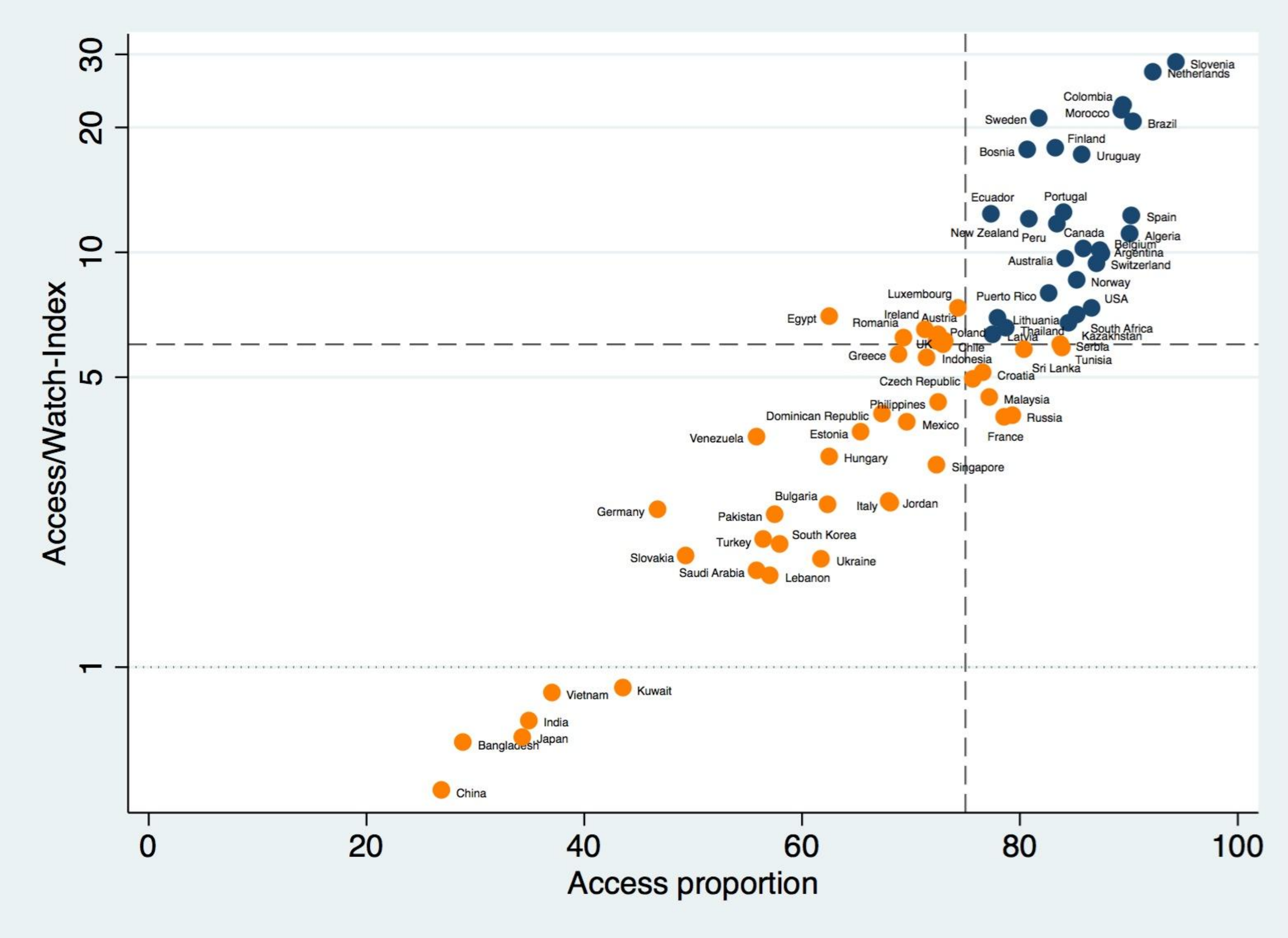

Figure S1: Scatterplot of Access percentage and Access/Watch-Index.

Dark blue dots: countries with Access percentage and AW-I above the rounded median (indicated by dashed lines, Access percentage 75%, AW-I 6). Orange dots: Access percentage or AW-I or both equal to or below median. Dotted line indicates AW-I of 1 where Access use equals Watch use. For countries below the dotted line more Watch standard units are sold than Access standard units.

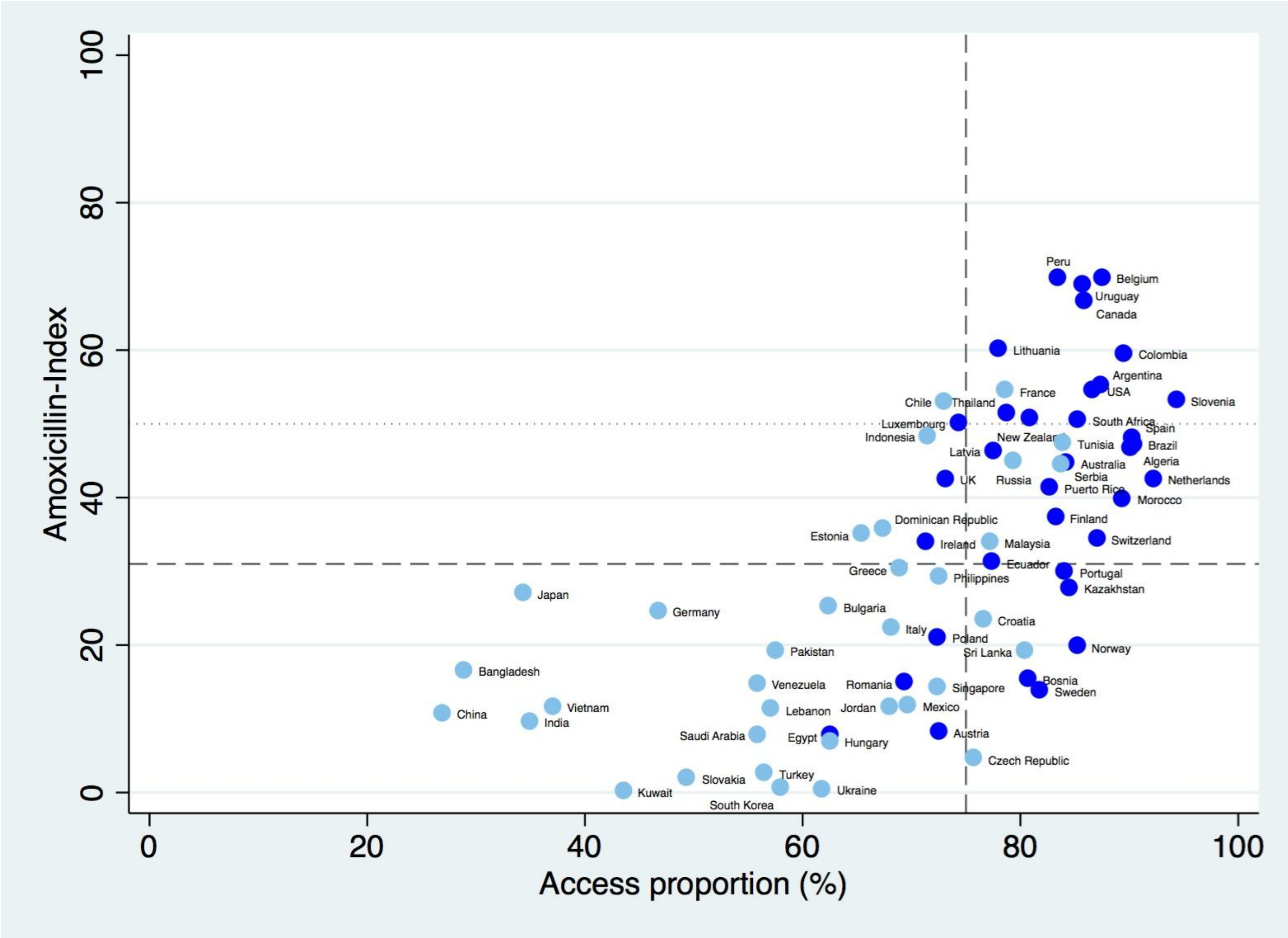

Figure S2: Scatterplot of Access percentage and Amoxicillin-Index.

Dark blue dots: Countries with an AW-I above the median of 6. Light blue dots: Countries with an AW-I equal to or below the median. The dashed lines indicate the rounded median Access percentage (75%) and Amox-I (30%), the dotted line indicates the rounded upper Amox-I quartile (50%).