Proposal for the deletion of amoxicillin for the empiric treatment of lower urinary tract infections from the WHO Model List of Essential Medicines and WHO Model List of Essential Medicines for Children

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1. Summary statement of the proposal for inclusion, change or deletion.
This application concerns the updating of the forthcoming WHO Model Lists of Essential Medicines (EML and EMLc) to delete oral amoxicillin as a first choice option for the empiric treatment of lower urinary tract infections both in adults and children. This application proposes an amendment to the core list in section *6.2.1 Access group antibiotics* as per the latest edition of the main EML (21st list). Other antibiotics listed in the EML as alternative first choice options for this indication are: nitrofurantoin, sulfamethoxazole-trimethoprim, trimethoprim and amoxicillin-clavulanic acid.

Amoxicillin is a cheap and widely available antibiotic with a broad spectrum of activity against many Gram-positive and Gram-negative bacteria including *Escherichia coli*, the most frequent causative pathogen of lower urinary tract infections. Amoxicillin has been widely used to treat lower urinary tract infections especially in patients at low risk of adverse outcomes (e.g. young non-pregnant females with no known urological abnormalities or comorbidities).

However, widespread resistance has emerged over the years as reported by GLASS (the Global Antimicrobial Resistance Surveillance System) in their most recent 2020 report (1). GLASS data indicate a high prevalence of urinary *Escherichia coli* isolates that are resistant to amoxicillin. Data on ampicillin can be extended to amoxicillin given the similarities between the two antibiotics (i.e. amoxicillin differs from ampicillin only by the addition of a hydroxyl group on the benzene ring (2). In particular, data from 22 countries indicate a median value of 75% (range 45-100%) of *Escherichia coli* urinary isolates that are resistant to amoxicillin.

In 2017 the inclusion of amoxicillin as an option for the empiric treatment of lower urinary tract infections was justified primarily from an antibiotic stewardship perspective - the Committee placed a relatively high value on the potential risk of favouring antibiotic resistance with the use of antibiotics with a broader spectrum of activity and a relatively low value to the possible limited risk of treatment failure. However this option would be no longer considered acceptable for the empiric treatment of lower urinary tract infections as in most settings the widespread of resistance levels encountered among urinary *Escherichia coli* isolates would lead to a significant number of treatment failures. The new GLASS data overturn the assumption made by the Committee in 2017.

For the same reason – increased rate of resistance- several guidelines do not indicate amoxicillin for the empiric treatment of lower urinary tract infections.

In particular the empiric use of amoxicillin for the treatment of lower urinary tract infections is explicitly discouraged by:

- the European association of Urology in their 2019 guidelines: "Aminopenicillins are no longer suitable for empirical therapy because of worldwide high *Escherichia coli* resistance"(3).
- the Société de Pathologie Infectieuse de Langue Française in their 2015 guidelines for the treatment of community-acquired urinary infections in adults : "l'amoxicilline n'est pas indiqué du fait d'un taux de résistance élevé [Amoxicillin is not indicated due to a high rate of resistance]"(4).
- the Infectious Diseases Society of America (IDSA) in their 2011 guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: "Amoxicillin or ampicillin should not be used for empirical treatment given [..] the very high prevalence of antimicrobial resistance to these agents worldwide" (5).

2. Relevant WHO technical department and focal point (if applicable).
WHO AMR Departments of Global Coordination and Partnership (GCP) and Surveillance, Prevention and Control (SPC).

3. Name of organization(s) consulted and/or supporting the application.
Department of Health Research Methods, Evidence and Impact, McMaster University, Canada.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN	ATC
Amoxicillin	J01CA04

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).
Not applicable since the application is to remove an antibiotic for a specific indication.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.
The application is for the exclusion of oral amoxicillin for the treatment of lower urinary tract infections as an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis
7. Treatment details (requirements for diagnosis, treatment and monitoring).
Not applicable since the application is to remove a drug for a specific indication.

8. Information supporting the public health relevance.

- **Epidemiological information on disease burden**

Lower urinary tract infections are very common worldwide and can affect people of any age. According to the Global Burden of Disease study, in 2017 there were an estimated 274 million new cases of urinary tract infections (lower and upper) globally, combining all ages and both sexes (6). The incidence of urinary tract infections is highest in women and increases with age (e.g. urinary tract infections increase after menopause) and frequency of sexual activity. These infections are particularly common in women because of the anatomy of their lower urinary tract; women have a shorter urethra than men and so microorganisms colonizing the skin of the perineal area can more easily reach the bladder. However, after 65 years of age, rates of lower urinary tract infections in men and women tend to be more similar (7). It is estimated that more than 50% of women experience at least one episode of lower urinary tract infection in their lifetime. After a first episode, the risk of recurrence in young women has been estimated to be about 70% within a year (8). Risk factors include anatomical and functional abnormalities of the urinary tract (e.g. conditions that predispose to incomplete emptying of the bladder, renal insufficiency and urinary incontinence). Behavioural risk factors are also implicated (e.g. frequency of sexual intercourse). Defective host immune factors (e.g. poorly controlled diabetes or neutropenia) and instrumentation of the urinary tract (e.g. urinary catheters and stents) are also predisposing factors.

- **Estimate of total patient exposure to date**

Amoxicillin has been in use since the 1970s and is the most widely used penicillin (either alone or in combination with clavulanic acid) (2). Amoxicillin is listed in the Access AWaRe category and it is recommended as first choice option for the empiric treatment of several syndromes (in addition to lower urinary tract infections). In particular in the current version of the EML, amoxicillin is recommended for the treatment of acute pharyngitis, acute sinusitis, mild community-acquired pneumonia, dental infections, exacerbations of chronic obstructive pulmonary diseases, otitis media and acute malnutrition in children. Amoxicillin is also recommended as first choice option in combination with gentamicin for the treatment of sepsis and severe community-acquired pneumonia (in children).

- **Target population(s) and assessment of current use**

Amoxicillin is widely used among children and adults. In 2015, globally the amoxicillin index (i.e. % of amoxicillin use over the total antibiotic consumption) had a median value of 18.5% (data from 76 countries were analyzed) and varied across income classes (9).

Pediatric use is favoured by the existence of many child-appropriate formulations such as syrups or dispersible tablets and in 2015, approximately 4 billion standard units of amoxicillin (a standard unit is equivalent to a single dose of any child-appropriate formulation) were sold globally representing the most widely sold oral Access antibiotic in children (among those antibiotics available in child-appropriate formulations) (10).

- **Likely impact of treatment on the disease**

The deletion of amoxicillin for the empiric treatment of lower urinary tract infections should not pose problems in terms of effective antibiotic alternatives to use. The EML/EMLc currently list four other effective alternatives as first choice options. These are: nitrofurantoin, sulfamethoxazole-trimethoprim, trimethoprim and amoxicillin-clavulanic acid. The deletion of amoxicillin for this indication would therefore not imply other changes to the list of recommended options for lower urinary tract infections since multiple alternatives are already listed both for the treatment of children and adults.

9. **Review of benefits: summary of evidence of comparative effectiveness.**

Evidence supporting this application relies on data from the 2020 GLASS report on global antimicrobial resistance (results reported in the first section of this application "Summary statement of the proposal for inclusion, change or deletion") and on a selection of guidelines for the treatment of uncomplicated lower urinary tract infections all discouraging the empiric use of amoxicillin for the treatment of lower urinary tract infections due to the high prevalence of *Escherichia coli* isolates that are resistant to this antibiotic.

Among the other options recommended in the EML for the treatment of lower urinary tract infections, the only other antibiotic for which GLASS data are reported is sulfamethoxazole-trimethoprim. The GLASS 2020 report indicates a median value of 55% (range 40-70%) of *Escherichia coli* urinary isolates that are resistant to this antibiotic (compared to a median value of 75% of isolates resistant to amoxicillin).
Data about amoxicillin-clavulanic acid and nitrofurantoin are not reported by GLASS for urinary isolates of *E. coli* however several sources of data indicate that susceptibility among *E. coli* urinary isolates remains generally high especially to nitrofurantoin including among multidrug resistant isolates (11, 12), this also applies to the pediatric population (13).

10. **Review of harms and toxicity: summary of evidence of safety.**

Not applicable since the application is to remove an antibiotic for a specific indication.

11. **Summary of available data on comparative cost and cost-effectiveness of the medicine.**

Not applicable since the application is to remove an antibiotic for a specific indication.

12. **Regulatory information**
No regulatory information is presented since the application is to remove an antibiotic for a specific indication.

13. References

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