# Proposal for the addition of the 875 mg + 125 mg oral amoxicillin + clavulanic acid formulation to the WHO Model List of Essential Medicines

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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 List of Essential Medicines (EML) to add a 875mg + 125mg strength tablet formulation of amoxicillin + clavulanic acid, for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. These are indications for which amoxicillin + clavulanic acid is already currently included on the EML in other formulations and strengths. Therefore, this application is not proposing to add any new medicines to the EML but only to include an additional formulation of an already listed medicine, amending the core list in section *6.2.1 Access group antibiotics* as per the latest edition of the WHO Model List (21st edition).

**Dosages currently listed are:**

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|---|
| Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL [c]. |
| Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt). |
| Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial. |

The main reason for the addition of the 875mg +125mg formulation is to allow the use of a higher dose of amoxicillin while maintaining the activity of clavulanic acid for the treatment of community-acquired pneumonia and intra-abdominal infections that are likely to be caused by beta-lactamase-producing bacterial isolates in patients that can tolerate oral treatment. The higher dose of amoxicillin is recommended for the empiric treatment of more severe infections or those caused by resistant organisms.

Amoxicillin + clavulanic acid has been on the core list of the EML for more than two decades, having been listed since 1997. Empiric treatment with amoxicillin + clavulanic acid is recommended in the EML for treatment of several bacterial infections.

**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 + clavulanic acid | J01CR02 |

**5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).**
Tablet: 875mg + 125mg

**6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.**
The application is for the inclusion of the 875mg +125mg tablet formulation drug as an individual medicine.

**Treatment details, public health relevance and evidence appraisal and synthesis**
**7. Treatment details (requirements for diagnosis, treatment and monitoring).**
Amoxicillin + clavulanic acid is currently recommended in the Model Lists for the treatment of several syndromes both in children and adults. Specifically, it is recommended as first choice for the treatment of mild intra-abdominal infections, lower urinary tract infections, acute sinusitis, exacerbations of chronic obstructive pulmonary diseases, low-risk febrile neutropenia and mild skin and soft tissue infections. For other syndromes it is recommended as a second-choice option, for example for the treatment of mild community-acquired pneumonia.

For this application, we focus on the use of amoxicillin + clavulanic acid for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults because these are the two syndromes for which a formulation with a higher dose of the amoxicillin component could be used reducing pill burden.

**8. Information supporting the public health relevance.**

**Epidemiological information on disease burden**

**Community-acquired pneumonia**
Community-acquired pneumonia is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (1). According to the Global Burden of Disease study, in 2017 there were an estimated 471 million new cases of lower respiratory tract infections (including CAP) globally among all ages and sexes combined (2). The prevalence of CAP varies with age and a country's income level. The most common causative pathogen worldwide is *Streptococcus pneumoniae* and viruses and viral–bacterial coinfections are not unusual. In low-income countries, lower respiratory tract infections (including CAP) were the leading cause of death in 2016 with a crude yearly attributable mortality of about 75 per 100 000 population (3). In general, the incidence of CAP and risk of death increase with age (4).

CAP is curable and preventable. Most people who develop CAP can be successfully treated with a 5-day drug regimen; Vaccines are also available to prevent CAP caused by certain pathogens (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and influenza)

**Intra-abdominal infections**
This includes uncomplicated infections with no involvement of the peritoneal cavity and no abscess formation or complicated infections with mild symptoms. Of note, treatment of these infections usually requires a combination of antibiotic treatment and surgery to achieve adequate control of the source of infection.
Among intra-abdominal infections the most frequent are:

- **Acute appendicitis** is a common surgical emergency worldwide, especially in young adults. The yearly incidence of appendicitis has been declining in western European and North American countries since the 1990s and has stabilized in the past 20 years to about 100–150 cases per 100 000 person-years. However, increasing trends are reported in Asia, South America and the Middle East with the incidence of appendicitis higher than in many western European and North American countries (5). In 2017, 19 million new cases were reported worldwide (2). Most cases are uncomplicated (70%). The lifetime risk of appendicitis varies across countries (6). Mortality attributable to appendicitis has declined and with prompt diagnosis and management, mortality is now < 1% in uncomplicated cases in most settings (7). Complicated cases or cases in the elderly are associated with a higher mortality.
- **Acute cholecystitis** is a common surgical emergency worldwide. However, the incidence of acute cholecystitis is declining because cholecystectomy (surgical removal of the gallbladder) has become a common procedure in cases of recurrent attacks of biliary colic (i.e. intermittent pain in the upper abdomen, usually on the right side). Acute cholecystitis mostly affects adults; children are rarely affected. The disease

is more prevalent in men and elderly people. Obesity and diabetes are also well-known risk factors (8, 9). Short-term 30-day mortality is about 5% in severe cases and 1% in mild cases (10).

- **Acute cholangitis** is a condition associated with high mortality if left untreated. Choledocholithiasis and malignant obstruction by tumours are the most common causes of cholangitis and their risk factors overlap (11).
- **Acute diverticulitis** is common in high-income countries and mostly affects adults older than 50 years; its incidence increases with age. The condition is less frequent in many low- and middle-income countries, probably because of differences in the fibre content of diets. The risk of developing acute diverticulitis in patients with diverticulosis is low (12, 13) and most cases (> 80%) are uncomplicated. Nonetheless, acute diverticulitis is still a common indication for colonic resection (14).
- **Pyogenic liver abscess** is the most common type of visceral abscess (15). It is frequently associated with male sex and diabetes. While pyogenic liver abscess is a rare disease in Western Europe and North America, the annual incidence is much higher in South-East Asia (16) probably due to the different epidemiology of certain causative pathogens (e.g. *Klebsiella pneumoniae*). Underlying hepatobiliary or pancreatic diseases (e.g. malignancy, cirrhosis, recent abdominal or biliary surgery) are common risk factors. Abscess rupture is a rare but severe complication associated with a high mortality if not treated immediately.

**Estimate of total patient exposure to date**

Amoxicillin + clavulanic acid is a combination of amoxicillin a semisynthetic penicillin in use since the 1970s and clavulanic acid a beta-lactamase inhibitor. Amoxicillin with or without clavulanic acid is the most widely prescribed penicillin worldwide. To date hundreds of millions of people worldwide have been treated with amoxicillin with or without clavulanic acid. When first it was introduced, a dose of 250 mg (of amoxicillin) plus 125 mg of clavulanic acid three times a day was suggested for adults. However, over time this ratio of amoxicillin to clavulanic acid has increased (from the initial 2:1 formulation to 4:1, 7:1, 8:1 up to a 16:1 formulation) mostly to allow for the treatment of more severe infections including those caused by resistant organisms.

**Target population(s)**

Adult patients diagnosed with mild community acquired pneumonia (second choice) or mild community acquired intra-abdominal infections (first choice). This application applies to adolescents. Other formulations (e.g. liquid formulations) are more appropriate for children and are recommended in the EMLc.

**Likely impact of treatment on the disease**

**Mild community-acquired pneumonia**

Amoxicillin + clavulanic acid is recommended for the treatment of mild community-acquired pneumonia because it is effective against the most likely bacterial pathogens responsible for this syndrome (notably *Streptococcus pneumoniae* and *Haemophilus influenzae* including strains that produce beta-lactamases) and because it is safe, inexpensive and readily available in many settings.

In general, however amoxicillin alone remains effective in treating *Streptococcus pneumoniae* isolates in most cases because these isolates are not known to produce beta-lactam enzymes (17). However, other pathogens (mostly *Haemophilus influenzae*) can produce beta-lactamases in a considerable proportion of cases (e.g. 16.9% of *Haemophilus influenzae* isolates in one study (18) and 12.6% *Haemophilus influenzae* isolates in another study produced beta-lactamases (19)) and could therefore be resistant to amoxicillin alone and benefit from treatment with amoxicillin + clavulanic acid.

One of the key elements of the treatment of community-acquired pneumonia is to maximize the chance of bacterial eradication in order to achieve clinical success and to reduce the risk of resistance development. For beta-lactam agents, maximal clinical efficacy depends on the time that the plasma concentration of the drug remains above the level of the minimal inhibitory concentration (MIC) for the target pathogen (T>MIC). For amoxicillin, a T>MIC of at least 30-40% between dosing intervals is required to effectively treat most pathogens responsible of mild

community-acquired pneumonia. Therefore, the advantage of a formulation with a higher dose of amoxicillin is that it can improve the efficacy of amoxicillin + clavulanic acid for the treatment of pathogens with higher MICs (20).
In particular the 875mg +125mg formulation (given three times per day) would achieve bacteriological efficacy against strains with amoxicillin MICs of up to 4mg/L (T>MIC 34% for MIC s of 4mg/L, 57% for MICs of 2 mg/L and 69% for MICs of 1 mg/L) while the 500mg + 125mg formulation (three times per day) would only achieve bacteriological efficacy against strains with MICs of up to 2mg/L (T>MIC 43% for MICs of 2 mg/L and 55% for MICs of 1 mg/L) (21).

An additional advantage of amoxicillin + clavulanic acid that applies to both its use for the treatment of mild community-acquired pneumonia and mild community-acquired intra-abdominal infections is its lower potential for resistance compared to other antibiotic options that are sometimes used for the treatment of these syndromes, most notably fluoroquinolones (e.g. levofloxacin, ciprofloxacin).

In patients with community-acquired pneumonia, amoxicillin + clavulanic acid is a particularly valid option in patients that would be at higher risk of poor outcomes in case of inadequate initial empiric treatment (e.g. patients with multiple comorbidities which are often more vulnerable to infections or patients with a higher risk of resistant infections due to frequent antibiotic exposure).

The clinical and bacteriological efficacy of the 875mg +125mg formulation is high (>90% for clinical efficacy and approximately 80-90% for microbiological efficacy at the end of treatment in trials where this formulation has been used (22)) including in settings with high prevalence of penicillin-resistant *Streptococcus pneumoniae* (23). Of note, higher doses of amoxicillin + clavulanic acid (2000mg + 125mg formulation) were also tested and did not result in significantly better clinical or microbiological efficacy when compared with the 875mg +125mg formulation but were well tolerated (comparable rates of minor side effects, mostly mild diarrhea with both formulations) confirming the safety of this medication.

The EML currently recommends amoxicillin + clavulanic acid as a second-choice option for community-acquired pneumonia because in most cases there is no need to broaden the spectrum of antibacterial activity to cover for more resistant pathogens and amoxicillin (or phenoxymethylpenicillin) can safely be used. The other reason is that amoxicillin + clavulanic is associated with more frequent side effects than amoxicillin alone (mostly diarrhoea, including *Clostridioides difficile* infection (24)).

**Mild intra-abdominal infections**
Amoxicillin + clavulanic acid is also recommended in the EML as a first-choice option for the empiric treatment of community-acquired mild intra-abdominal infections which refers to patients that are not critically ill, with no suspicion of sepsis or septic shock. These infections can be complicated when there is involvement of the peritoneal cavity or abscess or uncomplicated when these conditions are not present.
Many patients with intra-abdominal infections may not be able to tolerate oral treatment in the initial phase, especially those with complicated infections that require surgery therefore patients are often started with intravenous treatment and major guidelines (e.g. guidelines of the Infectious Diseases Society of America (25) and of the World Society of Emergency Surgery (26)) indicate doses for intravenous treatment only.

Therefore, the use of the 875mg +125mg oral formulation of amoxicillin + clavulanic would apply to selected circumstances:

- Initial empiric treatment of mild cases in patients that can tolerate oral treatment (e.g. patients managed in the outpatient setting)
- Intravenous to oral switch to complete the course of treatment when oral feeding is resumed

Amoxicillin + clavulanic acid has a spectrum of antibacterial activity that allows for the coverage of the most likely pathogens responsible for intra-abdominal infections (most notably *Escherichia coli,* enteric streptococci and anaerobic bacteria) even though amoxicillin + clavulanic resistance rates amongst *Escherichia coli* isolates may be of concern in some settings (25). GLASS does not yet currently report data about amoxicillin + clavulanic acid resistance among *Escherichia coli* isolates from blood cultures.

To the best of our knowledge, no trial has directly compared the efficacy of using different doses of oral amoxicillin + clavulanic acid for intra-abdominal infections. However, the 875mg +125mg formulation has been used in several trials especially for the treatment of uncomplicated acute appendicitis with antibiotics alone (27, 28) while lower doses of amoxicillin + clavulanic acid (500-125 mg) are generally used when treatment is started intravenously and then later switched to oral treatment (29).

As detailed in the section above about community-acquired pneumonia, the use of a higher dose of amoxicillin in combination with clavulanic acid, improves efficacy for the treatment of pathogens with higher MICs therefore the 875mg +125mg is preferable to fulfil the curative as well as the resistance preservative intent when the oral route is chosen. In serious infections such as intra-abdominal infections, high protein binding of beta-lactams and rapid elimination can reduce the amount of antibiotic available in both the plasma and tissue, increasing the risk of treatment failure especially in case of pathogens with higher MICs (30). Therefore, doses should be increased and the interval between doses reduced, especially when oral beta-lactam treatment is used.

In order to appropriately treat resistant pathogens, the daily dose of amoxicillin can be more safely increased compared to the dose of other antibiotics used to treat intra-abdominal infections such as fluoroquinolones. These have a worse safety profile, both related to gastrointestinal and neurological mild reactions – nausea, vomiting, dizziness, insomnia, headache- but more importantly related to more serious adverse events such as tendinitis / tendon rupture (31), risk of arrythmias (32) or possibly rupture of an aortic aneurysm (33).

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

The rationale for the inclusion of the 875mg +125mg formulation is to increase the amoxicillin to clavulanic acid ratio from 4:1 (500-125 mg formulation) to 7:1 (875mg +125mg formulation).

There is limited evidence about differences in clinical and microbiological efficacy of the different ratios of amoxicillin to clavulanic acid. However, the main advantage of the 875mg +125mg formulation (ratio amoxicillin: clavulanic acid is 7:1) is to increase the dose of amoxicillin (from 500 to 875 mg per dose) while maintaining the same dose of clavulanic acid (125 mg per dose). The reason for wanting to limit the exposure to clavulanic acid is that increasing its dose exposes patients to a higher risk of gastrointestinal side effects (especially diarrhoea) with only minimal benefits in terms of efficacy against beta-lactamases (17). This is because beta-lactamases have a high affinity for clavulanic acid and can be inhibited even by low doses of this beta-lactamases inhibitor.

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

The potential benefits and harms of amoxicillin + clavulanic acid has been extensively reviewed and summarised at the time of the original application of the medicine to EML. Potential harms associated with the 875-125 mg formulation are not expected to differ from the 500mg + 125mg preparation, mostly because the dose of clavulanic acid (responsible of common side effects such as diarrhoea) remains the same. Moreover, even higher doses of amoxicillin + clavulanic acid (2000mg + 125mg) have been safely used and were well tolerated in published trials (22).

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

The reason for the inclusion of the amoxicillin + clavulanic acid 875mg +125mg tablet is to increase the daily dose of the amoxicillin component without increasing the daily dose of clavulanic acid.

There are several suppliers of the 875mg +125mg formulation globally at a cost of approximately 10 USD per pack of 12 tablets in high-income countries.

**Regulatory information**

**12. Summary of regulatory status and market availability of the medicine.**

The amoxicillin + clavulanic acid 875mg +125mg has regulatory approval globally and is available in most countries around the world.

**13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia)**

Amoxicillin + clavulanic acid is listed in multiple pharmacopoeias including the United States Pharmacopeia and European Pharmacopoeia.

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