VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Sinus infection (Acute bacterial sinusitis)
Sinus infection (upper respiratory infection) is short-lived infection of the sinuses, air-filled passageways in the bones around the nose and eyes. Viruses cause most such infections. Viral illness can be complicated with bacterial infection. Approximately 0.5 % to 2% of viral sinusitis results in subsequent sinusitis caused by bacteria[1,2].

Middle ear infection (Acute otitis media)
Short-lived infection of the ear (Acute otitis media) is very common in childhood. Middle ear inflammation often begins when infections that cause sore throats, colds or other respiratory problems spread to the middle ear. It is the most common condition warranting medical therapy in children less than five years of age. Three out of four children will have at least one ear infection by their third birthday. Adults can also get ear infections, but they are less common. Viruses or bacteria can cause the inflammation. If bacteria are the cause, antibiotics should help.

1.8.2 clean	Amoxicillin trihydrate + Clavulanate potassium
Risk Management System	film-coated tablets

Lower respiratory tract infection (Acute exacerbations of chronic bronchitis and Community acquired pneumonia)
These infections are bacterial worsening of chronic (long lasting) bronchitis and bacterial pneumonia. The first one is inflammation of the airways that carry air to lungs. It causes a cough that often brings up mucus, as well as shortness of breath, wheezing, and chest tightness. Chronic bronchitis is seen in 3.4% to 22.0% of adults. This wide range of prevalence estimates may be due to varying definition[3].

Pneumonia is an infection in one or both of the lungs. People most at risk are older than 65 or younger than 2 years of age, or already have health problems. Community-acquired pneumonia (an infection of the lungs that is caught outside of hospital) is a common disease, with an annual incidence of 5 to 11 cases per thousand adults[4].

Urinary tract infections (Cystitis and pyelonephritis)
Cystitis is an urinary bladder inflammation. It is most commonly caused by a bacterial infection. In women, urinary tract infections are the most common form of bacterial infection with 10% developing urinary tract infections yearly. Urinary tract infections occur four times more frequently in females than males. Recurrences are common, with nearly half of people getting a second infection within a year.
A predisposition for bladder infections may run in families. Other risk factors include diabetes, being uncircumcised, and having a large prostate.
Pyelonephritis (a kidney infection) is a severe bacterial infection that affects upper part of the urinary tract. Pyelonephritis occurs between 20–30 times less frequently than cystitis.

Skin and soft tissue infections including dental infections
Skin infections are folliculitis (folliculitis is inflammation of one or more hair follicles. It can occur anywhere on the skin), cellulitis (inflammation of the deeper layers of the skin), erysipelas (inflammation of the upper layers of the skin). The bacteria enter the body when one get an injury such as a bruise, burn, surgical cut, animal bites or wound. The epidemiology is less completely defined and may differ from those in industrialized countries and in developing countries.

Bone and joint infections, in particular osteomyelitis
Like other parts of the body, bones and joints can get infected. The infections are usually bacterial, but can also be fungal. They may spread to the bone or joint from nearby skin or muscles, from another part of the body through the bloodstream or by direct contamination if you have broken a bone so severely that part of it is sticking out through your skin. Direct contamination can also occur during surgeries to replace joints or repair fractures. In children, osteomyelitis most commonly affects the long bones of the legs and upper arm, while adults are more likely to develop osteomyelitis in the bones that make up the spine (vertebrae). People who have diabetes may develop osteomyelitis in their feet if they have foot ulcers. You may also be at risk if you are having hemodialysis.

VI.2.2 Summary of treatment benefits

The combination of amoxicillin and clavulanic acid is used to treat certain infections caused by bacteria, including dental infections, infections of the ears, lungs, sinus, skin, bones, joints and urinary tract. Amoxicillin is in a class of medications called penicillin-like antibiotics. It works by stopping the growth of bacteria. Clavulanic acid is in a class of medications called beta-lactamase inhibitors. It works by preventing bacteria from destroying amoxicillin. Antibiotics will not work for colds, flu, or other viral infections. Amoxicillin/clavulanic acid is available as 500 mg/125 mg film-coated tablet, 875 mg/125 mg and 400 mg/57 mg/5 ml powder for oral suspension. The medicine can only be obtained with a prescription.
Prescribers should consider official guidance on the use of antibacterial agents and local levels of resistance (resistance of a bacteria to an antibiotic that was originally effective for treatment of infections caused by it) to antibiotics. The combination of amoxicillin and clavulanic acid is prescribed when doctor presumed that causative bacteria could be resistant to amoxicillin alone or there is a possibility that the infection is caused by several different bacteria.
Amoxicillin/clavulanic acid was as effective as the comparator antibiotics (in many studies) for upper respiratory tract infections (~90 %), lower respiratory tract infections, urinary tract, skin and soft tissue infections. The main measure of effectiveness was the proportion of patients who were cured at the end of treatment as determined by a reduction in symptoms and reduction of bacteria[5].

VI.2.3 Unknowns relating to treatment benefits

The substance amoxicillin/clavulanic acid has been used for many years to successfully treat different infections. Many studies have been performed and a lot of data have been obtained from the patients treated with this drug. The patients with special conditions, such as liver disease, allergic reactions, an inflammation of the gut associated with diarrhea are considered to be well evaluated.
Data on the use of this medicine during pregnancy in humans is limited. Therefore use of this medicine should be avoided during pregnancy, unless considered essential by the physician.
Both substances are excreted into breast milk. Consequently, diarrhoea and fungal infections are possible in the breast-fed infant. Therefore use of this medicine should be avoided during breastfeeding, unless considered essential by the physician.
In patients with stage 4 kidney disease (creatinine clearance less than 30 ml/min), the use of this medicine is not recommended, as no recommendations for dose adjustments are available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Inflammation of the large intestine associated with the use of antibiotics (medications to treat infections caused by bacteria) **(Antibiotic associated colitis)**	Antibiotic-associated colitis is an inflammation of the intestines that sometimes occurs following antibiotic treatment and is caused by toxins produced by the bacterium *Clostridium difficile*. When most of the other intestinal bacteria have been killed, *Clostridium difficile* grows rapidly and releases toxins that	If you or your child experience inflammation of the large intestine, causing watery diarrhoea usually with blood and mucus, stomach pain and/or fever you or your child need to stop taking the medicine and contact a doctor immediately so that an

	damage the intestinal wall. The disease and symptoms are caused by these toxins, not by the bacterium itself. Symptoms of antibiotic-associated colitis usually begin four to ten days after antibiotic treatment has begun. The early signs and symptoms of this disease include lower abdominal cramps, an increased need to pass stool, and watery diarrhea. As the disease progresses, the patient may experience a general ill feeling, fatigue, abdominal pain, and fever. If the disease proceeds to a more severe form (pseudomembranous enterocolitis), the patient may also experience nausea, vomiting, large amounts of watery diarrhea, and a very high fever (104-105°F/40-40.5°C).	appropriate therapy can be initiated.
Kidney problems and the risk of convulsions **(Renal impairment and risk of convulsion)**	This medicine is excreted mostly by the kidney. The kidneys are a vital organ because they remove waste products from the blood. Kidney problems (Renal impairment) may be the result of a variety of diseases. A lessening of the kidney function leads to buildup of these waste products and can lead to kidney failure if left unchecked. Also, in patients with reduced urine output the formation of crystals in the urine (crystalluria) has been observed and this too can lead to renal failure. As the toxins continue to build-up in the body, convulsions can occur. Additionally, convulsions can occur also in people taking high doses of this medicine.	If you or your child has kidney problems the dose might be changed. A different strength or a different medicine may be chosen by your doctor. Your doctor might be monitoring you or your child for crystals in urine. Contact a doctor immediately if you or your child experience convulsions.
Interaction with medicines that you take orally to help stop blood clots from forming **(Interaction with oral anticoagulants)**	Medicines that you take orally to help stop blood clots from forming (Oral anticoagulants) and penicillin antibiotics (such as the medicine you have been prescribed) have been widely used in practice without reports of interaction. However, in the literature cases of slower blood clot formation (increased international normalised ratio) have been found. If you need to take both kinds of medicine together, the markers used to determine the clotting tendency of blood (prothrombin time or	Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take medicines that help stop blood clots from forming as extra blood tests may be needed and adjustments of the dose of oral anticoagulants may be necessary. Contact a doctor immediately if you notice that your or your child's blood takes longer to clot.

	international normalised ratio) should be carefully monitored to see if adjustments of the dose of oral anticoagulants may be necessary.	
Patients who are not passing water regularly **(Patients with reduced urine output)**	In patients who are not passing water regularly, formation of crystals in the urine (crystalluria) has been observed very rarely, predominantly when this medicine is given by injection. When high doses of this medicine are given, it is advisable that you drink enough so that you are passing urine regularly. This helps reduce the possibility of formation of crystals in the urine (amoxicillin crystalluria). In patients with bladder catheters, a regular check of patency should be maintained.	Talk to your doctor or pharmacist before taking this medicine if you are not passing water regularly. When high doses of this medicine are given, it is important that you drink enough in order to reduce the possibility of formation of crystals in the urine caused by the medicine (amoxicillin crystalluria). If you have a bladder catheter, a regular check of patency should be maintained.
Faulty laboratory test results **(False positivity of laboratory findings)**	During treatment with this medicine your laboratory test results may indicate the presence of glucose in urine. The presence of this medicine may falsely indicate that you have an immune-mediated disease with antibodies against red blood cells (false positive Coombs test). Also, when using this medicine you may falsely test positive for a fungal infection (Aspergillus infection). Enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine and other test results (Coombs, test for aspergillosis) need to be interpreted cautiously.	If you or your child is having blood tests (such as red blood cell status tests or liver function tests) or urine tests (for glucose), let the doctor or nurse know that you or your child is taking this medicine. This is because this medicine can affect the results of these types of tests.
Serious allergic skin reactions (including acute generalised exanthemous pustulosis - AGEP)	Allergic skin reactions have been reported to occur with this medicine: Skin rash, itchiness, and hives (Urticaria) are uncommon skin reactions that may affect up to 1 in 100 people. Erythema multiforme is a rare skin condition which looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge), that may affect up to 1 in 1,000 people, while the frequency of the life-threatening skin conditions Stevens-Johnson	If you notice a skin rash, which may blister, and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge – erythema multiforme), you need to contact a doctor urgently. Other serious skin reactions are: - a widespread rash with blisters and peeling skin, particularly around the mouth,

	syndrome, which looks like a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals and the even more severe form, Toxic epidermal necrolysis, causing extensive peeling of the skin (more than 30% of the body surface), Bullous exfoliative-dermatitis, a widespread red skin rash with small pus-containing blisters, and acute generalised exanthemous pustulosis (AGEP), a red, scaly rash with bumps under the skin and blisters, are not known.	nose, eyes and genitals (Stevens-Johnson syndrome), and a more severe form, causing extensive peeling of the skin (more than 30% of the body surface – toxic epidermal necrolysis) - widespread red skin rash with small pus-containing blisters (bullous exfoliative dermatitis) - a red, scaly rash with bumps under the skin and blisters (exanthemous pustulosis) - acute generalised exanthemous pustulosis (AGEP), a red, scaly rash with bumps under the skin and blisters. These reactions require the discontinuation of the medicine and contra-indicates any subsequent administration of amoxicillin, its active ingredient.
Hypersensitivity to any antibiotic of this class or a past severe immediate hypersensitivity reaction to a similar class of antibiotics **(Hypersensitivity reaction to any penicillins and history of sever immediate hypersensitivity reaction to another beta-lactam agent (cephalosporin, carbapenem, monobactam)**	Hypersensitivity reaction refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. The combination of the two active ingredients of this medicine, amoxicillin and clavulanate, is a commonly used antibiotic which is active against many bacterial organisms that cause different infections. The combination consists of amoxicillin which belongs to the antibiotic class of penicillin, and clavulanate, which inhibits beta lactamase, the main bacterial enzyme responsible for penicillin resistance. A penicillin allergy is an allergic reaction that occurs when the body's immune system overreacts to penicillin and related antibiotics. Common allergic reactions to penicillin include rashes, hives, itchy eyes, and swollen lips, tongue, or face. In rare cases, an allergy to	Before initiating therapy with this medicine (amoxicillin/clavulanic acid), careful inquiry should be made regarding previous hypersensitivity reactions to other antibiotics of the same or similar classes (penicillins, cephalosporins, carbapenems or monobactams). If an allergic reaction occurs, the medicine should be discontinued and appropriate therapy instituted. Do not take the medicine - if you are allergic (hypersensitive) to amoxicillin, clavulanic acid, penicillin or any of the other ingredients of this medicine; - if you have ever had a severe allergic (hypersensitive) reaction to any other antibiotic. This can include a skin rash or swelling of the face or neck.

	penicillin can cause a serious allergic reaction that is rapid in onset and may cause death (anaphylactic reaction). Symptoms include difficulty breathing, hives, wheezing, dizziness, loss of consciousness, rapid or weak pulse, skin turning blue, diarrhea, nausea, and vomiting. Penicillin antibiotics are the most common cause of drug allergies, with about 10 in 100 people reporting an allergy. Mild to moderate allergic reactions to penicillins may affect up to 5 in 100 people. Some people who are allergic to penicillin are also allergic to other closely related antibiotics, including cephalosporins, carbapenems and monobactams. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxicillin/clavulanic acid, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or monobactams. If an allergic reaction occurs, amoxicillin/clavulanic acid should be discontinued and appropriate therapy instituted.	Allergic reactions that can be caused by this medicine: - skin rash - inflammation of blood vessels (*vasculitis*) which may be visible as red or purple raised spots on the skin, but can affect other parts of the body - fever, joint pain, swollen glands in the neck, armpit or groin - swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing - collapse. Allergic reactions can sometimes occur delayed. Contact a doctor immediately if you get any of these symptoms. Stop taking the medicine.
Liver problems or liver problems in the past due to this antibiotic (amoxicillin/clavulanic acid) **(Hepatic impairment and history of hepatic impairment due to amoxicillin/clavulanic acid)**	Liver disease is any disturbance of liver function that causes illness. The liver is responsible for many critical functions within the body and should it become diseased or injured, the loss of those functions can cause significant damage to the body. The medicine you are taking (Amoxicillin/clavulanate) is currently the most common cause of clinically apparent, drug induced acute liver problems (injury/inflammation of the liver and jaundice (yellowing of the skin)) both in the United States and Europe. Liver problems are usually reversible; however, deaths have been reported. Amoxicillin is associated	Do not take this medicine if you have ever had liver problems or jaundice (yellowing of the skin) when taking an antibiotic. Talk to your doctor or pharmacist before taking this medicine if you are being treated for liver problems. If you have liver problems you may have more frequent blood tests to check how your liver is working. Increase in some substances (enzymes) produced by the liver may show up in your blood tests.

	with a very low rate of mild liver problems when used alone. When amoxicillin is combined with the clavulanic acid, the estimated risk of liver problems increases from 3 to 17 people out of 100.000 people who have been prescribed this medication presumably due to the clavulanate component. Men over the age of 50 appear to be at increased risk of liver problems as are patients who receive prolonged or repeated courses of treatment. A delayed liver injury pattern has typically been reported with this medication that usually has a benign course and resolves within 2 months. Liver function should be monitored at regular intervals in patients with hepatic problems.	Contact a doctor immediately if you get any of these symptoms: - inflammation of the liver (hepatitis); - jaundice (yellowing of the skin and whites of the eyes), caused by increases in the blood of bilirubin (a substance produced in the liver).
Severe reduction in the number of white blood cells (**leucopenia, agranulocytosis**)	Agranulocytosis is a rare condition that occurs when the bone marrow does not make enough neutrophils, the white blood cells needed to fight infections. Agranulocytosis can turn minor infections into serious ones. Amoxicillin/clavulanic acid can cause this adverse reaction. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena (some kind of alergic reaction).	Periodic assessment of number of blood cells is advisable during prolonged therapy.
Occurrence of a morbilliform rash if Amoxicillin/clavulanic acid is used in infectious mononucleosis (Infectious mononucleosis - glandular fever, is an infection caused by the Epstein-Barr virus. The virus spreads through saliva, which is why it's sometimes called "kissing disease")	Certain type of rash (morbilliform rash) may appear, if the patient has mononucleosis while taking amoxicillin.	Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected.

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Increases in number of bacteria, that do not respond to this antibiotic – prolonged use **(Overgrowth of non-susceptible organisms and antibiotic resistence – prolonged use)**	Sometimes an infection caused by bacteria does not respond to a course of an antibiotic. One of the commonest reasons for this to occur is because the bacteria causing the infection are resistant to the antibiotic that is being taken. This means that they can survive and even multiply despite the antibiotic. Bacteria can become resistant to antibiotics for many reasons. Using antibiotics carefully can help to reduce the chance of bacteria becoming resistant to them. You need every dose to help fight the infection. If some bacteria survive they can cause the infection to come back.
Concomitant use with allopurinol, a medicine used for gout **(Concomitant use with allopurinol)**	If you are taking allopurinol (used for gout) with this medicine, it may be more likely that you'll have an allergic skin reaction.
Concomitant use with methotrexate, a medicine used to treat cancer or rheumatic diseases **(Concomitant use with methotrexate)**	Certain antibiotics such as the medicine you are taking (Penicillins) may reduce the excretion of methotrexate (a medicine used to treat cancer or rheumatic diseases), causing a potential increase in methotrexate toxicity. This medicine can affect how methotrexate (a medicine used to treat cancer or rheumatic diseases) works.
Concomitant use with probenecid, a medicine used for gout **(Concomitant use with probenecid)**	Concomitant use of probenecid (used for gout) is not recommended. Probenecid decreases the excretion of this medicine in urine. Therefore, concomitant use of probenecid may result in increased and prolonged blood levels of this medicine. If you are taking probenecid (used for gout), your doctor may decide to adjust the dose of this medicine.

Missing information

Risk	What is known
Use in pregnancy and lactation	<u>Pregnancy</u> Animal studies do not indicate any harmful effects with this medicine. Data on the use of this medicine during pregnancy in humans is limited; however, it does not indicate an increased risk of congenital malformations. In a single study in women giving birth prematurely this medicine was associated with an increased risk of necrotising enterocolitis in neonates, a condition when tissue in the small or large intestine is injured or begins to die off, which is considered to be the most common and serious intestinal disease among preemies. Therefore use of this medicine should be avoided during pregnancy, unless considered essential by the physician.

	Breastfeeding Both substances are excreted into breast milk. Consequently, diarrhoea and fungal infections are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Therefore use of this medicine should be avoided during breastfeeding, unless considered essential by the physician.
Dosage of this medicine in patients with stage 4 kidney disease **(Dosage of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30 ml/min)**	In patients with stage 4 kidney disease (creatinine clearance less than 30 ml/min), the use of this medicine is not recommended, as no recommendations for dose adjustments are available.