An Investigation of Aspects Affecting Availability and Grading of High-risk Antibiotics in Sweden

Group 1

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Abstract

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This thesis examined 39 antibiotics that, according to Folkhälsomyndigheten, were most likely to be affected by availability problems on the Swedish market. The aim was to investigate possible factors affecting the availability of the antibiotics, to grade the antibiotics based on these factors and, if possible, identify some pattern or general trend. A grading system for assessing the risk of availability problems for each antibiotic was created based on a number of factors, such as number of market authorization holders, number of active pharmaceutical ingredient manufacturers and risk of natural disasters in the countries where the antibiotic is produced. Each antibiotic got a final value based on all the factors, which was then compiled in a final table. The results were evaluated and discussed, both in general and for the specific antibiotics. In the discussion, relevant information that was not included in the grading system, such as isolated incidents at manufacturing sites, was taken into account. The information was successfully gathered and used to grade the antibiotics, but no pattern or general trends were identified.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>DMF</td>
<td>Drug Master File</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>The US Food and Drug Administration</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>MAH</td>
<td>Market Authorization Holders</td>
</tr>
<tr>
<td>TLV</td>
<td>Tandvårds- och läkemedelsförmånsverket</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United states of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1 Introduction

Antibiotics are a group of medicines used to combat bacterial infections. Bacteria developing resistance to these medicines is a natural evolutionary process, however, due to excess use of antibiotics over the last century, antibiotic resistance has become a global problem. In the European Union (EU) alone, infections by antibiotic resistant bacteria killed 33000 people in 2015 [1]. Furthermore, this number is likely to rise drastically over the years, not only in Europe but also globally. To fight the problem of antibiotic resistant bacteria, a wide arsenal of medicines is necessary for the safety of patients. However, many of the antibacterial medicines used to treat infections are at risk for having accessibility problems or disappearing completely from the Swedish market.

PLATINEA (Plattform för Innovation av Existerande Antibiotika) is a collaborative platform in Sweden for healthcare professionals, academia, the industry and governmental actors with regard to improving the availability of antibiotics and improving their use. They work with issues such as how antibiotic use can be optimized and to map supply chains to identify where problems regarding accessibility can arise and how they can be minimized [2].

In 2017, Folkhälsoomyndigheten developed a model to investigate which antibiotics on the Swedish market were most likely to be affected by accessibility problems [3]. Factors included in the model where economic factors, approval date, whether the drug is included in the benefit system or not and if the medicine is especially necessary for a working healthcare system. Other factors which can affect accessibility such as how and where the drug is manufactured and supply chains where not included in the model.

The main aim of this thesis is to build on the work done by Folkhälsoomyndigheten by exploring other potential factors which are thought to have an effect on the accessibility of the listed antibiotics in Figure 1. Additional aims are to grade the antibiotics based on these factors and, if possible, identify any patterns or general trends.

<table>
<thead>
<tr>
<th>Antibiotika</th>
<th>Formulering/styrka</th>
<th>Summa</th>
<th>Antal lander som tillhandahåller</th>
<th>Antal MAH i Europa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolistin</td>
<td>injektion/infusion</td>
<td>20</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Ceftazidim/avibactam</td>
<td>injektion/infusion</td>
<td>14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>tablet 5 mg</td>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ceftolozan/tazobactam</td>
<td>injektion/infusion</td>
<td>12</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Fenoximepenicillin</td>
<td>tablet 250 mg</td>
<td>12</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>oral suspension, kapse 150 mg</td>
<td>12</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>kapse 300 mg</td>
<td>10</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Bedakillin</td>
<td>tablet 100 mg</td>
<td>10</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Formulation</td>
<td>Time 1/2 (h)</td>
<td>Peak (h)</td>
<td>Area (h)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Amikacin</td>
<td>injectionsvättska</td>
<td>10</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>injektion/ infusion</td>
<td>10</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>injektion/ infusion</td>
<td>10</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Meropenem</td>
<td>injektion/ infusion</td>
<td>10</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Trimetoprim/sulfa</td>
<td>oral lösning/ susp.</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Amoxicillin/clavulansyr</td>
<td>oral suspension</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>tablet 250/120 mg</td>
<td>8</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Fenostrimetybenicillin</td>
<td>tablet 500 mg</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>oral suspension</td>
<td>8</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>oral suspension, 50 mg/ml</td>
<td>8</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Ticycyclin</td>
<td>injektion/ infusion</td>
<td>8</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Metronidazol</td>
<td>injection/ infusion</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazol</td>
<td>oral suspension</td>
<td>8</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Metronidazol</td>
<td>tablet</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Flukloxacillin</td>
<td>oral susp. 50 mg/ml</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flukloxacillin</td>
<td>tablet 125 mg</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>tablet 300 mg</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ceftarolin fosamil</td>
<td>injektion/ infusion</td>
<td>8</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>injektion/ infusion 10 mg/ml</td>
<td>8</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>injektion/ infusion 40 mg/ml</td>
<td>8</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>injektion/ infusion</td>
<td>8</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Erytomycin</td>
<td>oral suspension</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Linezolid</td>
<td>oral suspension</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Teikoplanin</td>
<td>injektion/ infusion</td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>oral suspension 100 mg/ml</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Vankomycin</td>
<td>injektion/ infusion</td>
<td>8</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>injektion/ infusion</td>
<td>8</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Klindamycin</td>
<td>oral lösning</td>
<td>8</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 1: The antibiotics from Folkhälsomyndighetens report.
2 Background

2.1 Factors affecting accessibility

There are various factors that influence the availability of an antibiotic according to PLATINEA. Broadly speaking, these factors include the number of actors in the supply chain, complexity of the production process, economic aspects such as profitability and demand, and risk of natural disasters or other occurrences that might disrupt the supply of a drug.

If there are few actors in the supply chain, a dependence on these actors is created. If, on the other hand, it is profitability that fails, companies might choose to produce and sell other, more profitable drugs. Furthermore, the risk of natural disasters in a country could potentially affect the availability of a certain antibiotic produced in the country.

It can be difficult to get an insight into the supply chains of antibiotic drugs, since market authorization holders (MAHs) and other actors tend to keep such information secret.

The production of an antibiotic with irregular demand is usually not profitable. This can lead to the company choosing to stop production of the antibiotic which increases the accessibility risk.

As far as the financial aspects are concerned, the accessibility risk can increase partly because of purchasing-related factors and partly because of profitability. Purchasing-related factors can, for example, be that the order quantities are too low, but also that the cheapest supplier does not deliver as expected.

One last factor taken in consideration is natural disasters. The climate is a fast changing factor which affects natural disasters like flooding and earthquakes. This means that the risk of natural disasters can be hard to predict [4]. ThinkHazard! is a website that the Global Facility for Disaster Reduction and Recovery developed with other partners such as universities. They try to illustrate the probability of natural disasters occurring in different countries [5].

2.2 Regulations

There are many regulations that have to be followed within the pharmaceutical industry. These guidelines and rules are set in place to ensure that medicinal products are of high quality and to ensure that every step in the production upholds the highest quality while minimizing all the risks that encompasses the production of medicines.

Good manufacturing practice (GMP) encompasses a set of rules and standards that a medicine/active substance manufacturer has to uphold. The majority of rules and standards set forth by GMP for manufacturing of medicines/active substances are based on quality assurance. The manufacturers have to follow a certain set of rules regarding the quality control, manufacturing facilities, trained personnel and so on. It covers some legal elements but also importation and distribution elements. These rules ensure that the produced medicine or active substance is of highest quality with minimal contamination and that the information on the label is accurate [6].

A manufacturer can be GMP-certified after an inspection by the national medicine agency that is coordinated by the European medicines agency (EMA). A GMP-certificate is issued to a site if the site complies with all GMP rules and standards. The validity of the GMP-certification lasts three years and it can only be renewed through a new inspection [7]. If the inspections finds critical
errors or flaws, a non-compliance report is issued. This can lead to product recalls or withdrawals of licences. It could also lead to an end of manufacturing operations. Compliance with GMP is not the only requirement to carry out operations, as an authorization for manufacturing or importing is also required. The authorizations are given out by the national medicine agency and are only given out if the company is compliant with GMP. Importers also have to make certain that its third country manufacturer (country outside EEA) or its European manufacturer complies with GMP.

A MAH is an organization that has the right to sell and market medicines within a specific region. The MAH also has to make certain that the medicine it markets is manufactured in a facility that is GMP-certified.

2.3 Back orders

Back orders occur when an expected medicine cannot be delivered on time by the MAH. There are several reasons for which a medicine can become back-ordered, such as if problems occur during manufacturing of the drug, a shortage of raw materials or if there is an unexpected rise in demand for the product.

In Sweden, it is mandatory for a MAH to report in advance any back order if it is predicted to last for more than three weeks, or if it will bring a security risk to the patients. If a medicine gets a back order, Läkemedelsverket will recommend alternative medicines to use during the time the medicine is not available. All ongoing back orders and those that have ended (since February 2018) are available for free to the public from Läkemedelsverket’s website.

2.4 Production of antibiotics

There are three main methods of producing an antibiotic. These are via fermentation, fully synthetic and through a semisynthetic procedure. The general production procedure for all methods follows according to Figure 2. The production starts from raw material which is in turn either directly turned into the API, or in multiple steps to the API via a single or multiple intermediate compounds. Intermediate compounds are derived from the raw material(s) that later is converted to the API.

![Figure 2: Flowchart showing API production steps.](image)

2.4.1 Fermentation

A process for the production of antibiotics is by fermentation. The process involves the cultivation of microorganisms in large containers containing a liquid growth medium. In order for this process to be possible, certain conditions are required, such as adequate oxygen concentration, temperature, pH-value and nutritional levels.
Before the fermentation process is started, a starter culture is isolated of the microorganism which is used in the production of the specific antibiotic. This microorganism is grown on an agar containing plate and then transferred to shake flasks. The shake flasks contain different growth factors. This growth occurs with constant agitation and continuous addition of sterilized air.

The fermentation product is purified by various purification methods, depending on the antibiotic produced and the properties thereof. With organic chemicals, the dissolved antibiotic is then recovered so that a purified powdered form is obtained [12].

### 2.4.2 Synthetic

There are several groups of synthetic antibiotics on the market, such as antifolates. According to EMA [13], a synthetic antibiotic manufacturing process is normally less complex than a fermentation process due to it being more controllable and having less variables to keep a track of.

### 2.4.3 Semisynthetic

Semisynthetic antibiotics are produced synthetically from a non-synthetic starting material [13]. This starting material can either be extracted from a fermentation culture, which is common for many types of antibiotics [14], or be extracted from other sources. A semisynthetic production procedure is in general more complex compared to fully synthetic [15].

### 3 Method

39 antibiotics from a report by Folkhälsovmdigheteten were shared among three groups of students. Twelve antibiotics got distributed to our group and were handed out to the five group members for information search. The information was then summarized in a table and shared with all the groups.

#### 3.1 Delimitations

Some delimitations were set in place for the project. Instead of the supply chains being investigated, the main focus of this thesis is API-manufacturers and MAHs. The MAHs will be restricted to Europe and the search for API-manufacturers will be done for Europe and USA. To be regarded as an API-manufacturer a given company would have to either synthesize the crude substance or produce it via fermentation. Many API-manufacturers also produce intermediates to the API.

#### 3.2 API-manufacturers

To find the manufacturers of the API, the database EudraGMDP [16] was used. API-manufacturers in the EEA and 3rd countries were searched for. GMP-certificates of factories were also retrieved from EudraGMDP.

The Drug Master File (DMF) database provided by the US Food and Drug Administration (FDA) [17] was used to find the API-manufacturers for the USA. The DMF database contained a list of all...
API-manufacturers whose products are sold in the USA since several decades back in time. Because of this, only active manufacturers as of today were searched for. [18].

The total number of API-manufacturers is the sum of the number of API-manufacturers listed on EudraGMDP and the number of API-manufacturers listed on the FDA.

3.3 Market authorization holders

Information about MAHs was retrieved from the EMA. The gathered information was used to identify all the MAHs in Europe for the antibiotics of interest. The list from the EMA did not specify formulation of the medicines, and thus had to be checked if the formulation of interest existed or not manually by searching for the medicine in national medicinal agencies and pharmacies in corresponding European countries.

If multiple registered MAHs in different countries were obviously subsidiaries of the same holding company (judging by name), they were counted as one. No more thorough investigation of subsidiaries was done.

3.4 Grading

To assess the risk of a specific antibiotic being lost from the Swedish market, either short-term or long-term, a grading system was made based on a number of factors. The factors included were the following: if the country was inside or outside EEA, number of API-manufacturers, number of MAHs, the manufacturing process, risk of natural disasters in manufacturing countries, back orders reported in Sweden, uncertainty in annual sales income in Sweden, uncertainty in annual sales volume in Sweden, assumed profitability per dose, average sales income in Sweden, and the number of products currently not provided in Sweden. A higher point indicates a higher risk for accessibility problems. The accessibility problems include risks of supply shortages, which could lead to back orders or withdrawals on the Swedish market, depending on the shortage length.

The risk assessment is based on factors that every group can use to assess the risk for every antibiotic and not factors such as rare, isolated events, like accidents in factories.

The countries where the API-manufacturing took place were ranked according to following rules: a third country is defined as being outside of EEA. An active substance can gain a whole point value between one and five. If the country of an API-manufacturer is inside of EEA, it gets one point. If the country of an API-manufacturer is outside EEA, it gains five points. If the active substance has API-manufacturers in several countries, both inside and outside of EEA, it was ranked according to the amount of countries in respective area. An active substance with more manufacturers outside EEA would for example gain four points. If an active substance has the same amount of manufacturers inside and outside EEA, it gained three points. Third countries are given a higher points due to the longer distance from Sweden and possibly more complex supply chains compared to EEA countries. The criteria can be seen in Table 1.
Table 1: Grading of supply risk related to geographical locations of API producers.

<table>
<thead>
<tr>
<th>Number of API-manufacturers in EEA/third countries</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only in EEA-countries</td>
<td>1</td>
</tr>
<tr>
<td>Number of EEA-countries &gt; Number of third countries</td>
<td>2</td>
</tr>
<tr>
<td>Number of EEA-countries = Number of third countries</td>
<td>3</td>
</tr>
<tr>
<td>Number of third countries &gt; Number of EEA-countries</td>
<td>4</td>
</tr>
<tr>
<td>Only in third countries</td>
<td>5</td>
</tr>
</tbody>
</table>

As for the API-manufacturers the following equation was used:

\[
\frac{5}{n_{API-manufacturers}}
\]  

(1)

This equation gives more weight to the active substance with less API-manufacturers compared to the active substance with more API-manufacturers. This is because it is a bigger problem if an API with a few manufacturers loses a manufacturer rather than if an API with many producers loses a manufacturer. This specific equation was used to scale the points between zero and five, where an API with only one manufacturer receives the maximum of five points and an API with many manufacturers receives a point close to zero. The more API-manufacturers an API has, the less points it will receive according to equation 1.

The grading of the number of MAHs was done in the same way as for the grading of the number of API-manufacturers. The equation used to grade the number of API-manufacturers was also used here, only that \(n_{API-manufacturers}\) were replaced with \(n_{MAHs}\).

To grade the production process, points were set depending on the type of process that was performed. Higher points are aimed at more difficult processes, refer to Table 2 for criteria. For combined antibiotics, the production process was graded according to the one of the two substances made via the more complicated process. A semisynthetic production process which includes raw material produced via fermentation, which we will call semisynthetic (fermentation), is considered as more complex and possibly more expensive method compared to both a solely fermentation process and a semisynthetic process (where the starting material is not produced via fermentation).

Table 2: The grading system for the different processes.

<table>
<thead>
<tr>
<th>Process</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic</td>
<td>1</td>
</tr>
<tr>
<td>Semisynthetic</td>
<td>2</td>
</tr>
<tr>
<td>Fermentation</td>
<td>3</td>
</tr>
<tr>
<td>Semisynthetic (Fermentation)</td>
<td>4</td>
</tr>
</tbody>
</table>

The risk of natural disasters occurring in manufacturing countries was also taken in account. To
rank the risks for each active substance, a website, ThinkHazard! [5], was used. The website displayed the risks for several types of natural disasters for each country, where every type of natural disaster had a risk associated with it. The risks were divided into four types: very low, low, medium and high. These risks were assigned a value, the higher the risk, the higher value it got assigned, see Table 3.

Table 3: The grading system for the natural disaster risks.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>1</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
</tr>
<tr>
<td>Medium</td>
<td>3</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
</tr>
</tbody>
</table>

A total risk value for each country was calculated by adding together all risk values for every type of natural disaster the country can experience. A total risk value for each active substance was then calculated by adding together all total risk values for each respective country of the API-manufacturers for the active substance. These values were added up according to how many countries an active substance had API-manufacturers in it. The values were converted to a scale of zero to five. For example, colistin has four API-manufacturers where two are based in China, one is based in Poland and one is based in Denmark. The total risk value for colistin would then be the sum of all total risk values for China, Poland and Denmark divided by the number of API-manufacturers for colistin. The value received after dividing by the amount of API-manufacturers is then converted to a scale of zero to five, meaning that the maximum risk value for natural disasters an antibiotic can receive is five, and that the lowest risk value for natural disasters is zero.

All the back orders between February 2018 and May 2019 were used to grade the antibiotics according to how many weeks each antibiotic was back-ordered in total during this period. The grading is based on scale from zero to five. If an antibiotic has not had any back orders, it received 0 points. 1 point was given if the total time of back orders is between 1 week and 20 weeks and so on. Table 4 displays the criteria for each point.

Table 4: The grading system for the back orders.

<table>
<thead>
<tr>
<th>Points</th>
<th>Total length (weeks) of back orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1-20</td>
</tr>
<tr>
<td>2</td>
<td>21-40</td>
</tr>
<tr>
<td>3</td>
<td>41-60</td>
</tr>
<tr>
<td>4</td>
<td>61-80</td>
</tr>
<tr>
<td>5</td>
<td>80&lt;</td>
</tr>
</tbody>
</table>

Uncertainty in annual sales income was calculated as the relative standard deviation of the annual sales income expressed as amount of standard units sold as well as the standard deviation of the annual sales income. The grading of the uncertainty in annual sales income was done by dividing the value by 20 to put it on a scale of 0 to 5. For example, zero points would be given if the relative standard deviation was zero percent, and five points would be given if the relative standard
deviation was 100 percent. Any point between zero and five can be given depending on the standard deviation.

Uncertainty in annual sales volume was calculated and graded exactly in the same way as uncertainty in annual sales income.

Table 5: The grading system for assumed profitability of each API.

<table>
<thead>
<tr>
<th>Profitability</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Medium</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
</tr>
</tbody>
</table>

Each API had a low, medium or high assumed profitability per dose, corresponding to three, two or one points as seen in Table 5. The assumed profitability was estimated by looking at the production process as well as if the medicine had market-protection or not. A semisynthetic production process based on a fermentation-extracted starting material was assumed to have the highest production cost. A solely fermentation-based production process was assumed to have the second highest cost followed by semisynthetic (non-fermentation starting material) and lastly synthetic. We assumed that selling a market-protected medicine would allow for higher profit-margins for the MAHs (due to the non-existing competition) and thus would increase the profitability of the medicine. Notice that if a medicine has market-protection we assumed high profitability, regardless of the production process. This is because having a market-protection on a medicine makes it possible, more or less, for MAHs to set their own price for the medicine. For example, if a medicine was produced semisynthetically with a fermentation-based starting material, and also did not have market-protection, we would grade the profitability as low. Another example, if a medicine lacked market-protection and was produced by fermentation, we would grade the profitability as medium.

Table 6: The grading system used for annual sales income in Sweden for each antibiotic

<table>
<thead>
<tr>
<th>Average annual income</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1,5 mil. SEK</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 1,5 mil. SEK</td>
<td>1</td>
</tr>
</tbody>
</table>

The average annual sales income was graded by looking at the total income generated in Sweden of the medicine. The grading was done by looking at the sales income for each antibiotic. If the income exceeds 1,5 million Swedish Crowns (SEK), we give it 1 points, otherwise we give the medicine 3 points (see Table 6), meaning that high income leads to a lower risk for availability problems.

For some of the antibiotics, one or more products are currently not provided in Sweden by MAHs. This factor is regarded as a large back order and it could also indicate that a product is possibly up for withdrawal on the Swedish market. More unavailable products could lead to availability problems for certain antibiotics and is thus an important factor to take into account. This factor was graded as seen in Table 7.
Table 7: The grading system for the number of products that are currently not provided in Sweden.

<table>
<thead>
<tr>
<th>Number of products currently not provided</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>3.34</td>
</tr>
<tr>
<td>1</td>
<td>1.67</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The total risk for each antibiotic substance equals the sum of all the individual point scores. A high value indicates a higher risk of being exposed to availability problems.

4 Results

In this section, gathered information is presented for the first 12 APIs one by one from Figure 1 in section 4.1. The risk assessment results are then presented for all 39 antibiotics in section 4.2.

4.1 Description of 14 antibiotics assigned for closer analysis

The following subsections will present the results for 14 antibiotics (12 different APIs). Only 14 antibiotics were investigated, as the two other groups investigated the rest of antibiotics seen in Figure 1.

4.1.1 Colistin

Colistin, also known as polymyxin E, is a polypeptide antibiotic that belongs to the class polymyxins, for chemical structure of colistin, see Figure 2. Polymyxins were discovered in late 1940s, and were being used in the late 1950s clinically. However, this usage lasted for about two decades as the toxicity of polymyxins outweighed its positive antibacterial effect. In modern times, as multi resistant Gram-negative bacteria are becoming more and more common, polymyxins have been reintroduced to the clinics to combat this [19]. Colistin is used as a last resort antibiotic when no other treatment options are available [20].

Polymyxins are produced by certain strains of the bacteria Bacillus polymyxa. Polymyxins are used against infections caused by aerobic Gram-negative bacteria, such as E. coli, Salmonella and

Figure 3: Chemical structure of colistin.
Shigella\textsuperscript{21}. Colistin is isolated from \textit{Bacillus polymyxa} via fermentation\textsuperscript{22}.

Colistin is administered as either colistimethate sodium (a chemically modified form of colistin) or colistin sulphate, where the former is the one administered in Sweden. In Sweden, colistimethate sodium is administered through two different routes of administration, inhalation and intravenous injection/infusion. In regards to accessibility problems, the formulation injection/infusion is likely to experience accessibility problems according to Folkhalsomyndigheten.

According to Fass,\textsuperscript{23} colistin is sold in Sweden under three product names: Colineb, Colobreate and Tadim. Colineb is sold by Teva and is a powder for a nebuliser solution. Colobreate, also sold by Teva, is an inhalation powder within a capsule. Tadim is sold as a powder for infusion liquid, and as a powder for nebulisers. Tadim is sold by Nigaard Pharma.

However, Xellia Pharmaceuticals ApS also sells colistimethate sodium in Sweden under the name of Kolistimetatnatrium Xellia, in form of a powder for infusion liquids. This drug is not available at the moment according to Fass.

One manufacturer of colistimethate sodium in Europe is Polfa SA Tarchomin. The Polish company produces the active substance intermediate, crude active substance and they also form the salt. Primary, secondary packaging is also taken care of, as well as several quality control tests. All ongoing operations are GMP-certified.

Xellia Pharmaceuticals ApS is another manufacturer of colistimethate sodium and colistin sulfate based in Denmark.

There are two API-manufacturers of colistin outside Europe, Livzon Group Fuzhou Fuxing Pharm and Zhejiang Apeloa Pharmaceutical Company Limited. Both companies are based in China.

There are 2 MAHs in Sweden and in total, there are 20 MAHs in Europe.

During June in 2016, Colistin Xellia was deregistered\textsuperscript{24}. Colistin Xellia was sold as a powder for injection/infusion liquids.

\subsection*{4.1.2 Ceftazidime/Avibactam}

Ceftazidime/Avibactam is a combination drug sold in Europe under the name Zavicefta\textsuperscript{®} and was released onto the European market in 2016. It is used to treat complicated intra-abdominal infections, complicated urinary tract infections including pyelonephritis, hospital-acquired pneumonia and infections caused by Gram-negative bacteria when other treatments might not do or not work. The drug is only sold as a powder for intravenous use\textsuperscript{25} \textsuperscript{26}.

The active substances are ceftazidime and avibactam, for chemical structures, see Figure 4. Ceftazidime is a cephalosporin with a broad spectrum of antibacterial activity\textsuperscript{27}, and is sold separately in Sweden under the names

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig4}
\caption{Chemical structure of ceftazidime (above) and avibactam (below).}
\end{figure}
Zeftacidim Sandoz® and Fortum®, also as powders for intravenous use, with a currently broader spectrum of indications. Avibactam is not by itself an antibiotic but works by inhibiting β-lactamases [28].

There are five API-manufacturers of ceftazidime in Europe. These are Fresenius Kabi in Italy, ACS DOBFAR in Italy, Sandoz GmbH in Austria, SIC Borshchahivskiy Chemical in Ukraine and Glaxo Operations UK Limited in the UK. There are an additional eight ceftazidime manufacturers worldwide; Harbin Chemical Group Limited (China), Hanni Fine Chemical Company Limited (Republic of Korea), Orchid Pharma Limited (India), Antibioticos Do Brasil Limiteda (Brazil), Aurobindo Pharma Ltd (India), Qilu Antibiotics Pharmaceutical Co Ltd (China), Parabolic Drugs Ltd (India) and Nectar Lifesciences Ltd (India).

The normal treatment time with Zavicefta is 5-14 days with an infusion every eight hours [25].

4.1.3 Nitrofurantoin

Nitrofurantoin is a nitrofuran derivative, for chemical structure of nitrofurantoin, see Figure 5. It is used in lower uncomplicated urinary tract infections. The substance has a bactericidal effect against a number of bacterial species by inhibiting enzymes and by damaging bacterial DNA. The substance has good activity against Escherichia coli, Enterococcus faecalis and Staphylococcus saprophyticus [29]. Nitrofurantoin is produced synthetically [30].

The active substance with a strength of 5 mg is sold in Sweden by the company Meda AB under the product name Furadantin® [31]. According to the Folkhälsmyndigheten, nitrofurantoin, in the formulation tablet 5 mg has a risk of getting accessibility problems.

In Europe, there are two API-manufacturers of the active substance nitrofurantoin with a strength of 5 mg; the Italian company F.I.S. Fabbrica Italiana Sintetici S.p.A and the Latvian company Aiciju sabiedriba ”Olainfarm”. The Chinese company Jinan Jinda Pharmaceutical Chemistry Co. Ltd., Teva Pharmaceuticals Industries Ltd. located in Israel and the two Indian companies Unimark Remedies Ltd. and Macleods Pharmaceuticals Ltd. are four API-manufacturers.

There is one MAH for nitrofurantoin 5 mg in Europe: Meda AB, located in Sweden and Norway [29]. On February 1, 2018, Meda AB received a higher price for Furadantin® 5 mg in the pack size of 50 tablets. The reason for applying for a higher price was that the costs for production, transport and distribution have increased. The motivation for the grant of Tandvårds- och läkemedelsförmånsverket (TLV) was that there is no alternative drug to Furadantin® 5 mg [32].

The Furadantin tablet with a strength of 5 mg has a completed back order listing that lasted during the period 2017-11-24 to 2018-06-15.

During an inspection in June 2016, it was found that Jinan Jinda Pharmaceutical Chemistry Co. Ltd. did not comply with GMP and thus, its GMP-certificate got withdrawn according to EudraGMDP.
4.1.4 Ceftolozane/Tazobactam

Ceftolozane/Tazobactam is a combination of the cephalosporin antibiotic ceftolozane and the β-lactamase inhibitor tazobactam. For chemical structure of ceftolozane/tazobactam, see Figure 6. It is used to treat complicated intra-abdominal infections, pyelonephritis and complicated urinary tract infections.

![Chemical structure of ceftolozane](image)

Figure 6: Chemical structure of ceftolozane.

Ceftolozane/tazobactam is administered intravenously. It is sold with market protection in Sweden by Merck Sharp & Dohme BV under the trade name Zerbaxa \[33\].

Ceftolozane is synthesized from the commercially available compound ACLE, which is derived from penicillin G \[34\]. Penicillin G is produced via fermentation \[35\], thus ceftolozane is a semisynthetic compound.

Only one API-manufacturer of ceftolozane could be found, ACS Dobfar SPA in Italy.

Ten API-manufacturers of tazobactam were identified in total, two of which are located in the EU. The European API-manufacturers are Fresenius Kabi Ipsum SRL in Italy and Sandoz Industrial Products SA in Spain. Eight non-European API-manufacturers of tazobactam were found. These are Qilu Tianhe Pharmaceutical Co. Ltd. in China, Zhejiang Hisun Pharmaceutical Co. Ltd. in China, Otsuka Chemical Co. Ltd. in Japan, Jiangxi Fushine Pharmaceutical Co. Ltd. in China, Zhejiang Huabang Co. Ltd. in China, Pfizer Healthcare India, Sterile India Pvt. Ltd. and Aurobindo Pharma Ltd. in India.

Merck Sharp & Dohme BV is the only MAH for ceftolozane/tazobactam in Europe, due to market protection.

The duration of treatment with ceftolozane/tazobactam is usually between 4 and 14 days.

4.1.5 Phenoxy methylpenicillin

Phenoxy methylpenicillin is a β-lactam antibiotic within the penicillin subgroup, for chemical structure of phenoxy methylpenicillin, see Figure 7. The substance is also called penicillin V. This antibiotic has a good effect on Gram-positive bacteria such as pneumococci and streptococci which can cause common infections such as ear inflammation, sinus infection, pneumonia or throat infection \[36\]. In Sweden, the active antibacterial substance is sold under the name Kåvepenin® as a potassium salt \[37\].
In regards to accessibility problems, the formulation tablet 250 mg is likely to experience problems according to Folkhälsmyndigheten.

Phenoxymethylpenicillin is manufactured semisynthetically via fermentation. The drug is synthesized from a simple derivate of 6-APA and phenoxyacetic acid [30].

There are two API-manufacturers in Europe. Biotika AS, located in Slovakia are responsible for the fermentation, cell culture cultivation and the purification which they have a GMP-certificate for. The other API-manufacturer is Sandoz GmbH located in Austria.

There are two API-manufacturers outside Europe. The first one is DSM Anti-infectives India Ltd. located in India. The second manufacturer is Hebei North China Pharmaceutical Huaheng Pharmaceutical Co. Ltd., located in China.

There is one MAH in Sweden that sells phenoxymethylpenicillin and that is Meda AB. There are in total 13 MAHs in Europe.

Meda also sells phenoxymethylpenicillin 250 mg under the name Tikacillin but according to Fass, they do not currently provide it. Tikacillin is the only exchangeable drug for Kåvepenin [38].

The drug is orally administered, the treatment lasts from five to ten days according to Fass.

### 4.1.6 Rifampicin

Rifampicin, also called rifampin, is a drug used mainly in the treatment of tuberculosis [39], for chemical structure of rifampicin, see Figure 8. Rifampicin has been in use since the late 1960’s and is in the treatment of tuberculosis always used together with additional antibiotics to decrease the risk of bacteria developing resistance to the drug [40]. Rifampicin is on the World Health Organization’s List of Essential Medicines, the most effective and safe medicines needed in a healthcare system [41].

Rifamycin, a intermediate in the synthesis of rifampicin, is extracted from a fermentation culture of the bacteria *Amycalutopsis rifamycinica*. Rifampicin is a derivative of rifamycin [42].

There are seven API-manufacturers of rifampicin, three of which are located in Europe (Sanofi SPA in Italy, OLON SPA in Italy and SIC Borshchahivskiy Chemical in Ukraine). The remaining four are Hetero Drugs Ltd. and Lupin Ltd. in India, CDK Bio Corporation in the Republic of Korea and Shenyang Antibiotic in China.

The treatment time of tuberculosis with rifampicin is at a minimum six months [43].
4.1.7 Bedaquiline

Bedaquiline is a diarylquinoline, for chemical structure of bedaquiline, see Figure 9. The drug is combined with at least three other active antibacterial drugs to treat multi-resistant pulmonary tuberculosis. It is only given when no other treatment is possible. In regards to accessibility problems, the formulation tablet 100 mg is likely to experience problems according to Folkhälsomyndigheten. In Sweden, the antibacterial active substance bedaquiline fumarate is sold as Sirturo® in tablet form [44].

Bedaquiline is manufactured synthetically [45]. There are no API-manufacturers for bedaquiline in Europe. There are two companies in India. Dishman Carbogen Amcis Ltd. which has two factories that both produce the active substance. The other company is MSN Life Sciences Pvt. Ltd. based in India.

There is one MAH in Europe, Janssen-Cilag International N.V. located in Belgium. They have the authority to sell the drug to all countries within the EEA.

The duration of the treatment is 24 weeks according to Fass. Bedaquiline is not exchangeable for another treatment.

Since bedaquiline is a last resort antibiotic, the FDA gave an accelerated approval for treatment of patients before the phase-III clinical trials were done [46]. The prognosis for the clinical trials to be done is 2022 [47].

4.1.8 Amikacin

Amikacin is an antibiotic of the aminoglycoside type, used to treat a number of infections by susceptible Gram-negative bacteria, including bone and joint infections, intra-abdominal infections, meningitis and urinary tract infections [48]. For chemical structure of amikacin, see Figure 10.

Amikacin is administered intravenously. It is sold in Sweden under the name Biklin® by Vianex SA [49]. The drug is synthesized from kanamycin which is isolated from bacteria [30]. Amikacin is thus a semisynthetic compound.

Five API-manufacturers in total have been identified for this substance, only one of which is located in the EU, ACS Dobfar SPA in Italy. There are four non-European API-manufacturers. Qilu Pharmaceutical Co. Ltd. in China, Zhejiang Jinhua Conba Bio-Pharm
Co. Ltd. in China, Interquim SA in Mexico and Chongqing Daxin Pharmaceutical Co. Ltd. in China.

There are 38 MAHs in the EEA and only one (Vianex SA) in Sweden.

Amikacin is imported in parallel by Orifarm AB [49]. It was previously imported and sold by an additional company, Omnia Läkemedel AB, but their product was deregistered in 2015 [50].

4.1.9 Benzylpenicillin

Benzylpenicillin, also called penicillin G, is a β-lactam antibiotic within the penicillin subgroup, for chemical structure of benzylpenicillin, see Figure 11. It is a natural penicillin antibiotic and is used to treat infections caused by Gram-positive bacteria such as staphylococci, pneumococci and streptococci [51]. Benzylpenicillin is produced semisynthetically (fermentation). The penicillin is a secondary metabolite originating from the fungal species Penicillium chrysogenum [30].

In Sweden, the active substance is sold in the salt form benzylpenicillin sodium, with the formulation injection/infusion, under the product names Benzylpenicillin® Meda and Benzylpenicillin Panpharma [51]. The MAH for Benzylpenicillin® Meda is Meda AB. Benzylpenicillin Panpharma is sold by Panpharma SA. According to Folkhälsomyndigheten, benzylpenicillin, in the formulation injection/infusion, risks getting accessibility problems.

The API-manufacturer Sandoz GmbH, located in Austria, manufactures benzylpenicillin in the forms benzylpenicillin benzathine, benzylpenicillin sodium, benzylpenicillin potassium and benzylpenicillin procaine. The Chinese company CSPC Zhongnuo Pharmaceutical (Shijiazhuang) Co. Ltd. and the Mexican company Fresina GB, S.A. de C.V. produces the active substance benzylpenicillin potassium. Hebei Huari Pharmaceutical Co. Ltd. is an API-manufacturer located in China, the company manufactures the active substance benzylpenicillin sodium and procaine benzylpenicillin. The Chinese company Jiangxi Dongfeng Pharmaceutical manufactures the active substance benzylpenicillin sodium.

There are four additional API-manufacturers: Spic Ltd. in India, the Italian companies Fresenius Kabi iPSUM S.R.L., ACS Dobfar S.p.A and the Chinese company: Yili Chuanning Biotechnology Co. Ltd.

In Europe, there are 17 MAHs for the following salt forms of benzylpenicillin; sodium and potassium.

Penicillin G is a narrow spectrum antibiotic, which means that there is a low risk of resistance development. Resistance is found to Gram-negative bacteria. The administration occurs intravenously or intramuscular, since the antibiotic is not acid-stable and thus not completely absorbed during oral administration [51].
4.1.10  Piperacillin/Tazobactam

Piperacillin/Tazobactam is a combination drug in which piperacillin and tazobactam are the active substances. For chemical structure of piperacillin/tazobactam, see Figure 12. Piperacillin is a broad-spectrum β-lactam antibiotic that is used in conjunction with the β-lactamase inhibitor, tazobactam. Piperacillin being a broad-spectrum antibiotic makes it effective against Gram-positive and Gram-negative bacteria. It is used with tazobactam as it prevents inactivation of piperacillin by β-lactamase enzymes. This allows piperacillin to be more effective.

Both active substances are produced semisynthetically (fermentation). According to a Chinese patent, tazobactam is produced from (+)-6-aminopenicillanic acid (6-APA) following several synthetic steps. Thus, tazobactam is a semisynthetic fermentation product. Piperacillin has ampicillin as a starting material which is produced from 6-APA, making piperacillin a semisynthetic fermentation product as well.

Piperacillin/tazobactam is mainly used for treating urinary tract infections, pneumonia, intra abdominal infections and skin infections. The route of administration being used is intravenous injections/infusions. Piperacillin/tazobactam is sold as a powder for infusion liquids in Sweden. Four different companies sell the powders: Fresenius Kabi, Sandoz, Stragen and Reig Jofre. The powder from respective company comes in two dosage strengths, 4 g piperacillin per 0.5 g tazobactam and 2 g piperacillin per 0.25 g tazobactam. In regards to accessibility problems, the formulation injection/infusion is likely to experience the accessibility problems according to Folkhälsomyndigheten.

There are two API-manufacturers in Europe of both piperacillin and tazobactam. In total, there are nine manufacturers of piperacillin and ten manufacturers of tazobactam around the world. Seven companies produce both piperacillin and tazobactam.

The European companies that produce both active substances are Sandoz Industrial Process SA and Fresenius Kabi iPSUM. The former is based in Spain and the latter is based in Italy.

The remaining five companies that produce both piperacillin and tazobactam are Sterile India Pvt. Ltd., Aurobindo Pharma, Pfizer Healthcare India, Qilu Tianhe Pharmaceutical and Jiangxi Fushine Pharmaceutical. The first three companies are based in India and the last two are based in China.

The three remaining manufacturers of tazobactam are Zhejiang Hisum Pharmaceutical, Zhejiang Huabang Medical & Chemical and Otsuka Chemical. The first two companies are based in China and the last one in Japan.

The two remaining manufacturers of piperacillin are Yuhan Chemical and Shandong Ruiying Pioneer Pharmaceutical. The former company is based in Republic of Korea and the latter company is based in China.

There are 7 MAHs in Sweden for piperacillin/tazobactam and in total, there are 54 MAHs in
One interesting fact is that in October of 2016, according to several sources such as Läkemedelsverket and Södra Älvsborgs hospital, a factory in China exploded. According to the report released by Södra Älvsborgs hospital, this factory stood for a large portion of the world's piperacillin and tazobactam production. The company affected was Qilu Tianhe Pharmaceutical Company.

Sohu, a Chinese internet company reported on an accident that occurred in a facility belonging to Qilu Tianhe Pharmaceutical Company where ten maintenance workers were killed in an accident in April of 2019. Additionally, during the last of April in 2015, an explosion occurred in one of the manufacturing sites which caused a fire. Another accident took place in August of 2016 where another fire broke out.

According to Fass, since the end of 2011, there has been seven deregistrations of piperacillin/tazobactam medicines in Sweden. Three occurred in the span of two weeks in the summer of 2016. Another two deregistrations took place in 2018. At the moment, there are two piperacillin/tazobactam drugs, Piperacillin/Tazobactam Eberth and Piperacillin/Tazobactam Noridem, that are not available according to Fass.

As for back orders, there are two ongoing back orders for piperacillin/tazobactam Fresenius Kabi. One started in September of 2018 and it was set to end in the middle of January of 2019, but it has not ended yet. The other back order started at the end of December 2018 and was set to end in the end of April 2019, but it has not ended yet. As for ended back orders, there was one back order in July of 2018 that ended in the end of October 2018. This was also for Piperacillin/Tazobactam Fresenius Kabi.

4.1.11 Meropenem

Meropenem is a carbapenem antibiotic used to treat infections such as severe pneumonia, complicated urinary tract infections, complicated intra-abdominal infections and acute bacterial meningitis. For chemical structure of meropenem, see Figure 13. The drug is administered intravenously. In Sweden, meropenem is sold under various trade names, such as Meronem®, Meropenem Bradex, Meropenem Fresenius Kabi and Meropenem Hexal.

Meropenem is synthesized from a commercially available intermediate called β-methyl vinyl phosphate (MAP).

Ten API-manufacturers of meropenem were found. These are Savior Lifetec Corporation in Taiwan, Shenzhen Haibin Pharmaceutical Co. Ltd. in China, SIC Borshchahivskiy Chemical in Ukraine, Aurobindo Pharma Ltd. in India, Auronext Pharma Private Ltd. in India, Unimark Remedies Ltd. in India, Sterile India Pvt. Ltd., Qilu Antibiotics Linyi Pharmaceutical Co. Ltd. in China, Sumitomo Dainippon Pharma Co. Ltd. in Japan and ACS Dobfar SPA in Italy.
There are 41 MAHs for meropenem in the EEA and 6 in Sweden. The Swedish MAHs are Pfizer AB, Bradex SA, Accord Healthcare BV, Fresenius Kabi AB, Hexal A/S and Medipha Sante.

There are four back orders for meropenem, with a duration of 121, 133, 12 and 11 weeks respectively.

4.1.12 Trimethoprim/Sulfamethoxazole

Trimethoprim/Sulfamethoxazol, also called co-trimoxazol, is a combination antibiotic that consists of one part trimethoprim and five parts sulfamethoxazole \[63\] \[64\]. For chemical structure of trimethoprim/sulfamethoxazole, see Figure 14. Sulfamethoxazole belongs to the drug class antibacterial sulfonamides and trimethoprim belongs to the drug class antifolates \[65\]. Trimethoprim is produced synthetically \[30\] and sulfamethoxazole is produced semisynthetically \[30\], from a derivative of chitosan \[66\].

Co-trimoxazole is used for treating urinary tract infections, acute exacerbation of bronchitis and shingellosis. It is also used as a preventative medicine against infections caused by \textit{Pneumocystis jirovecii}. Sulfamethoxazole is only sold as a combination antibiotic with trimethoprim in Sweden. Trimethoprim, however, is sold individually with indication urinary tract infection and as a preventative medicine against urinary tract infections. In regards to accessibility problems, the formulation oral solution/suspension is the most likely to experience accessibility problems according to Folkhälsovårdens rapport.

Oral suspension of co-trimoxazole is sold in Sweden under the name Bactrim® and Eusaprim®. Bactrim® is sold by Roche and Eusaprim® by Aspen Nordic.

In total, there are ten companies that produce trimethoprim and four that produce sulfamethoxazole. There are two companies that produce both trimethoprim and sulfamethoxazole. These companies are Southwest Synthetic Pharmaceutical and Shougang Fukang Pharmaceutical. Both companies are based in China.

The two remaining companies that produce sulfamethoxazole are Virchow Laboratories and Andhra Organics Ltd. Both companies are based in India. There are eight more companies that produce trimethoprim. The following four companies out of the eight are based in India: Inventaa Chemicals Ltd., Ipca Laboratories Ltd., Punjab Chemicals and Crop Protection Ltd., GSK India. The remaining four companies that produce trimethoprim are Shandong Xinhua Pharmaceutical, PKU Healthcare Corp. Ltd., Aspen Global Incorporotated and IPTeva API B.V. The first two companies are based in China, the third one is based in Mauritius and the last company is based in Israel.

There are two MAHs in Sweden, and in total, there are 11 MAHs in Europe.

There are two importers of both sulfamethoxazole and trimethoprim in Europe. Both companies have GMP-certifications for preparation of powders for oral suspensions and for packaging. These
companies are Adamed Pharma based in Poland and Purna Pharmaceuticals in Belgium.

### 4.2 Risk assessment for 39 antibiotics

Table 8 and 9 shows the summarized result, ordered as Figure 1. Table 8 contains the result from section 4.1 and Table 9 contains the result retrieved from other groups. The countries in which the API production takes place can be found in Table 13 (see appendix).

The uncertainty in annual sales volume (sold standard units), uncertainty in annual sales income, average sales income in Sweden as well as part of assumed profitability per dose was retrieved from sales figures provided by PLATINEA partners. Note that no uncertainty in annual sales volume and uncertainty in annual sales income could be gathered for ceftazidime/avibactam due to the fact that this medicine only has been sold for one year at the time of writing this thesis.

Most antibiotics, as seen in Table 8 and 9, are produced semisynthetically (17 out of 39), with only one of these produced without any fermentation-extracted intermediates (trimethoprim/ sulfamethoxazole). Furthermore, 12 of the antibiotics are produced solely by fermentation, meaning that 29 out of 39 antibiotics are, in some way, produced by fermentation.

Table 8: Compilation of all the information about every antibiotic that was assigned to group 1. The colours represent the production process for each antibiotic where red is semisynthetic (fermentation), yellow is semisynthetic, blue is synthetic and green is a fermentation process.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Class</th>
<th>Number of API-manufacturers found</th>
<th>MAH EEA (Sweden)</th>
<th>Number of back orders</th>
<th>Currently not provided in Sweden (Number of MAH)</th>
<th>Assumed profitability per dose</th>
<th>Uncertainty in annual sales volume</th>
<th>Uncertainty in annual sales income</th>
<th>Average sale income in Sweden</th>
<th>Parallel import</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin (Injection/Infusion)</td>
<td>Polymyxin</td>
<td>4</td>
<td>20 (2)</td>
<td>0</td>
<td>1</td>
<td>Medium</td>
<td>18.00%</td>
<td>19.00%</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Ceftriaxone/avibactam</td>
<td>β-lactam/β-lactamase</td>
<td>13/1</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>Medium</td>
<td>12.00%</td>
<td>8.00%</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Nifurinterfil (Tablet 5 mg)</td>
<td>Nifuril</td>
<td>6</td>
<td>1 (1)</td>
<td>1 (32 weeks)</td>
<td>0</td>
<td>Medium</td>
<td>12.00%</td>
<td>8.00%</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Cefuroxax/azobacter</td>
<td>β-lactam/β-lactamase inhibitor</td>
<td>1/10</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>High</td>
<td>66.00%</td>
<td>66.00%</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Phenoxymethy/penicillin (Tablet 250 mg)</td>
<td>β-lactam</td>
<td>4</td>
<td>13 (1)</td>
<td>0</td>
<td>1</td>
<td>Low</td>
<td>6.00%</td>
<td>17.00%</td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Rifampicin (Oral suspension)</td>
<td>Amikacin</td>
<td>7</td>
<td>4 (1)</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>7.00%</td>
<td>12.00%</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Rifampicin (Capsule 150 mg)</td>
<td>Amikacin</td>
<td>7</td>
<td>11 (2)</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>28.00%</td>
<td>33.00%</td>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Rifampicin (Capsule 300 mg)</td>
<td>Amikacin</td>
<td>7</td>
<td>13 (1)</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>18.50%</td>
<td>16.00%</td>
<td>High</td>
<td>5</td>
</tr>
<tr>
<td>Bedaquiline (Tablet 100 mg)</td>
<td>Diarylquinoline</td>
<td>3</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>High</td>
<td>65.00%</td>
<td>60.00%</td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Ampicillin (Injection/liquid)</td>
<td>Aminoglycoside</td>
<td>5</td>
<td>36 (2)</td>
<td>0</td>
<td>1</td>
<td>Low</td>
<td>53.00%</td>
<td>53.00%</td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Benzopyridilin (Injection / infusion)</td>
<td>β-lactam</td>
<td>9</td>
<td>17 (2)</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>2.00%</td>
<td>6.00%</td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Pencillin/macrolides (Injection / infusion)</td>
<td>β-lactam/β-lactamase inhibitor</td>
<td>9/10</td>
<td>54 (7)</td>
<td>1 (16 weeks)</td>
<td>3</td>
<td>Low</td>
<td>10.00%</td>
<td>16.00%</td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Meropenem (Injection / infusion)</td>
<td>β-lactam</td>
<td>10</td>
<td>41 (6)</td>
<td>4 (121/133/12/11 weeks)</td>
<td>3</td>
<td>Low</td>
<td>3.00%</td>
<td>27.00%</td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Trimethoprin/Sulfadoxime (Oral suspension)</td>
<td>Trimethoprin/Sulfadoxime (Oral suspension)</td>
<td>10/4</td>
<td>11 (2)</td>
<td>1 (11 weeks)</td>
<td>0</td>
<td>Medium</td>
<td>12.00%</td>
<td>9.00%</td>
<td>Low</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 9: Compilation of all the information found about every antibiotic assigned to group 2 & 3. The colours represent the production process for each antibiotic where red is semisynthetic (fermentation), yellow is semisynthetic, blue is synthetic and green is a fermentation process.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Class</th>
<th>Number of API manufacturers found</th>
<th>MAH EEA (Sweden)</th>
<th>Number of back orders</th>
<th>Currently not provided in Sweden (Number of MAH)</th>
<th>Assumed profitability per dose</th>
<th>Uncertainty in annual sales volume</th>
<th>Uncertainty in annual sales income</th>
<th>Average sales income in Sweden</th>
<th>Parallell import</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/Clavulanate acid (Oral suspension 50 mg/ml + 12.5 mg/ml)</td>
<td>β-lactam</td>
<td>16/11</td>
<td>5 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate acid (Oral suspension 80 mg/ml + 12 mg/ml)</td>
<td>β-lactam</td>
<td>16/11</td>
<td>6 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate acid (Tablet 250 mg/125 mg)</td>
<td>β-lactam</td>
<td>16/11</td>
<td>5 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Pivmoxacin (Oral solution)</td>
<td>β-lactam</td>
<td>4</td>
<td>5 (1)</td>
<td>0</td>
<td>1</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>8.00%</td>
</tr>
<tr>
<td>Ceftadolin (Oral suspension)</td>
<td>β-lactam</td>
<td>7</td>
<td>16 (1)</td>
<td>1 (91 weeks (ongoing))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76%</td>
<td>78%</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 50 mg/ml)</td>
<td>β-lactam</td>
<td>16</td>
<td>10 (2)</td>
<td>1 (61 weeks)</td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>Erythromycin (Injection)</td>
<td>Glycerol</td>
<td>11</td>
<td>6 (1)</td>
<td></td>
<td></td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>Metronidazole (Injection)</td>
<td>Nitroimidazol derivative</td>
<td>7</td>
<td>32 (1)</td>
<td>0</td>
<td>0</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>Metronidazole (Oral suspension 40 mg/ml)</td>
<td>Nitroimidazol derivative</td>
<td>7</td>
<td>1 (1)</td>
<td></td>
<td>0</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Metronidazole (Tablet 300 mg)</td>
<td>Nitroimidazol derivative</td>
<td>7</td>
<td>10 (1)</td>
<td></td>
<td>0</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>Metronidazole (Tablet 400 mg)</td>
<td>Nitroimidazol derivative</td>
<td>7</td>
<td>18 (1)</td>
<td>1 (30 weeks)</td>
<td>0</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>Flucloxacillin (Mg) (Oral suspension 500 mg/ml)</td>
<td>β-lactam</td>
<td>1</td>
<td>2 (1)</td>
<td>2 (7/7 weeks (ongoing))</td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Flucloxacillin (Na) (Tablet 250 mg)</td>
<td>β-lactam</td>
<td>3</td>
<td>1 (1)</td>
<td></td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>Ibuprofen (Tablet 100 mg)</td>
<td></td>
<td>6</td>
<td>6 (1)</td>
<td></td>
<td>0</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>Ceftriaxone (Injection)</td>
<td>β-lactam</td>
<td>1</td>
<td>1 (1)</td>
<td></td>
<td>0</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Tobramycin (Injection 10 mg/ml)</td>
<td>Aminoglycoside</td>
<td>5</td>
<td>6 (1)</td>
<td></td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>58%</td>
</tr>
<tr>
<td>Tobramycin (Injection 40 mg/ml)</td>
<td>Aminoglycoside</td>
<td>5</td>
<td>10 (1)</td>
<td></td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Gentamicin (Injection)</td>
<td>Aminoglycoside</td>
<td>6</td>
<td>31 (1)</td>
<td></td>
<td>1 (parallel import)</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Aztreonam (Oral suspension)</td>
<td>Macrolide</td>
<td>9</td>
<td>7 (1)</td>
<td></td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Lincomycin (Oral suspension 20 mg/ml)</td>
<td></td>
<td>25</td>
<td>1 (1)</td>
<td>1 (21 weeks)</td>
<td>0</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>31%</td>
</tr>
<tr>
<td>Telithromycin Powder for injection/injection</td>
<td>Glycopeptide</td>
<td>8</td>
<td>9 (2)</td>
<td></td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 100 mg/ml)</td>
<td>β-lactam</td>
<td>14</td>
<td>4 (1)</td>
<td></td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Vancomycin (Injection/Intravenous)</td>
<td>Glycopeptide</td>
<td>13</td>
<td>19 (4)</td>
<td></td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Meropenem (Powder for injection/refractory infusion)</td>
<td>Carbapenem</td>
<td>7</td>
<td>7 (2)</td>
<td></td>
<td>0</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>Clarithromycin (Oral solution)</td>
<td></td>
<td>11</td>
<td>2 (1)</td>
<td>1 (3 weeks)</td>
<td>0</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td>20%</td>
</tr>
</tbody>
</table>
Table 10: Table showing the results of the grading based on each factor for each antibiotic.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Process</th>
<th>Number of API-manufacturers</th>
<th>API-manufacturers geographic location</th>
<th>MAH EEA</th>
<th>Back orders</th>
<th>Natural disasters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin (Injection/Infusion)</td>
<td>3</td>
<td>1.3</td>
<td>3</td>
<td>0.25</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Ceftazidime/Avibactam (Injection/Infusion)</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>3.1</td>
</tr>
<tr>
<td>Nitrofurantoin (Tablet 5 mg)</td>
<td>1</td>
<td>0.83</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>4.2</td>
</tr>
<tr>
<td>Ceftolozan/Tazobactam (Injection/infusion)</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin (Tablet 250 mg)</td>
<td>4</td>
<td>1.3</td>
<td>3</td>
<td>0.38</td>
<td>0</td>
<td>3.8</td>
</tr>
<tr>
<td>Rifampicin (Oral suspension)</td>
<td>4</td>
<td>0.71</td>
<td>4</td>
<td>1.3</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Rifampicin (Capsule 150 mg)</td>
<td>4</td>
<td>0.71</td>
<td>4</td>
<td>0.45</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Rifampicin (Capsule 300 mg)</td>
<td>4</td>
<td>0.71</td>
<td>4</td>
<td>0.38</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Bedaquiline (Tablet 100 mg)</td>
<td>1</td>
<td>1.7</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>4.7</td>
</tr>
<tr>
<td>Amikacin (Injection fluid)</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>0.14</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Benzylpenicillin (Injection/Infusion)</td>
<td>4</td>
<td>0.55</td>
<td>4</td>
<td>0.29</td>
<td>0</td>
<td>4.7</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam (Injection/Infusion)</td>
<td>4</td>
<td>0.55</td>
<td>4</td>
<td>0.09</td>
<td>1</td>
<td>4.6</td>
</tr>
<tr>
<td>Meropenem (Injection/Infusion)</td>
<td>4</td>
<td>0.50</td>
<td>4</td>
<td>0.12</td>
<td>5</td>
<td>4.6</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole (Oral suspension)</td>
<td>2</td>
<td>1.3</td>
<td>5</td>
<td>0.45</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Oral suspension 50 mg/ml + 13 mg/ml)</td>
<td>4</td>
<td>0.45</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Oral suspension 80 mg/ml + 12 mg/ml)</td>
<td>4</td>
<td>0.45</td>
<td>3</td>
<td>0.83</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Tablet 250mg/125 mg)</td>
<td>4</td>
<td>0.45</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3.9</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin (Tablet 500 mg)</td>
<td>4</td>
<td>1.3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3.9</td>
</tr>
<tr>
<td>Cefadroxil (Oral suspension)</td>
<td>4</td>
<td>0.71</td>
<td>3</td>
<td>0.31</td>
<td>5</td>
<td>4.3</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 50 mg/ml)</td>
<td>4</td>
<td>0.31</td>
<td>4</td>
<td>0.5</td>
<td>4</td>
<td>4.2</td>
</tr>
<tr>
<td>Tigecycline (Injection/Infusion)</td>
<td>1</td>
<td>0.45</td>
<td>4</td>
<td>0.83</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>Metronidazol (Infusion liquid 5 mg/ml)</td>
<td>1</td>
<td>0.71</td>
<td>4</td>
<td>0.16</td>
<td>0</td>
<td>4.9</td>
</tr>
<tr>
<td>Metronidazol (Oral suspension 40 mg/ml)</td>
<td>1</td>
<td>0.71</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>4.9</td>
</tr>
<tr>
<td>Metronidazol (Tablet 200 mg)</td>
<td>1</td>
<td>0.71</td>
<td>4</td>
<td>0.5</td>
<td>0</td>
<td>4.9</td>
</tr>
<tr>
<td>Metronidazol (Tablet 400 mg)</td>
<td>1</td>
<td>0.71</td>
<td>4</td>
<td>0.28</td>
<td>1</td>
<td>4.9</td>
</tr>
<tr>
<td>Fluoxacillin (Mg) (Oral suspension 50 mg/ml)</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>2.5</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>Fluoxacillin (Na) (Tablet 125 mg)</td>
<td>3</td>
<td>1.7</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>4.1</td>
</tr>
<tr>
<td>Isoniazide (Tablet 300 mg)</td>
<td>1</td>
<td>0.83</td>
<td>4</td>
<td>0.83</td>
<td>0</td>
<td>4.1</td>
</tr>
<tr>
<td>Ceftaroline fosamil (Injection/Infusion)</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>Tobramycin (Injection 10 mg/ml)</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0.83</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Tobramycin (Injection 40 mg/ml)</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0.5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Gentamicin (Injection/Infusion)</td>
<td>3</td>
<td>0.85</td>
<td>4</td>
<td>0.16</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Erythromycin (Oral suspension)</td>
<td>3</td>
<td>0.56</td>
<td>4</td>
<td>0.71</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>Linezolid (Oral suspension)</td>
<td>1</td>
<td>0.20</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>4.4</td>
</tr>
<tr>
<td>Teikoplanin (Injection/infusion)</td>
<td>3</td>
<td>0.63</td>
<td>3</td>
<td>0.56</td>
<td>0</td>
<td>4.1</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 100 mg/ml)</td>
<td>4</td>
<td>0.36</td>
<td>4</td>
<td>1.3</td>
<td>0</td>
<td>3.7</td>
</tr>
<tr>
<td>Vankomycin (Injection/Infusion)</td>
<td>3</td>
<td>0.38</td>
<td>4</td>
<td>0.26</td>
<td>0</td>
<td>3.7</td>
</tr>
<tr>
<td>Ertapenem (Injection/Infusion)</td>
<td>1</td>
<td>0.71</td>
<td>5</td>
<td>0.71</td>
<td>0</td>
<td>4.6</td>
</tr>
<tr>
<td>Clindamycin (Oral suspension)</td>
<td>4</td>
<td>0.45</td>
<td>4</td>
<td>2.5</td>
<td>1</td>
<td>4.9</td>
</tr>
</tbody>
</table>

26
Table 11: Table showing the results of the grading based on each factor for each antibiotic.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Uncertainty in annual sales income</th>
<th>Uncertainty in annual sales volume</th>
<th>Currently not provided in Sweden</th>
<th>Assumed profitability per dose</th>
<th>Average sale income in Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin (Injection/Infusion)</td>
<td>0,95</td>
<td>0,9</td>
<td>1,67</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ceftazidime/Avibactam (Injection/Infusion)</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nitrofurantoin (Tablet 5 mg)</td>
<td>0,4</td>
<td>0,6</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ceftolozan/Tazobactam (Injection/infusion)</td>
<td>3,3</td>
<td>3,3</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Phenoxy methylpenicillin (Tablet 250 mg)</td>
<td>0,85</td>
<td>0,3</td>
<td>1,67</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Rifampicin (Oral suspension)</td>
<td>0,6</td>
<td>0,35</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rifampicin (Capsule 150 mg)</td>
<td>1,7</td>
<td>1,4</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rifampicin (Capsule 300 mg)</td>
<td>0,8</td>
<td>0,9</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Bedaquiline (Tablet 100 mg)</td>
<td>3</td>
<td>3,25</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Amikacin (Injection fluid)</td>
<td>2,7</td>
<td>2,7</td>
<td>1,67</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Benzylpenicillin (Injection/Infusion)</td>
<td>0,3</td>
<td>0,1</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam (Injection/Infusion)</td>
<td>0,8</td>
<td>0,5</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Meropenem (Injection/Infusion)</td>
<td>1,4</td>
<td>0,15</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole (Oral suspension)</td>
<td>0,45</td>
<td>0,6</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Oral suspension 50 mg/ml + 13 mg/ml)</td>
<td>1,8</td>
<td>1,9</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Oral suspension 80 mg/ml + 12 mg/ml)</td>
<td>1,7</td>
<td>1,6</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Tablet 250mg/125 mg)</td>
<td>2,7</td>
<td>2,6</td>
<td>1,67</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Phenoxy methylpenicillin (Tablet 500 mg)</td>
<td>0,9</td>
<td>0,4</td>
<td>1,67</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Cefadroxil (Oral suspension)</td>
<td>3,9</td>
<td>3,8</td>
<td>1,67</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 50 mg/ml)</td>
<td>1,1</td>
<td>0,95</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tigecycline (Injection/Infusion)</td>
<td>1</td>
<td>0,85</td>
<td>1,67</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Metronidazol (Infusion liquid 5 mg/ml)</td>
<td>0,6</td>
<td>0,8</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Metronidazol (Oral suspension 40 mg/ml)</td>
<td>0,5</td>
<td>0,3</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Metronidazol (Tablet 200 mg)</td>
<td>1,5</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Metronidazol (Tablet 400 mg)</td>
<td>1,2</td>
<td>0,8</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Flucloxacillin (Mg) (Oral suspension 50 mg/ml)</td>
<td>0,3</td>
<td>0,5</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Flucloxacillin (Na) (Tablet 125 mg)</td>
<td>1,4</td>
<td>0,55</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Isoniazide (Tablet 300 mg)</td>
<td>2,1</td>
<td>1,35</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ceftaroline fosamil (Injection/Infusion)</td>
<td>2,1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tobramycin (Injection 10 mg/ml)</td>
<td>2,8</td>
<td>2,9</td>
<td>1,67</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tobramycin (Injection 40 mg/ml)</td>
<td>0,55</td>
<td>0,7</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Gentamicin (Injection/Infusion)</td>
<td>0,65</td>
<td>0,45</td>
<td>1,67</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Erytromycin (Oral suspension)</td>
<td>0,65</td>
<td>0,3</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Linezolid (Oral suspension)</td>
<td>1,6</td>
<td>1,55</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Telkoplanin (Injection/infusion)</td>
<td>1,1</td>
<td>0,8</td>
<td>1,67</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 100 mg/ml)</td>
<td>0,45</td>
<td>0,2</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Vankomycin (Injection/Infusion)</td>
<td>1,1</td>
<td>0,15</td>
<td>3,34</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ertapenem (Injection/Infusion)</td>
<td>1,1</td>
<td>0,6</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Clindamycin (Oral suspension)</td>
<td>0,75</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 12: Table showing all antibiotics ranked from highest risk value to lowest risk value.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Risk value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefadroxil (Oral suspension)</td>
<td>32.7</td>
</tr>
<tr>
<td>Ceftolozan/Tazobactam (Injection/Infusion)</td>
<td>29.9</td>
</tr>
<tr>
<td>Meropenem (Injection/Infusion)</td>
<td>28.8</td>
</tr>
<tr>
<td>Cefaroline fosamil (Injection/Infusion)</td>
<td>27.4</td>
</tr>
<tr>
<td>Bedaquiline (Tablet 100 mg)</td>
<td>25.7</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Tablet 250 mg / 125 mg)</td>
<td>25.3</td>
</tr>
<tr>
<td>Amikacin (Injection fluid)</td>
<td>25.2</td>
</tr>
<tr>
<td>Tobramycin (Injection 10 mg/ml)</td>
<td>25.2</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 50 mg/ml)</td>
<td>25.1</td>
</tr>
<tr>
<td>Linezolid (Oral suspension)</td>
<td>24.8</td>
</tr>
<tr>
<td>Clindamycin (Oral suspension)</td>
<td>24.6</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam (Injection/Infusion)</td>
<td>24.5</td>
</tr>
<tr>
<td>Amoxicillin/Clavanic acid (Oral suspension 80 mg/ml + 12 mg/ml)</td>
<td>24.5</td>
</tr>
<tr>
<td>Amoxicillin/Clavunic acid (Oral suspension 50 mg/ml + 13 mg/ml)</td>
<td>24.1</td>
</tr>
<tr>
<td>Nitrofurantion (Tablet 5 mg)</td>
<td>23</td>
</tr>
<tr>
<td>Flucloxacillin (Na) (Tablet 125 mg)</td>
<td>22.8</td>
</tr>
<tr>
<td>Rifampicin (Capsule 150 mg)</td>
<td>22.5</td>
</tr>
<tr>
<td>Ceftazidime/Avibactam (Injection/Infusion)</td>
<td>22.1</td>
</tr>
<tr>
<td>Vankomycin (Injection/Infusion)</td>
<td>21.9</td>
</tr>
<tr>
<td>Flucloxacillin (Mg) (Oral suspension)</td>
<td>21.6</td>
</tr>
<tr>
<td>Metronidazol (Oral suspension 40 mg/ml)</td>
<td>21.4</td>
</tr>
<tr>
<td>Rifampicin (Oral suspension)</td>
<td>21.2</td>
</tr>
<tr>
<td>Teikoplanin (Injection/Infusion)</td>
<td>20.9</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole (Oral suspension)</td>
<td>20.8</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin (Tablet 500 mg)</td>
<td>20.2</td>
</tr>
<tr>
<td>Colistin (Injection/Infusion)</td>
<td>20.1</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 100 mg/ml)</td>
<td>20.0</td>
</tr>
<tr>
<td>Erytromycin (Oral suspension)</td>
<td>19.5</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin (Tablet 250 mg)</td>
<td>19.3</td>
</tr>
<tr>
<td>Rifampicin (Capsule 300 mg)</td>
<td>19.0</td>
</tr>
<tr>
<td>Gentamicin (Injection/Infusion)</td>
<td>19.0</td>
</tr>
<tr>
<td>Metronidazol (Tablet 400 mg)</td>
<td>18.9</td>
</tr>
<tr>
<td>Metronidazol (Tablet 200 mg)</td>
<td>18.6</td>
</tr>
<tr>
<td>Benzylpenicillin (Injection/Infusion)</td>
<td>17.9</td>
</tr>
<tr>
<td>Isoniazide (Tablet 300 mg)</td>
<td>17.2</td>
</tr>
<tr>
<td>Tigecycline (Injection/Infusion)</td>
<td>17.1</td>
</tr>
<tr>
<td>Tobramycin (Injection 40 mg/ml)</td>
<td>16.8</td>
</tr>
<tr>
<td>Ertapenem (Injection/Infusion)</td>
<td>16.7</td>
</tr>
<tr>
<td>Metronidazol (Infusion liquid 5 mg/ml)</td>
<td>15.2</td>
</tr>
</tbody>
</table>
Table 10 and 11 compile the risk values to which the respective antibiotics were rated for each risk factor based on the results in Table 8 and 9. Eleven factors have been considered when grading the risk of an antibiotic disappearing from the market in Sweden. The factors included in the grading are according to which process the antibiotic is manufactured with, the number of MAHs and API-manufacturers, whether the APIs are in the EEA or outside, if there is any reported back orders and whether the product is currently provided in Sweden, the risk of a country experiencing a natural disaster, the assumed profitability per dose, the average sale income in Sweden and the uncertainty in the annual sales volume and sale income.

Table 12 shows the antibiotics ranked from highest risk value to lowest risk value. It shows the sum of all risk factors seen in Table 10 and 11 for each antibiotic. The maximum amount of points that could be assigned to an antibiotic is 49. The minimum is five points.

5 Discussion

5.1 Antibiotics

In the first part of the discussion, we discuss qualitative and specific information that was not included in the grading. In this section not all antibiotics will be considered, only those for which relevant information was found that could potentially affect availability (beyond what was considered in the grading).

The second part of the discussion includes general information about several antibiotics that might affect availability of some antibiotics and was not included in the grading.

The first two parts can be considered a qualitative risk assessment.

The next part considers the sources of error that were observed during the project. This includes lack of information from the databases and problems with the grading system.

The last part that is taken in consideration is further research.

5.1.1 Specific antibiotics

According to the FDA, Xellia Pharmaceuticals ApS provides colistine sulfate and colistimethate sodium to the USA. In Sweden, one of their products is currently not available and another product was deregistered in Sweden. This could mean that less resources are being spent on Sweden, as it is a smaller market than the USA.

Another possible reason for accessibility problems for colistin could be that only two API-manufacturers exist in Europe. It could be that these two API-manufacturers can not keep up with the demand and thus, accessibility problems are created as an consequence.

One thing to consider about the manufacturer of avibactam, which is sold as a combination with ceftazidime, is that the factory as well as the manufacturer is located in the UK. According to EU law, for a company to be able to market a medicine in the EU/EEA, they must perform at least some essential operations within the EU/EEA. Since the UK might leave the EU in the coming months, this fact could make selling the drug to the countries within the EU/EEA more difficult.
In June 2016, an API-manufacturer in China, Jinan Jinda Pharmaceutical Chemistry Co. Ltd. lost its GMP-certificate for the manufacturing of nitrofurantoin. A little more than a year later, a back order started between November 2017 and June 2018. Jinan Jinda Pharmaceutical Chemistry Co. Ltd. manufactures and exports nitrofurantoin to several companies, which probably means that the factory stands for a large part of the production. European companies must not do business with companies that do not have GMP-certificates. It may have meant that the availability of nitrofurantoin was due to the other API-manufacturers and the stock that Jinan Jinda Pharmaceutical Chemistry Co. Ltd. may have already built up before the GMP-certificate was withdrawn.

After the stock piles have run out due to the withdrawn GMP-certificate at Jinan Jinda Pharmaceutical Chemistry Co. Ltd., and coupled with the possibility that no increased production of nitrofurantoin takes place at other API-manufacturers, this could potentially lead to back orders.

If the antibiotic can be exchanged with another drug, the accessibility risk is reduced. Meda have both phenoxymethylpenicillin 250 mg as Kåvepenin and Tikacillin. Tikacillin is the only drug Kåvepenin can be exchanged to according to Fass but Tikacillin is not currently on the market so this could be a problem. However, Kåvepenin exists in both 125 mg and 500 mg dosages so if 250 mg would have accessibility problems the dose still could be found.

Because bedaquiline is still in clinical trials all the side effects might not be known or properly understood. If it’s shown that the drug causes too severe side effects the treatment might have to end. Another aspect to take into consideration is that all the API-manufacturers of bedaquiline are located in India. If a nationwide economic or political crisis, or similar event were to happen in India, it could thus affect all the API-manufacturers of bedaquiline which would likely lead to accessibility problems. Bedaquiline is also the only diarylquinoline on the market and can not be exchanged to another drug.

The difficulty of treating infections increases with antibiotic resistance as the antibiotic becomes less effective. The result of resistance leads to longer hospital stays, higher medical costs and increased mortality [68]. If an antibiotic has a high risk of developing resistance, this antibiotic will probably, if possible, be removed during treatment, which will lead to a decrease in the demand for the antibiotic. This, in turn, will lead to an antibiotic with a greater risk of resistance development running the greater risk of accessibility problems. If an antibiotic instead has a low risk of resistance development, as for benzylpenicillin, then this antibiotic will become more profitable to produce and thus reduce the accessibility risk.

As mentioned in the results, there were three deregistrations of piperacillin/tazobactam medicines in a span of two weeks under 2016. This is highly unusual. The reason to this could be high competition between the different MAHs in the Swedish market. This could cause other MAHs to not sell their medicine in Sweden anymore as it is not profitable because of low sales volumes.

There is a high probability, based on the results, that the Qilu Tianhe Pharmaceutical Co. in China is the root for the accessibility problems regarding piperacillin/tazobactam. Accidents at their facilities are frequent and the factory explosion in 2016 caused a shortage in piperacillin/tazobactam medicines in Europe and Sweden. It is not ideal for MAHs having a unstable API-manufacturer with frequent accidents, as it can make deliveries and other operations non-frequent. Furthermore, a lot of companies import from Qilu Tianhe Pharmaceutical Co., so many importers and distributors are dependent on this company and its operations.

The two ongoing back orders can not be linked to Qilu Tianhe Pharmaceutical Co. as Fresenius
Kabi imports **piperacillin** and **tazobactam** from other suppliers. But as Fresenius Kabi also produces both APIs, there might be a shortage of raw materials causing them to not being able to keep up with the demand. Since there is a large amount of MAHs in Europe and Fresenius Kabi is the only confirmed manufacturer based on our research, there is a possibility that Fresenius Kabi produces the medicine for some of these MAHs. It is possible that Fresenius Kabi is not able to provide enough medicine for the MAHs and this could in turn lead to shortages in some countries.

As mentioned in results, **piperacillin/tazobactam** has had many deregistrations since 2011. In the summer of 2016, three deregistrations occurred in the span of two weeks. The reason for this could be fierce competition between the MAHs. Even today, Sweden has seven MAHs which is a lot compared to the other studied antibiotics. This competition could lead to less sales and profitability for the MAHs, which in turn leads to deregistrations and worse availability.

In the case of **trimethoprim/sulfamethoxazol**, there are no API-manufacturers in Europe. However, there were two importers of both active substances with a GMP-certification for preparation of powders for oral suspension. Based on this, it is highly likely that these two companies prepare co-trimoxazol.

**Meropenem** is, as previously stated, synthesized from the commercially available compound MAP. MAP is most likely produced via fermentation, which would mean that **meropenem** is a semisynthetic fermentation product. However, no confirmation could be found for this assumption.

### 5.1.2 General

In the case of **ceftazidime/avibactam**, **nitrofurantoin**, **ceftolozane/tazobactam** and **bedaquiline**, only one MAH exists in the EU. This could lead to problems if this single MAH withdraws the drug from the market. However, it could also mean that the MAH is able to increase the price of the drug since no competition exists. This could lead to higher profit margins, leading to a more profitable product which could decrease the risk of availability problems occurring.

There are differences in treatment time between some of the antibiotics. **Phenoxymethylpenicillin** has a minimum treatment time of five days, compared to **rifampicin** which has a minimum treatment time of six months. For the MAHs it is presumably more profitable to sell a drug that is administrated for a longer time, since this will ensure a minimum volume sold. **Phenoxymethylpenicillin** is produced through fermentation, which is a quite expensive method, and has a treatment time of only five days. Because of this it might not be a very profitable antibiotic, and therefore have a higher risk for accessibility problems.

Of the studied antibiotics, **rifampicin** and **amikacin** are the only ones which are imported in parallel to Sweden from other countries in the EEA. Parallel importation might affect availability negatively long term, due to prices on the Swedish market potentially being driven down which affects profitability. Conversely, parallel importation likely increases availability in the short term since it makes it possible to purchase antibiotics from a greater number of MAHs.

In some of the factories there seems to be security problems, based on several accidents in a Chinese factory. This might lead to the GMP-certificate being withdrawn and the factory becoming unable to provide the API, causing availability issues.

No pattern or general trend could be established based on the gradation of the antibiotics seen in Table 12 when comparing with Table 8, 9, 10 and 11. This either means that no pattern or
trends exist or, more likely, that the specific grading system used was inadequate or information was lacking (the problems of the grading system are discussed under sources of error). Further research that improves upon this project might be successful in establishing a pattern or trend, which could be used to better understand and predict availability problems of antibiotic drugs.

5.2 Sources of error

All the desired information could not be found on the databases that were used. Everything might not be documented because of company secrets. For example, no information could be found regarding why Meda no longer provides Tikacilin at 250 mg dosages.

A model was made to grade the risks of natural disasters in different countries. For this model, statistics from the website ThinkHazard! were used. The different risk levels got one point. The total sum for all risks in each country was calculated using the score on the risk levels. An average was calculated to obtain a grading sum for the respective antibiotic’s location of API-manufacturers (see Table 10 & 11). This type of grading is subjective, which means that a different grading procedure would lead to a different risk assessment.

In Sweden, it has been mandatory since February 2018 for MAHs to report back orders expected to last more than three weeks, and the ones that are deemed to have an impact on patient security, to Läkemedelsverket. To get a better picture of the problem of back orders, it would have been preferred if this list would go back further into the past since it would have made it a lot easier to see which drugs were affected, and possibly to find a pattern for which drugs would most likely be affected. Another thing to consider is that if a back order is expected to be shorter than three weeks, it is not necessarily included in the list of back orders from Läkemedelsverket. This could mean that there exists many more, short-term, back orders than we know about.

During the investigation of the API-manufacturers, GMP-certificates were used to confirm the API-manufacturers operations. EudraGMDP was used for this but the results were inconsistent. Certain API-manufacturers would have all their GMP-certifications in place and it was possible to confirm that they were an API-manufacturer. For other API-manufacturers, a GMP-certificate simply did not exist even though their documentation about manufacturing was recent. For some API-manufacturers, there existed a GMP-certificate, but it did not specify for what operations, making it impossible to confirm their operations stated in their manufacturing documentation.

An observation we made when researching ceftazidime/avibactam was that avibactam is not listed on the database of API-manufacturers by the FDA even though it has been marketed in the USA since 2014. This makes trusting the FDA more difficult, since something clearly is missing. Another note on the data retrieved from the FDA is that it is not possible to get the exact address of the factory at which the API is manufactured.

In certain cases, the information about API-manufacturers listed on EudraGMDP seemed to be inconsistent with the information provided by the manufacturers themselves on their respective websites. For example, a company could be listed as a manufacturer of a certain API on EudraGMDP, but on the company’s own website, the API in question could not be found on the list of available products. This would either mean that the information on EudraGMDP is incorrect, or that the company website isn’t fully up-to-date. Such inconsistencies are a potential source of error.

The grading model that was used has many potential problems. First, the group of factors taken into account in the model is not necessarily conclusive. There are likely a number of other factors,
that affect the availability of a certain antibiotic drug, which were not taken into account in the model. Second, some factors are likely more important than others, but there was no reliable way of determining the relative importance of each factor. Instead, every factor is given between zero and five points, so that they all contribute the same amount to the total score of each antibiotic. This is most likely not realistic, but since the alternative was to assign a more or less arbitrary importance to each individual factor, it was deemed to be the most objective method. See Table 10 & 11 for grading.

One of the major limitations of the grading model is that it does not take into account single isolated events that can play a substantial role in accessibility for a certain antibiotic. One example of such event is an explosion of a factory where piperacillin/tazobactam was produced. Events like these could have huge consequences for the accessibility of an antibiotic and it would be ideal to include it as a factor while grading. But as every antibiotic does not have similar events associated with it, it would give skewed results if included.

5.3 Further research

Since our work could be used for further research, we have highlighted some issues to be considered.

As has been stated under delimitations, the supply chains for each antibiotic have not been investigated in detail. The actors in between the API-manufacturers and MAHs, such as importers and distributors, remain unknown. This is therefore a subject for potential further research, although it is likely a far more difficult task, since companies usually do not share any of this information freely.

Another area for further research is to properly analyze the relationships between MAHs and investigate which companies are subsidiaries and which are holding companies. In this report, it was assumed that MAHs with the same name were subsidiaries of the same holding company, and were thus counted as one. This is likely to be correct, but there is also a possibility that MAHs with completely different names are subsidiaries of a mutual holding company. A proper investigation of the MAHs is needed as the number of MAHs might be overestimated by just judging by company names.

The fact that we only covered API-manufacturers whose products ended up in either Europe or the USA makes it very likely, however not necessary, that more manufacturers exists, but have not been covered in this thesis. To get a clearer picture of the global API-manufacturing situation, it would obviously be prefered to know about every API-manufacturer. To work around this problem, it might be possible to find similar databases where information about API-manufacturers can be found, such as EudraGMDP, for other countries.

By comparing the list of antibiotics from Folkhälsomyndigheten in Figure 1 (which is ordered from high risk to low risk), and the length of back orders seen in Table 8 and Table 9, we see that the antibiotics thought to have a high risk of having accessibility problems occurring does not necessarily have more or longer back orders. This might indicate some inaccuracy in the model developed by Folkhälsomyndigheten, and thus, since our work is only based on the antibiotics from Figure 1, there might be many other antibiotics that are at risk according to the model developed in the thesis. Due to this, it might be interesting to do a similar study as what we have done for all antibiotics available on the Swedish market.

When calculating the uncertainty in sales, we where only interested in the uncertainty of a specific
antibiotic substance and its formulation. To assess the risk of a specific product being lost from the market or experiencing availability problems, it might be more interesting to look at the uncertainty in sales for each MAH, since this is most likely to cause trouble and being a factor behind the removal of a product by a MAH.

6 Conclusion

The aims that were set out at the beginning of the project were broadly achieved. The information regarding API-manufacturers and MAHs was found, and together with additional information about manufacturing processes, environmental risks, back orders and annual sales, utilized to evaluate the risk of availability problems on the Swedish market for each antibiotic. No overarching pattern or general trend could be found based on the gradation of the 39 antibiotics.

7 Acknowledgement

First of all, we would like to thank PLATINEA for giving us an interesting and important mission. We would like to express our gratitude to our technical supervisor Bo Lassen for pointing us in the right direction and providing us with the tools necessary for the project.

We would also like to thank our supervisors Enrico Baraldi and Petter Bertilsson Forsberg for providing us with information and assisting us with the thesis.

Lastly, we would like to thank our classmates whose feedback and contribution was necessary to finish this thesis.

References


8 Appendix
Table 13: Geographic location of API-manufacturers of the respective antibiotic.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>API-manufacturer(s) geographic location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin (Injection/Infusion)</td>
<td>China (2), Denmark, Poland</td>
</tr>
<tr>
<td>Ceftriaxone/avibactam (Injection/Infusion)</td>
<td>India (5), China (2), Italy (2), Austria, Republic of Korea, Ukraine, Brazil / UK</td>
</tr>
<tr>
<td>Nitrofurantoin (Tablet 5 mg)</td>
<td>India (2), China, Israel, Italy, Latvia</td>
</tr>
<tr>
<td>Ceftriaxone/tazobactam (Injection/Infusion)</td>
<td>Italy / China (4), India (3), Italy, Japan, Spain</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin (Tablet 250 mg)</td>
<td>Austria, China, India, Slovakia</td>
</tr>
<tr>
<td>Rifampicin (Oral suspension)</td>
<td>Italy (2), India, China, Ukraine, Republic of Korea</td>
</tr>
<tr>
<td>Rifampicin (Capsule 150 mg)</td>
<td>Italy (2), India, China, Ukraine, Republic of Korea</td>
</tr>
<tr>
<td>Rifampicin (Capsule 300 mg)</td>
<td>Italy (2), India, China, Ukraine, Republic of Korea</td>
</tr>
<tr>
<td>Bedaquiline (Tablet 100 mg)</td>
<td>India (3)</td>
</tr>
<tr>
<td>Amikacin (Injection liquid)</td>
<td>China (3), Italy, Mexico</td>
</tr>
<tr>
<td>Bensylpenicillin (Injection / infusion)</td>
<td>China (4), Italy (2), Austria, India, Mexico</td>
</tr>
<tr>
<td>Piperacillin/tazobactam (Injektion / infusion)</td>
<td>China (3), India (3), Spain, Republic of Korea, Italy / China(4), India (3), Italy, Japan, Spain</td>
</tr>
<tr>
<td>Meropenem (Injection / infusion)</td>
<td>India (4), China (2), Italy, Taiwan, Ukraine, Japan</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole (Oral suspension)</td>
<td>China (4), China (4), Israel, Mauritius / India (2), China (2)</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Oral suspension 50 mg/ml + 13 mg/ml)</td>
<td>China (4), Spain (2), Netherlands (2), Unknown (2), UK, Austria, Singapore, India, Mexico, USA / UK (2), Slovenia (2), China (2), Spain, Portugal, Mexico, Republic of Korea, Italy</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Oral suspension 80 mg/ml + 12 mg/ml)</td>
<td>China (4), Spain (2), Netherlands (2), Unknown (2), UK, Austria, Singapore, India, Mexico, USA / UK (2), Slovenia (2), China (2), Spain, Portugal, Mexico, Republic of Korea, Italy</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid (Tablet 250mg/125 mg)</td>
<td>China (4), Spain (2), Netherlands (2), Unknown (2), UK, Austria, Singapore, India, Mexico, USA / UK (2), Slovenia (2), China (2), Spain, Portugal, Mexico, Republic of Korea, Italy</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin (Tablet 500 mg)</td>
<td>China (4), Spain (2), Netherlands (2), Unknown (2), UK, Austria, Singapore, India, Mexico, USA / UK (2), Slovenia (2), China (2), Spain, Portugal, Mexico, Republic of Korea, Italy</td>
</tr>
<tr>
<td>Cefadroxil (Oral suspension)</td>
<td>India (3), Italy (2), Netherlands, Israel</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 50 mg/ml)</td>
<td>China (4), Spain (2), Netherlands (2), Unknown (2), UK, Austria, Singapore, India, Mexico, USA / UK (2), Slovenia (2), China (2), Spain, Portugal, Mexico, Republic of Korea, Italy</td>
</tr>
<tr>
<td>Tigecycline (Injection/Infusion)</td>
<td>India (4), China (3), Ireland, Austria, Italy, Israel</td>
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<tr>
<td>Metronidazol (Infusion liquid 5mg/ml )</td>
<td>China (4), Italy (2), Italy</td>
</tr>
<tr>
<td>Metronidazol (Oral suspension 40 mg/ml)</td>
<td>China (4), India (2), Italy</td>
</tr>
<tr>
<td>Metronidazol (Tablet 200 mg)</td>
<td>China (4), India (2), Italy</td>
</tr>
<tr>
<td>Metronidazol (Tablet 400 mg)</td>
<td>China (4), India (2), Italy</td>
</tr>
<tr>
<td>Flucloxacin (Mg) (Oral suspension 50mg/ml)</td>
<td>Italy</td>
</tr>
<tr>
<td>Flucloxacin (Na) (Tablet 125 mg )</td>
<td>Spain (2), Italy</td>
</tr>
<tr>
<td>Isoniazide (Tablet 300 mg)</td>
<td>India (2), Ukraine, Ireland, China, Japan</td>
</tr>
<tr>
<td>Ceftaroline fosamil (Injection/Infusion)</td>
<td>Italy</td>
</tr>
<tr>
<td>Tobramycin (Injection 10 mg/ml)</td>
<td>China (2), Hungary, Bulgaria, Unknown</td>
</tr>
<tr>
<td>Tobramycin (Injection 40 mg/ml)</td>
<td>China (2), Hungary, Bulgaria, Unknown</td>
</tr>
<tr>
<td>Gentamicin (Injection/Infusion)</td>
<td>China (3), Slovenia, Ukraine, Italy</td>
</tr>
<tr>
<td>Erythromycin (Oral suspension)</td>
<td>China (2), India (2), Poland, Malaysia, USA, Ukraine, Spain</td>
</tr>
<tr>
<td>Linezolid (Oral suspension 20 mg/ml)</td>
<td>India (14), USA (3), China (2), Unknown (2), Spain, Czech Republic, Slovenia, Taiwan</td>
</tr>
<tr>
<td>Teikoplanin Powder for injection/infusion, 200 mg</td>
<td>Italy (3), Republic of Korea (3), Hungary, China</td>
</tr>
<tr>
<td>Amoxicillin (Oral suspension 100 mg/ml)</td>
<td>China (4), Spain (2), Netherlands (2), Unknown (2), UK, Austria, Singapore, India, USA, Mexico</td>
</tr>
<tr>
<td>Vankomycin (Injection/Infusion)</td>
<td>China (4), Republic of Korea (2), India (2), Slovenia, Hungary, USA, Spain</td>
</tr>
<tr>
<td>Ertapenem (Powder for concentrate for infusion, 1g)</td>
<td>India (5), Republic of Korea, China</td>
</tr>
<tr>
<td>Clindamycin (Oral solution)</td>
<td>China (6), India (3), Italy, Spain</td>
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</tbody>
</table>