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Availability of antibiotics

Reporting of Government commission



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Preface

There is a strong correlation between antibiotic resistance and the use of antibiotics, which entails that the antibiotics which exist must be used in a responsible manner. It is therefore important to ensure availability of both new and old antibiotics of special medical value where there is poor availability. However, sometimes economic incentives and logistical conditions for providing these in the Swedish market are lacking, which may jeopardise optimal treatment of the patients. Therefore the Public Health Agency of Sweden and the Dental and Pharmaceutical Benefits Agency (TLV) have been commissioned to review how these antibiotics can be made available, both now and in the future. The commission is formulated as follows:

The Government has commissioned the Public Health Agency of Sweden and the Dental and Pharmaceutical Benefits Agency (TLV) to develop proposals for one or several models of how new antibiotics, and old antibiotics where national availability is insufficient, can be made available in Sweden. This under forms where the risk of resistance development is minimised while enabling the best possible care for patients with infections caused by multi-resistant bacteria. The work should be based on the interim goals specified in the Public Health Agency of Sweden's reporting of Government decision III:3 of 20 August 2015 (ref. no.: S2015/05372/FS) on the availability of antibiotics.

The Government commission was conducted in collaboration between the Public Health Agency of Sweden and TLV and in consultation with the Medical Products Agency (MPA), National Board of Health and Welfare and Swedish Association of Local Authorities and Regions (SALAR). The Swedish Association of the Pharmaceutical Industry (LIF) was consulted during the course of the work.

Solna and Stockholm, 1 December 2017

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Acronyms

AIP: Pharmacy purchase price

EFPIA: The European Federation of Pharmaceutical Industries and Associations

GLASS: WHO's Global Antimicrobial Resistance Surveillance System

LIF: Swedish Association of the Pharmaceutical Industry

IMI: Innovative Medicines Initiative

MAH: Market authorisation holder

NPS: National Pharmaceutical Strategy

TLV: The Dental and Pharmaceutical Benefits Agency

WHO: World Health Organization

Glossary

Antibiotics of special medical value: This report refers to the antibiotics which have been identified as having a risk of insufficient availability and which are deemed to have special medical value for ensuring availability. The assessment is based on activity profile, available options, place in the therapy, ecological profile and specific strength or formulation of importance for specific patient groups.

Essential antibiotics: The term is only used in the directive of this Government commission (S2015/05372/FS (delvis)), we have instead chosen to use the term “antibiotics of special medical value” as the concept essential antibiotics can be confused with WHO’s definition of essential medicines.

Prescription antibiotics: An antibiotic which has been prescribed to a patient and which the patient then collects at an outpatient pharmacy. Sometimes the patient defrays the entire cost. In some instances the patient defrays some of the cost and the remaining costs are paid by the public sector through pharmaceutical benefits.

High-risk resistance types: bacteria with specific resistance properties relevant for this commission, for which there is now an explicit need of effective antibiotics.

Market protection: If a product has market protection, other companies are not permitted to start selling a corresponding generic product. As a rule this period is 10 or 11 years after approval nationally or by the European Medicines Agency.

Pull mechanisms: Compensation provided to reward companies for development of a product, aims to stimulate research in late development phases in order to ensure that the product is launched in the market.

Push mechanisms: Support for research within applicable area, for example, research grants or research subsidised in another manner.

In-patient antibiotics: Antibiotics which are procured and funded by medical care and which will later be used by health and medical care.

Stewardship: Coordinated initiatives aimed at measuring and reporting the opportunity to improve appropriate use of antibiotics through optimal antibiotics treatment including dosage, treatment duration and administration route.

Summary

Antibiotics are used in a relatively restrictive way in Sweden compared to many other countries. Consequently, some products face such low demand that there is a risk that pharmaceutical companies do not choose to have them available in the Swedish market. Availability problems arise when new products are not launched in the Swedish market and when existing products are withdrawn from Sweden.

The Public Health Agency of Sweden has in collaboration with the Dental and Pharmaceutical Benefits Agency of Sweden (TLV) put forward models to ensure the availability of antibiotics of special medical value:

- 1. Model for defining antibiotics of special medical value.** The model defines, prioritises and categorises antibiotics that are considered to be of special medical value with risk of insufficient availability. The value assessment is partly based on its activity against the identified high-risk resistance types and partly on its importance to Swedish medical care. We propose that the results should be re-evaluated and updated every, or every second year.
- 2. Economic compensation models.** For new antibiotics with market protection with low expected sales, we propose a model where a certain annual revenue to the pharmaceutical company is guaranteed from the national level. County councils and regions continue to pay for their usage. If the revenue of companies from county councils and regions is lower than the guaranteed revenue, the difference will be paid as agreed. For old prescription antibiotics without market protection, we instead propose that TLV, when assessing applications for price increases for these products, takes into account the relationship between the risk that a product is withdrawn from the market and a low sales value. For old in-patient antibiotics, we propose no new economic compensation model.
- 3. Models for storage and distribution methods.** Since we propose a guaranteed compensation for new antibiotics with market protection, the company's obligations and commitments need to be specified in an agreement. If the public sector is the payer, the issue of government subsidies also needs to be investigated in consultation with the Ministry of Enterprise and Innovation. For the in-patient antibiotics, we propose that a certain volume and security stock should be committed in the procurement. For prescription antibiotics, we do not propose any changes to today's handling procedures.
- 4. Models for rational use and monitoring.** Since Sweden already has a relatively good structure of rational use and monitoring, we propose that these models should be used in the same way as today.

We propose a pilot study to evaluate whether the models can ensure availability of new antibiotics with market protection that are considered to be of special medical value. This study could also show if it is feasible to implement the proposed model in the long term and how responsibility should be allocated to manage these antibiotics in the most efficient way.

Background

Antibiotic resistance is a major and increasing problem, both globally and in Sweden, and there is a strong correlation between usage of antibiotics and the development of antibiotic resistance. Antibiotics can be considered as a finite resource and few new antibiotic classes are being developed. This means that the antibiotics which exist must be used in a responsible manner and that there should be availability of both new and old antibiotics of special medical value.

This report focuses on new and old antibiotics of special medical value and where the availability nationally risks being insufficient. In the report the term antibiotics of special medical value is used to designate them. In the commission (S2015/05372/FS (delvis)) these are specified as essential antibiotics. We have chosen to deviate from this designation as it can be confused with WHO's definition and criteria for essential medicines, which includes more parameters than those we refer to, for example global disease prevalence and cost-efficiency.

Sweden still has a relatively favourable position compared to many other countries, but statistics show that the number of infection cases with very difficult to treat multi-resistant bacteria is increasing, and for these patients availability of a specific antibiotic may be crucial for the outcome. However, sometimes economic incentives and logistical conditions for providing these in the Swedish market are lacking, which may jeopardise optimal treatment. Thus, secure availability of these medically important antibiotics is required, both now and in the future.

In collaboration with the Dental and Pharmaceutical Benefits Agency (TLV), the Public Health Agency of Sweden has been commissioned by the Government to propose one or several models for making available both new antibiotics and old antibiotics where national availability is insufficient. This should be done in a manner which minimises the risk of resistance development while enabling the best possible care for patients with infections caused by multi-resistant bacteria.

The commission (S2015/05372/FS (delvis)) specifies the following interim goals:

1. "Develop a model for continuous monitoring of needs and future access for specifying which antibiotics are relevant and should be included in the model.
2. Prepare supporting material, including economic compensation models, in order to ensure availability of essential antibiotics.
3. Identify need of and develop models for storage and distribution methods which ensure availability of essential antibiotics.
4. Develop models for responsible use of new and old essential antibiotics.
5. Develop systems for monitoring consumption of the antibiotics which are included in the models.
6. Develop systems for monitoring of effects of the proposed models and their evaluation."

The project is also included as an activity in the National Pharmaceutical Strategy (NPS).

The commission entails ensuring availability of antibiotics of special medical value. The Public Health Agency of Sweden and TLV, hereinafter referred to as the agencies, have interpreted the concept availability as ensuring that antibiotics of special medical value are available for Swedish health and medical care, irrespective of whether they are new in the market or have existed for a long time. Thus, the commission does not focus on models for increasing incentives for research which enable production of new antibiotics. However, the agencies see the importance of the international work which focuses on facilitating production of new antibiotics, and assesses that it should continue in parallel to this work on ensuring availability of already approved antibiotics.

Drive-AB is an international initiative between the EU, European Federation of Pharmaceutical Industries and Associations (EFPIA) and Innovative Medicines Initiative (IMI). The project aims to promote development of new antibiotics. Their proposals for models differ depending on whether it entails promoting innovation and research, referred to as “push models” or whether it entails promoting the latter part of the development phase, referred to as “pull” models. Their report will be published at the end of 2017.

In Sweden the Swedish Research Council has been commissioned to establish a ten-year national research programme which should promote research of new antibiotics and increase knowledge of how resistance can be combatted. The Public Health Agency of Sweden has also been commissioned again to support international work concerning antibiotics resistance, for example, through WHO’s Global Antimicrobial Resistance Surveillance System (GLASS).

By means of a specific Government commission (S2015/05372/FS (delvis)), the agencies have also been commissioned to conduct a pilot study on the conditions for testing a compensation model in practice which has been developed by the Swedish Association of the Pharmaceutical Industry (LIF). This commission was reported to the Government on 1 December 2016 and in the report the agencies proposed waiting with a potential pilot study until final reporting of this commission takes place.

In the following chapters respective interim goals are summarised, in accordance with the specification in the Government commission. The report concludes with an overall assessment and discussion on continued work.

For interim goals 1–5, there are separate interim reports with detailed description and analysis, in Swedish.

Interim goal 1: Define and evaluate antibiotics with a risk of availability problems

The Public Health Agency of Sweden has been commissioned to develop a model for analysing all marketed antibiotic products in Sweden at present with respect to their medical value. The analysis is partly based on activity against the identified high-risk resistance types and partly on its importance within Swedish medical care. It also takes into account the risk of insufficient availability. Antibiotics can be deemed to have special medical value, partly for the individual patient or patient group, partly from a disease control perspective, but also from a social perspective with the aim of curbing the development of resistance.

Interim report 1 (in Swedish) contains a detailed account of the proposed model and an application for 2017.

Proposed model for identifying high-risk resistance

The proposed model is based on an analysis of the resistance situation in both Sweden and globally for identifying the resistance types which are deemed to have a high risk of lacking effective treatment and where it is consequently particularly important to ensure availability of effective antibiotics. In order to assess and foresee the situation in Sweden, analysis of data is required for prevalence and trends from published reports as well as national and international monitoring systems.

The resistance types which have been identified are assessed and prioritised based on the trend for each resistance type in Sweden, the different treatment options and needs and what impact each resistance type has on current health and medical care resources. In an assessment of availability for 2017, the following high-risk resistance types were identified; ESBL-CARBA, multi-resistant *Pseudomonas* and multi-resistant *Acinetobacter*, for more information on the assessment, see interim report 1 (in Swedish).

Proposed model in order to define risk of insufficient availability as well as define, prioritise and categorise antibiotics of special medical value

Define the risk

Available antibiotics as well as licence drugs are analysed based on the risk of insufficient availability, which we have chosen to define as follows:

- 1–2 market authorisation holders (MAH), excluding parallel imports, and
- annual sales value below SEK 4 million, and/or

- known shortages with medical consequences, and/or
- licence drugs.

Assessment of medical value

Antibiotics, for which availability risks being insufficient, are assessed and prioritised with respect to special medical value, based on for example activity profile, available treatment options, place in the therapy, ecological profile and specific strength or formulation of importance for specific patient groups. This assessment is performed by the Public Health Agency of Sweden in consultation with reference groups and selected experts.

Categorise for measures

Antibiotics of special medical value with availability problems are divided into different categories based on the need of specific measures. These measures may, for example, be economic compensation models or recommendations for security stock. The Public Health Agency of Sweden decides which or how many products should be categorised for specific measures.

Assessment

It is not possible to exactly predict which antibiotic products are in the risk zone of insufficient availability in Sweden. We have focused on products which last year were marketed by maximum two companies and which have an annual sales value below SEK 4 million. Parallel imported drugs are excluded as they often have a very uncertain delivery reliability. We assess that in cases where there are many pharmaceutical companies with market authorisation (i.e. large generic competition), the product is deemed to be profitable and therefore there has a smaller risk of availability problems. The assessment also takes into account sales and the number of generics in other European countries.

Our assessment is based on the levels: substance, formulation and strength. In many cases different packaging sizes of the same strength are marketed, which is often governed by applicable treatment recommendations, but we chose not to address this level of detail. If there is a shortage of a specific packaging size, this can often be solved. However, the need of specific packaging sizes should be taken into account during price adjustment considerations. It was revealed that oral suspensions or low strengths, which are intended for, for example, children, often have a high risk of insufficient availability in accordance with the model's parameters.

We have chosen to categorise antibiotics in the following manner based on different measures which are suitable for ensuring availability:

- New antibiotics with market protection

- In-patient antibiotics without market protection: old antibiotics which are procured and funded by medical care
- Prescription antibiotics without market protection: old antibiotics which are prescribed and then collected by the patient at an outpatient pharmacy
- Critical rare antibiotics: in-patient or prescription antibiotics which are so important that a shortage can have severe consequences for the individual and society, mainly applies to infectious disease medications (for example, antibiotics for treatment of tuberculosis)
- Licence antibiotics: antibiotics which are not approved in Sweden and which are prescribed on licence.

These categories are used for recommendation of compensation models as well as models for storage and distribution methods.

The assessment of future availability is further impeded by the continuous registration and deregistration of antibiotics, so the current number of MAHs can change quickly. The assessment and prioritisation of special medical value can also change depending on introduction of new antibiotics, changes to the resistance situation and updated treatment recommendations. We therefore propose that the analysis, which is based on data of the previous year, is updated regularly at least every other year.

Interim goal 2:

Economic compensation models

The risk of insufficient availability of antibiotics is often cited as resulting from low profitability for companies to maintain the products in the market. As an interim goal in this commission, we have therefore investigated possible compensation models in order to ensure availability of the antibiotics of special medical value which are specified in interim goal 1. Detailed analysis of compensation models, in Swedish, is contained in interim report 2.

Proposed models

New antibiotics with market protection

For new antibiotics of special medical value to be marketed in Sweden, despite low expected usage, a model is proposed in which pharmaceutical companies are guaranteed compensation irrespective of the size of consumption. The model aims to ensure a certain level of revenue for the companies to maintain the product in the Swedish market. We propose that this type of compensation model is tested in a pilot study for one or several products.

The compensation model means that the company is guaranteed a certain level of revenue in exchange for them in agreements guaranteeing to maintain a certain volume of the product. The guaranteed compensation can either be paid by the State or through agreements jointly by the State, county councils and regions. County councils and regions pay for their usage as usual. After each year the difference between the guaranteed compensation and the company's actual revenue from the usage is paid as agreed. The compensation model enables different parties to share the payment: the State and/or county councils/regions jointly pay for ensuring availability while each county council/region pays in proportion to the usage as it currently does.

The size of the guaranteed compensation is determined by defining the volume of antibiotics which needs to be available. The annual guaranteed compensation should correspond to the cost if the public sector was to purchase this security stock at market price.

The antibiotics which have recently been approved or are in a late development phase with activity towards defined high-resistance types are in-patient products. At present legislative support for conducting the intended pilot study for prescription antibiotics is lacking.

In-patient antibiotics without market protection

Antibiotics which are ordered for use within medical care or clinics are usually procured by county councils and regions, jointly or individually. As county councils and regions are responsible for health and medical care and accordingly

negotiate the prices, we believe that a national recommendation on economic compensation is irrelevant.

Prescription antibiotics without market protection

For old antibiotics of special medical value which are prescribed, we do not propose any new compensation model. Still the companies' revenue should come completely from payment per used package made by the patients and county councils.

An analysis which we performed shows that there is a relationship between the risk of a product disappearing and a low sales value. A low sales value can thus in general be an important indicator for the product risking to disappear from the market. Therefore, TLV will consider this aspect for applications on price increases for such antibiotics which the Public Health Agency of Sweden has assessed are of special medical value. However, it is important to state that a low sales value can never alone constitute a reason for price increase.

Critical rare antibiotics

Critical rare antibiotics can comprise both in-patient and prescription antibiotics. The recommendation on economic compensation model depends on the categorisation and follows the same structure as above.

Licence antibiotics

No specific compensation models are relevant for the category licence antibiotics.

Assessment

We assess that economic compensation models are an important part of the structure for ensuring availability of antibiotics of special medical value. There are several different problems of availability of different categories of antibiotics, and therefore we have assessed that several different models are required. A guaranteed compensation is, for example, not practically feasible for the products which are generic as compensation cannot be paid to individual companies without impacting competition in the market.

For new antibiotics with market protection, we propose a model which ensures a specific guaranteed compensation, irrespective of sales. The guaranteed annual compensation should correspond to a level which ensures availability in Sweden, even when the resistance situation has changed. In this manner a major sale entails that the security level has been attained, that companies have received at least the guaranteed compensation and that availability has been satisfied.

Interim goal 3:

Storage and distribution methods

The third interim goal aims to identify the need of and develop models for storage and distribution methods which ensure availability of antibiotics of special medical value. Availability problems related to storage or distribution channels may be temporary and the result of small stocks with the supplier, wholesalers or hospitals. They may also be the result of county councils finding it difficult to procure small quantities.

Availability problems for the antibiotics referred to in this investigation are largely the result of low usage and that county councils and regions generally do not procure drugs which are used to a small degree or which generate small costs. As a rule county councils and regions do not make any volume commitments for procurement of drugs, that is, they do not commit to purchase a certain volume. Consequently it becomes difficult for companies to plan their production and in the long run the risk of shortages increases if demand increases quickly.

In this project we have identified and evaluated a number of different models for storage and distribution, as a part of ensuring availability of antibiotics of special medical value. Interim report 3, in Swedish, provides a detailed account of all models, together with other relevant investigations related to the supply of drugs.

Proposed models for storage and distribution methods

The basis for models for storage and distribution methods has been that the models should:

- impact the rest of the pharmaceutical market as little as possible
- build on existing distribution channels and systems
- be based on the existing division of responsibility for health and medical care.

The developed models may differ based on the assessed need of specific measures, which is based on the five categories proposed in interim goal 1.

New antibiotics with market protection

Under interim goal 2, proposals were presented for a guaranteed compensation for the antibiotics which fall under the category new antibiotics with market protection. Then the State and/or county councils/regions jointly compensate the difference between the guaranteed annual compensation level and the company's actual sales revenue from the county councils purchasing the drug and paying per used package.

As consideration for the compensation, the pharmaceutical company should commit to a number of commitments which aim to ensure availability of the antibiotic in the Swedish market. The commitments are regulated in an agreement

between pharmaceutical companies and national level. Examples of commitments could include that the pharmaceutical company should maintain a stock in Sweden, that the stock should be large enough to minimise the risk of shortage even if demand were to increase markedly, that the company should be able to deliver to medical care within 24 hours and that the company should apply for longer shelf life within the approval when study results support this. The pharmaceutical company should also commit to keep the stock sellable, that is, replace products if the shelf life is about to elapse, and to regularly provide reports on the stock status and sales.

In order to ensure availability of new antibiotics with market protection to medical care, county councils and regions are advised to keep a certain volume in the relevant clinics. The volume depends on how important it is to quickly be able to start treatment and how many individuals are expected to require treatment simultaneously. County councils then order the drugs as usual, either based on the framework agreements in which they are a contracting party or on their negotiated prices, depending on how the compensation models are structured. At the end of the year, the difference is calculated for the pharmaceutical company to reach the annual guaranteed revenue.

In-patient antibiotics without market protection

In order to ensure availability of in-patient antibiotics, the amount of drugs in the supply chain primarily needs to increase. There should preferably be stocks at several levels in the supply chain as safety or a buffer in order to handle sudden increases in demand or unexpected shortages (delivery problems).

Therefore, for this category we recommend that county councils and regions procure these antibiotics with direct purchases which correspond to a number of months of sales, alternatively order a buffer if they do not procure. The buffer makes it easier to handle unexpected delivery problems or sudden increases in demand.

The number of months for direct purchases or orders must be calculated based on normal consumption and previous availability and how serious an out-of-stock situation is deemed to be. The buffer may be available in several levels: at clinics, at hospital pharmacies or region stocks.

Prescription antibiotics without market protection

Pharmacies should supply outpatient drugs within 24 hours of the consumer requesting it. This is regulated in the Act on trade with pharmaceuticals (2009:366).

Proposals for clearer regulation on storage have been made in a previous pharmacy inquiry (SOU 2012:75 page 540). If no such regulation is performed, we see a risk of medical care having to increase the use of emergency doses in order to ensure that patients can start their treatment, even if direct fulfilment cannot take place.

Critical rare antibiotics

In order to ensure availability of critical rare antibiotics, it is recommended that the county councils and regions procure these antibiotics with direct purchases for storage at the clinics which are responsible for the treatment. The treatment can then be provided as emergency doses by treating doctors at the clinic, which would ensure that patients can complete their treatment without a break.

Licence antibiotics

We propose that these antibiotics are assigned a special priority in the Medical Products Agency's assessment for upcoming licence applications and registration applications in order to ensure that clinics can obtain the antibiotics easily when necessary. It would be preferable if products which have been prescribed on licence for many years and prioritised highly in the developed model, for example, pyrazinamide, which is a part of recommended standard treatment for tuberculosis, could be offered a simple registration procedure.

Assessment

A part of the project has entailed evaluating practical and legal conditions for introducing new models and structures. The work shows that certain models could demand a change in the law or shifting of responsibility from county councils and regions to the State. The models we propose do not require any change in the law, but may entail some shifting of responsibility. However, there are other legal aspects which must be investigated further if new models are introduced. Interim report 3 describes the conditions for, among other things, government subsidies and different agreements (the Public Procurement Act, agreements between county councils and the State).

It should be possible to distribute and store antibiotics of special medical value in accordance with existing procedures for pharmaceutical logistics, irrespective of which model is selected for ensuring availability. However, precisely how storage and distribution should function and who is responsible for what may need to be regulated in agreements with the relevant company. The agreement should also contain requirements for the company to guarantee availability, which covers delivery reliability, distribution, storage, lead times to delivery and restocking, etc.

Some antibiotics have a very low estimated usage in in-patient care and for them a small volume should be available at, for example, county hospitals and/or university hospitals. This volume must be determined from case to case, but it should always cover the recommended dosage of an estimated number of patients over a specific number of days. It should be possible to restock for these hospitals within the agreed duration, for example, 24 hours. It should also be possible to receive quick deliveries in the case of emergency needs.

Interim goal 4:

Responsible usage

The fourth interim target in the commission was to develop models for responsible usage of new and old antibiotics of special medical value. Responsible antibiotics usage refers to right provision of antibiotics to the right patient, at the right time and with the right dose, and this is an important part of the work for reducing the development of antibiotic resistance. Sweden has good and restrictive use of antibiotics in comparison to other countries in Europe and globally.

Since the mid-1990s in Sweden there have been many activities and commissions, both at a local and national level, in order to have continued responsible usage. Examples of this are the local Strama groups, Programme Council Strama, national treatment recommendations, national action plan for agencies and national strategy for the work against antibiotic resistance.

The literature describes different effective work procedures and methods for improving antibiotic usage within both outpatient and in-patient care. Different forms of stewardship and antibiotic rounds with infection specialists have been described as effective methods, both in Sweden and internationally.

The project group has evaluated different proposals for models with responsible usage for antibiotics of special medical value. Detailed analysis of the models is contained in interim report 4 (in Swedish).

Assessment

The agencies assess that there should be regularly updated treatment recommendations for infections in both outpatient and in-patient care at national level. Regularly means that treatment recommendations always need to be monitored and updated if necessary. A national player can preferably receive this commission.

We also assess that it is important to retain the existing structures for implementation of treatment recommendations through, among other things, Strama groups and local pharmaceutical committees. *New antibiotics with market protection* should only be prescribed in consultation with an infection specialist. The request should be a part of national and regional treatment recommendations. For the rest, we propose that current models should continue to be used in the same way as today.

Interim goal 5:

Monitoring of antibiotic consumption

The Public Health Agency of Sweden should collect, analyse and actively convey knowledge on issues related to antibiotic resistance and promote initiatives at a local and regional level on issues related to rational antibiotic usage and antibiotic resistance. This is stipulated in the ordinance with instructions for the Public Health Agency of Sweden (SFS 2013:1020).

As a part of this, the Public Health Agency of Sweden develops statistics on antibiotic usage by analysing pharmaceutical statistics which are based on the sale of pharmacies and data on sale to in-patient and outpatient care.

In this commission, the Public Health Agency of Sweden should develop systems for monitoring consumption of the antibiotics which are a part of the models in interim goals 1–3. Detailed analysis of different systems and structures is contained in interim report 4 (in Swedish).

Assessment

The Public Health Agency of Sweden should annually specifically monitor the sale of antibiotic products which are the subject of measures in accordance with proposals in this report, as a part of the ongoing work on monitoring antibiotic consumption in Sweden. The monitoring can then follow the agency's existing work method and take place based on, among other things, the Swedish eHealth Agency's sales statistics.

When the Infection Tool is available for national compilations, it will be an important supplement which should be used in the monitoring. Then antibiotic usage can be analysed in relation to the patient's diagnosis. If the Public Health Agency of Sweden detects a significant increase in sale without a reasonable explanation, the agency should conduct detailed studies concerning this.

In the event of a pilot study, we propose that usage of the antibiotics which have received guaranteed compensation is monitored in more detail, for example, with an examination of medical records or by using a questionnaire for the clinics which have used these antibiotics.

Interim goal 6: Monitoring and evaluation of proposed models

We propose a pilot study of mainly the models for economic compensation as well as storage and distribution methods, in order to monitor that the proposed models ensure availability of antibiotics of special medical value.

We assess that new antibiotics with market protection are relevant for a pilot study. The study can be conducted for one or several antibiotics.

The following parameters should be monitored and evaluated after the study:

- Security level. Has the security level defined for ensuring minimum available volume been sufficient enough to ensure availability of antibiotics of special medical value?
- Unit price. Has the unit price used in the calculations of the guaranteed compensation been consistent with the price in other European countries? If not, how large was the deviation and what caused it?
- Delivery problems. Have there been delivery problems for these antibiotics despite implementation of the models?
- Usage. What was the actual usage of these antibiotics?

For old antibiotics without market protection, we propose that the occurrence of out-of-stock situations is monitored using information from the MPA and Apoteket's website on out-of-stock notes¹. If the monitoring shows that availability continues to be insufficient, it should be evaluated if other measures are required.

We also propose that all parameters which have been used for the definition of antibiotics of special medical value are monitored and evaluated. The purpose is to ensure that the definition includes the important antibiotics which risk facing availability shortages. As a suggestion this can be done by assessing how health and medical care have been impacted by antibiotic shortages which have *not* been defined as having special medical value and how these medicines could be assessed in an evaluation in accordance with the proposed model.

If the monitoring shows that a recommendation has not resulted in improved availability in medical care, other more governing regulation can be considered, such as regulations or ultimately in laws and ordinances.

¹ <https://www.apoteket.se/vard-foretag/lakemedel/restnoteringar/>

Discussion

The resistance levels in Sweden are relatively low compared to many other countries. We also have a restrictive antibiotic policy focusing on only treating when antibiotics are probably beneficial and not using strong antibiotics unnecessarily. This and the fact that Sweden is a small country, may entail that Sweden is not a particularly attractive market when it comes to registering or making certain antibiotics available, which can result in shortages. However, it is difficult to predict which antibiotics are in the risk zone of insufficient availability as it depends on which resistance types appear in Sweden and how the resistance situation will be in the future.

National models can increase availability

In order to increase the opportunity of having the most appropriate antibiotics for the purpose for relevant patients, national models are required to ensure availability. Structures which increase the probability of pharmaceutical companies providing antibiotics of special medical value in the Swedish market should therefore be implemented. We propose economic compensation models which aim to increase the economic incentives for providing products in Sweden, for example, through guaranteed compensation or through the opportunity of a higher price. We also propose different models for storage, for example, by procurement with volume commitments or having greater security margins in stock.

Research needs stronger incentives

A number of international initiatives highlight insufficient availability of functioning treatment for infections where the resistance situation becomes increasingly critical. Several of them highlight that incentives for research are too weak, first and foremost considering that usage of new antibiotics is only recommended to a small degree. Consequently, the return on invested capital is expected to be relatively low compared to the potential return for drugs within other therapy areas. Work on identifying new models for increasing incentives for research is mainly conducted at an international level, among others by, Drive-AB.

This commission mainly aims to ensure availability of antibiotics of special medical value. However, the model for new antibiotics with market protection can indirectly also stimulate research in late development phases by guaranteeing a certain level of revenue for the companies which introduce a new antibiotic to the Swedish market.

In October 2017 the Government assigned a new commission to the Public Health Agency of Sweden to provide proposals for measures which can be taken by Swedish players with the aim of contributing to progress in the work on incentive models for promoting the development of new antibiotics. TLV and the Swedish Governmental Agency for Innovation Systems (VINNOVA) will contribute to implementation of the commission.

Previous model proposals have not been tested

Previously LIF proposed a compensation model which will ensure availability of antibiotics of special medical value in Sweden. The model aims to calculate the social value of new antibiotics when no other treatment options are available. In a specific commission (S2015/05372/FS (delvis)) the Public Health Agency of Sweden and TLV was commissioned to evaluate that model, but chose not to test LIF's proposal for compensation model with the design at that time as the legal and financial conditions for a pilot study were considered to be weak or missing completely. In this commission we have evaluated several different models for ensuring availability of antibiotics of special medical value and there is an overall assessment below.

Overall assessment

In this commission we consider availability as health and medical care in Sweden having access to the antibiotics required for providing the best possible treatment to patients with infections. In the first instance, models are required for ensuring that new antibiotics are launched in the Swedish market after approval, and that old antibiotics deemed to be particularly important in terms of availability are not deregistered or made unavailable in another manner. This can be equated to the models which Drive-AB has defined as pull mechanisms.

National availability most important

We assess that Sweden in the first instance must ensure availability of both new and old antibiotics at a national level. This by implementing the models for economic compensation or storage and distribution proposed in this investigation.

In terms of greater incentives for research and development of new antibiotics, this has not been investigated within the commission. However, we assess that continued international work for increasing incentives for research and development is important for promoting the development and ensuring availability of antibiotics in the future as well.

Furthermore, we assess that county councils and regions should be involved in the work for ensuring that they have the support which they require in order to ensure regional availability as well.

For new antibiotics with market protection, we propose a guaranteed compensation which can be paid by the State or through agreements by the State, county councils and regions jointly. This means that the company's obligations and commitments need to be regulated in agreements. It is important to investigate thoroughly whether models for guaranteed compensation are deemed to be government subsidies before the models can fully be implemented. This investigation should be conducted together with the Ministry of Enterprise and Innovation.

Model for guaranteed compensation needs to be tested

We propose a pilot study of the model for guaranteed compensation to new antibiotics with market protection, with one or several products. The purpose of the study is to:

- evaluate how the models ensure availability of these antibiotics,
- ensure that it is possible to implement the model in a more long-term manner,
- evaluate that the proposed division of responsibility results in efficient logistical handling of these antibiotics.

The Public Health Agency of Sweden and TLV have investigated different models for ensuring availability of antibiotics of special medical value in Sweden. Different models for the definition of antibiotics, potential economic compensation models, models for storage and distribution as well as models for rational usage and monitoring have been identified and analysed. The report proposes that a pilot study should be conducted to test the models which are recommended in the investigation. It is proposed that the study starts immediately.

The report has been produced as a part of the Government commission of the agencies for ensuring availability of antibiotics of special medical value. The commission was reported to the Ministry of Health and Social Affairs on 1 December 2017.

The Public Health Agency of Sweden is a national expert authority working to improve public health. The agency achieves this by developing and supporting society's work to promote health, prevent illness and protect against various forms of health threats.

Our aim is to achieve a level of public health which strengthens society's development.



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