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Health Reform Monitor

The Swedish model for prioritising research on the use of antibiotics: Aligning public funding with research gaps

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ABSTRACT

Due to the meagre development of new antibiotics, optimising the use of currently available antibiotics is important to reduce resistance pressures and to safeguard existing treatment options. The Public Health Agency of Sweden (PHAS) was tasked in 2014 to (1) develop a model for identifying and prioritising research gaps and (2) initiate studies to improve knowledge on how to optimise the use of existing antibiotics. A survey addressing knowledge-gaps and suggesting studies needed was distributed to a broad network of Swedish and European clinicians and experts. An independent reference group prioritised the proposals, applying predefined criteria focusing on public health relevance. The PHAS sponsored and led two multi-centre RCTs in cooperation with clinical researchers and took part in additional studies. A second survey and prioritization exercise following the same model was performed in 2019. The Swedish case study described in this paper provides an example of the role that the public sector can play in order to support the improved use of existing antibiotics. National and international institutions are well suited to perform systematic reviews of research priorities with a focus on public health concerns. The ultimate success of the model depends on political engagement, a close dialogue with healthcare professionals, collaboration between international sister-authorities responsible for public health in other countries, the availability of research funding, harmonisation of regulatory issues and regular revisions of clinical guidelines. The experience from the Swedish model illustrates opportunities for meeting clinical needs and filling knowledge gaps on existing off-patent antibiotics.

1. Purpose of the policy

The main objective of this policy initiative was to find a successful model in which to invest public funding and engagement for gaining increased knowledge on how to optimise the use of existing antibiotics. The aim was to yield important and relevant information to clinicians, healthcare, policy makers and research funders, about the most significant knowledge gaps regarding antibiotic use. Ultimately, this approach aim for decreased resistance development pressure through improved use of current antibiotics, at the same time as negative side effects for patients and costs for society are reduced.

2. Political and economic background

The development of new antibiotics has declined while antibiotic resistance has continued to increase. Therefore, there is a need to optimise the use of currently available antibiotics in order to preserve newer antibiotics and to slow down development of resistance. In order to optimise use, evidence generation is required, which should thereafter be formalised and integrated into clinical practice. In the 2009 the European Council Conclusions on innovative incentives for effective antibiotics, all EU member states were urged to "ensure the development and use of integrated strategies to diminish the development and spread of antibiotic resistance" [1]. This was reaffirmed and further highlighted in the European Council Conclusion 2016 on the next steps under a One Health approach to combat antimicrobial resistance [2] as well as in the 68th World Health Assembly resolution adopting the Global action plan on antimicrobial resistance [3]. Sweden, with its long tradition of work against antibiotic resistance [4] launched its first national action plan in 2000. The political support has been significant, and in 2006 the Swedish Parliament adopted the proposition concerning cross-sectional work against antimicrobial resistance, which was formed into the Swedish Strategy to Combat Antibiotic Resistance in 2016 (updated 2020) [5]. The fundamental pillars in the strategy are 1) surveillance 2)

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prevention 3) responsible use of antibiotics 4) increased knowledge 5) improved awareness in society 6) supporting structures and systems, and 7) international leadership. In 2012, the Intersectoral coordinating mechanism against antibiotic resistance was established, jointly chaired by the Public Health Agency of Sweden (PHAS) and the Swedish Board of Agriculture, developing its multi-stakeholder action plan based on the pillars of the national strategy [6, 7]. In parallel with these activities, work was underway to form a National Pharmaceutical Strategy (NPS). The first NPS with its vision "Rational Use of Medicines to the Benefit of Patient and Society, was launched in 2011 [8]. This collaboration is led by the Ministry of Health and Social Affairs in cooperation with around 30 agencies and organizations. Finally, another important initiative is the National Research Programme within Antibiotic Resistance established by The Swedish Research Council on behalf of the government in 2019 [9].

A fundamental tool in Swedish antibiotic stewardship is the use of treatment guidelines, which requires regular revisions based on solid scientific data. Many of our widely used antibiotics were registered decades ago when the regulatory requirements were less stringent and knowledge for estimating optimal dose regimens was limited. Studies to fill such knowledge gaps are generally not driven by marketing considerations, since incentives for the pharmaceutical industry are too low to further develop off-patent medicinal products. Academic investigator-initiated studies in the area are often underfinanced and thus small and underpowered. Shorter treatment duration and improved dose regimens are often discussed and proposed as a means to slow down resistance development, but conclusive studies influencing clinical practice are scarce [10]. Thus, there is an obvious potential for enhanced engagement by society to support needs-driven studies to gain more knowledge on how to improve the use of established antibiotics. Another challenge for optimal antibiotic use is the fragile supply chains leading to frequent shortages. Clinical studies leading to internationally harmonised dosage regimens/packaging may lessen the burden of supply chains and at least partially contribute to a more reliable access to essential antibiotics [11].

3. Health policy processes

The first initiative to studies on optimisation of antibiotic use originated from the Swedish strategic programme against antibiotic resistance (Strama) [12, 13]. In 2003, Strama started discussions about building a national antibiotic clinical trial centre. A multi-centre randomised controlled trial (RCT), was performed by Strama in 2006–2008 which demonstrated that acute pyelonephritis in women can be successfully treated with 7 days of ciprofloxacin instead of the formerly recommended 10–14 days [14]. This meant that fluoroquinolone use could be decreased, and development of resistance could potentially be slowed down. The results from this study led to a change in the treatment guidelines for acute pyelonephritis in Sweden and later also in the EU. In 2010, the national Strama was incorporated in The Swedish Institute for Communicable Disease Control, which later was transformed into The Public Health Agency of Sweden (PHAS), which continued the close cooperation with health care. In 2013, the need for filling knowledge-gaps within the field of clinical antibiotic use was incorporated in the NPS. Subsequently, in 2014, the Swedish government commissioned the PHAS to evaluate existing antibiotics from new treatment perspectives. The aim was to investigate clinical needs and subsequently initiate studies to improve knowledge on how to optimise the use of existing antibiotics and, in the long run, to improve clinical practice. In order to assure mutual understanding of the commission and its expected effects, the PHAS invited representatives from several stakeholders, amongst which the trade association for the research-based pharmaceutical industry in Sweden (LIF).

4. Content of reform

After a mapping exercise and pilot test, a web-based survey was distributed to a broad network of Swedish and European clinicians, researchers, experts, and key stakeholders. The respondents were asked to list important knowledge gaps in the clinical use of existing antibiotics and to suggest appropriate studies to fill the identified gaps. The respondents could also inform about ongoing initiatives or studies as well as relevant publications in the field. The survey was sent to 255 experts and clinicians in Sweden as well as to 30 international experts. The PHAS published the survey on its website to maximise its reach and the recipients were also encouraged to pass it on to interested colleagues. Internationally, the enquiry was shared with infectious diseases societies of all the Nordic countries, relevant study groups within The European Society of Clinical Microbiology and Infectious Diseases (ESCMID), The European Centre for Disease Prevention and Control (ECDC), The European Medicines Agency (EMA) and The World Health Organisation (WHO). A process diagram of the model is shown in Fig. 1.

4.1. Structured prioritisation method

The design of the web-based survey and defined prioritisation criteria were based on previously published criteria [7, 15] of relevance to the project, Table 1. These criteria were used to prioritise incoming proposals and to identify the most urgent knowledge gaps in order to conclude which studies the PHAS should initiate. The PHAS sorted the incoming proposals into the following four main categories and assessed them separately: 1) Hospital care, including intensive care; 2) Outpatient care, including nursing homes and dental care; 3) in vitro studies, including PK/PD, *in silico*; and 4) register-based studies. The intention of the PHAS was to initiate or support studies within each of these categories. In order to get input from healthcare professionals and to support the PHAS in the assessment and prioritisation of the received proposals, an external independent reference group was formed, nominated by several departments of The Swedish Societies of Medicine and Dentistry. All participants submitted declaration of interest. The reference group participated in a workshop where all proposals were discussed and prioritised using the structured prioritisation criteria predefined by the PHAS. The final priority list of the reference group strongly guided the PHAS's subsequent decisions. Of importance for the PHAS's final decision of which studies to initiate or support were significance for public health, potential to influence clinical practice, and feasibility to yield conclusive results. Projects that could assess the ecological effect of antibiotics on the intestinal microbiota in order to diminish the spread of resistance were of particular interest. When assessing the priority list of needs-driven studies, the PHAS also considered study designs, cost efficacy, and relevance to the government commission.

4.2. Research activities initiated by the PHAS

Based on the reference group's recommendations the PHAS decided to initiate two multi-centre RCTs within the scope of the government commission. In addition to these clinical studies, the PHAS also participated in, or co-financed additional RCTs, observational-, *in vitro-, in silico-* and register-based studies, prioritised according to the above-described criteria [16–22].

RCT initiation, management and study findings: The PHAS established steering committees for the two RCTs, including external clinical experts and members from the PHAS' project group. One study involved patients treated by general practitioners, and the other study involved hospitalised patients. Study protocols and case report forms were developed internally, the PHAS acted as sponsor and project manager and a contract research organisation performed tasks such as monitoring and data management. Participating hospital clinics and primary health care centres received a symbolic payment for each included patient. The studies were conducted according to current ICH Good Clinical Practice

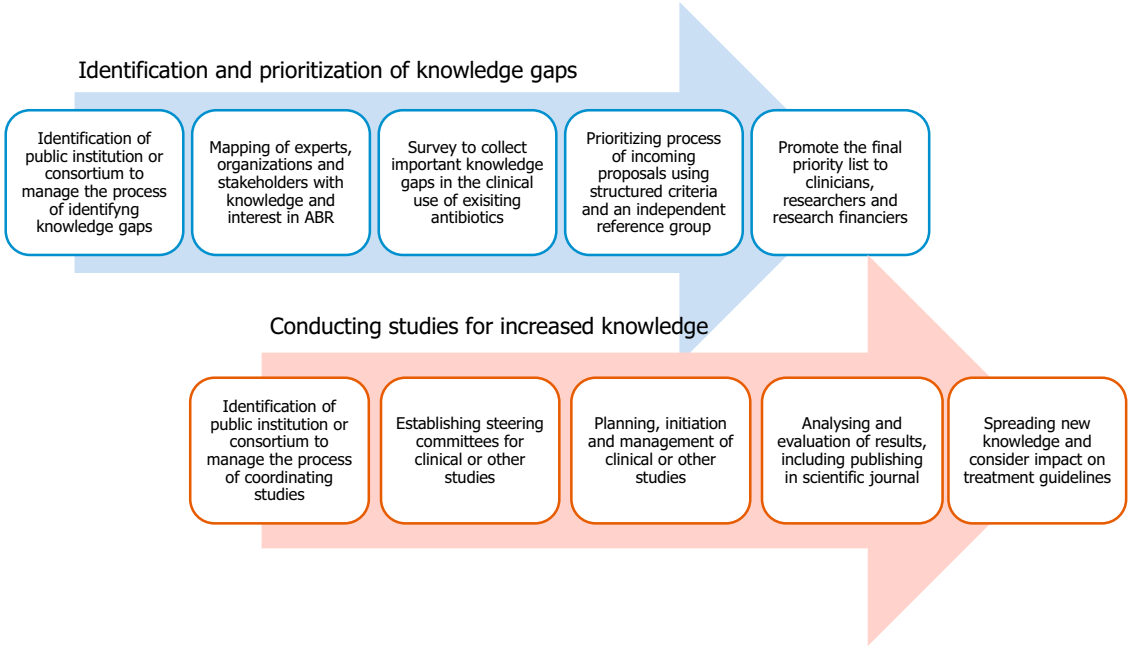

Fig. 1. A process diagram of the Swedish model to use public funding to gain more knowledge on how to optimise the use of off-patent antibiotics, and to influence and improve clinical practice.

Table 1
Prioritisation criteria for incoming proposals following the enquiry concerning knowledge gaps/suggestions of studies on antibiotic use, and possible points.

Type of study	Prioritisation criteria	Points
Clinical studies	Can the study outcome potentially contribute to a more effective and/or safer treatment within 2–5 years?	
	– Yes for a large patient group or for a very vulnerable group of critically ill patients.	0–3
	– Potential to avoid death, serious illness, or permanent disability.	0–1
	– Potential to avoid transient adverse effects.	0–1
	Can the study outcome potentially decrease total antibiotic exposure, i.e. being able to slow down future emergence of resistance (potential ecological benefits and number of affected patients should be taken into consideration)?	0–3
	Is there a risk of a negative impact that this treatment will prolong the time of illness or increase the risk of complications?	0,−1,−2,−3
In vitro studies, animal models, PK/PD	Clinical benefit and importance for public health	0–3
	– Can the outcome of the study potentially give valuable knowledge about PK/PD, dosing regimens, effect of combinations of antibiotics, length of treatment, risk for emergence of resistance, etc., where today's knowledge is severely limited?	
Register studies, patient record audits, literature studies	Clinical benefit and importance for public health	0–3
	– Can the outcome of the study potentially contribute with essential knowledge in line with the current commission?	

and approval standards. Ethical approval for each study was obtained from the Regional Ethical Review Boards. The outpatient RCT compared 5 days to the current 10 days of treatment with penicillin V against pharyngotonsillitis caused by group A streptococci. The study demonstrated non-inferiority with the shorter duration of treatment [23]. These results are in line with similar studies on other indications implying that treatment durations can be shortened, without hampering safety or efficacy [24]. The second RCT included hospitalised patients with febrile urinary tract infection randomised to treatment with either temocillin, a "forgotten" narrow-spectrum antibiotic, or cefotaxime, a commonly used broad-spectrum antibiotic. The main purpose was to find an ecologically beneficial and equally efficient alternative to today's empirical treatment. The findings of the study demonstrated that temocillin treatment resulted in less ecological disturbances in the microbiota compared to treatment with cefotaxime. This study was presented at the European Congress of Clinical Microbiology and Infectious Diseases, July 2021 [25].

4.3. Follow-on activities

In 2019, the PHAS in collaboration with the Platform for Innovation of Existing Antibiotics (PLATINEA) [26] updated the list of knowledge gaps, by inventorying present-day knowledge gaps and needs for scientific studies in the field of antibiotic use. In contrast to the previous survey, it was not initiated by a specific governmental assignment and there was no allocated budget for performing studies. The purpose of the updated list of proposals is to inspire clinical researchers to initiate studies in the priority areas, and to guide research funders when allocating funds and designing calls for proposals for these types of projects. The procedure of identification and prioritisation of the needed studies was performed in line with the inventory in 2014 and according to the structured and transparent process described above. The PHAS published the final updated list consisting of 16 proposals classified as "very urgently needed studies" and 15 proposals as "urgently needed studies" in February 2020 [27], Table 2. In addition to being widely distributed to clinicians and researchers, several Swedish research funders received the priority list with information on which studies the health care community considers to be urgently needed. All in line with the intentions of the NPS, the Swedish Strategy to Combat Antibiotic Resistance and the accompanying action plans.

Table 2
Final priority list from the 2019 inventory.

Clinical area	Knowledge gap	Specific clinical issue to be studied / study proposal	1 = Very urgent 2 = Urgent
Optimised dosage	**The benefit of TDM in clinical practice**	Evaluation of TDM (therapeutic drug monitoring) and individualised antibiotic dose regimens of antibiotics in Swedish hospitals. 1) Feasibility, probability of achieving defined PK/PD (pharmacokinetics/pharmacodynamics) targets, and clinical outcome measures. 2) Clinical trials in seriously ill patients.	1
	Pharmacokinetics in special patient populations	Studies of antibiotic pharmacokinetics in special patient populations at risk for therapy failure (under-dosage) or side effects (over-dosage) with standard therapy, for example, critically ill patients, elderly patients, patients with burn injuries, patients with renal impairment/dialysis, overweight patients, and patients with long-term high-dose treatment (endocarditis/meningitis). Clinical studies and *in silico* studies (based on collected data) in relevant patient populations.	1
	PK/PD targets for patients with atypical kinetics	Studies providing increased knowledge of PK/PD (pharmacokinetics/ pharmacodynamics) relationships for antibiotics to determine relevant PK/PD targets for patients with atypical kinetics with respect to efficacy and risk of resistance development. Preclinical, in vitro and *in silico* studies.	2
	Combinations of antibiotics	Preclinical and clinical studies of which combinations of antibiotics are effective in treating infections caused by multi-resistant gram-negative bacteria, and the development and clinical evaluation of in vitro methods to evaluate synergy and sensitivity to combinations.	2
Urinary tract infections	**Choice of antibiotics**	High-dose pivmecillinam as an alternative to ciprofloxacin in the treatment of febrile UTI, with or without initial intravenous treatment. Safety and efficacy.	1
	Choice of antibiotics	Identify and study oral treatment options for febrile UTI caused by ESBL-producing Enterobacterales.	1
	Choice of antibiotics	How safe and effective is treatment with pivmecillinam or nitrofurantoin in men with afebrile UTI?	1
	Predictive risk of resistance	Risk of resistant bacteria as a cause of febrile UTI in Sweden. Mapping and quantifying. The results may be used to predict which patients require non-standard therapy.	2
	Duration of treatment	Identify groups of women and men with febrile UTI where the duration of treatment can be shortened.	2
Upper respiratory tract infections	**Pharyngotonsillits with negative strep A-test**	Which patients with pharyngotonillitis benefit from penicillin V treatment when strep A test is negative? What is the prevalence of *Fusobacterium necrophorum* for patients with 4/ 4 Centor criteria and a negative strep A test?	1
	Complications of acute media otitis	Continued follow-up of complications of AOM (acute otitis media) to monitor the effect of active expectance of treatment as an alternative for patients with uncomplicated AOM.	1
Inpatient care	**The value of new work procedures**	Evaluation of new work procedures such as antibiotic rounds (prospective audits and feedback), the use of technical devices, and the involvement of additional professional groups to increase rational antibiotic use in Swedish hospitals.	1
	Duration of treatment	Develop methods/indicators to support shorter treatment durations/preliminary stop dates for a more rational use of antibiotics in seriously ill patients.	1
	Ototoxicity of aminoglycoside	Evaluate the risk of ototoxicity in association with aminoglycosides	2
Microbiota	**The effect of antibiotics on the human microbiota**	Clinical studies of antibiotic effects on the microbiota (intestinal, oral, respiratory, and vaginal flora), selection of resistance, and possible significance for outcome and side effects, including older antibiotics. Patients in hospitals, in open care, and healthy volunteers.	1
	The effect of antibiotics on the human microbiota	Is it right to claim that "step-down" from parenteral to oral antibiotics is always desirable from an ecological perspective?	1
	Restore a disrupted microbiota	Clinical studies of methods to restore a disturbed intestinal microbiota, eradicate carriage of resistant genes, and eradicate *Clostridoides difficile* in patients with relapsing *C. difficile* enteritis (e.g. administer probiotics, bacterial cultures, faecal capsules, or faecal transplantation).	1
Diagnostics	**Diagnostics in primary care**	Develop better evidence-based methods for diagnosing the most common treatment-requiring infections in outpatient care.	1
	Rapid, patient-close diagnostic methods	Evaluate the clinical benefit of patient-specific rapid diagnostics with high sensitivity and specificity for the detection of infections caused by bacteria, viruses, fungi, and parasites. Also, diagnostics for rapid information on resistance patterns.	1
Prophylaxis	**The value of antibiotic prophylaxis in dental care**	The value of antibiotic prophylaxis in connection with, for example, dental implant installation, bone regeneration, and other oral surgical procedures with a high risk of postoperative infections.	1
	Choice of antibiotic	Alternatives to ciprofloxacin and trimethoprim-sulpha as prophylaxis in transrectal ultrasound prostate biopsy (TRULP-B) – is fosfomycin an alternative?	2
Dentistry	**Treatment of oral infections**	Optimise antibiotic use in dental care. a) Placebo-controlled studies; antibiotics plus drainage vs. drainage alone, and implementation studies. b) Studies on shortened treatment duration in dental infections.	1
	Over prescribing	Facilitate follow-up so that incorrect prescribing can be tracked and corrected.	2
Children	**Resistance in *H. influenzae***	Occurrence of and resistance mechanisms in consecutive isolates of *Haemophilus influenzae* with resistance to beta-lactam antibiotics (beta-lactamase production and/or chromosomal resistance) in middle ear exudate and in nasopharynx cultures in children with acute otitis and with tympanostomy tube insertion.	2
Patient safety	**Risk assessment tools**	Validate risk assessment tools for serious infections in adults to determine if they work in a Swedish context.	2
Interventions	**Effect response**	Evaluation of interventions for rational antibiotic prescribing in outpatient care.	2
Resistance epidemiology	**Local resistance levels**	There is a lack of knowledge of resistance epidemiology in primary care. Proposed targeted study with more generous sampling over a certain period.	2
Skin and soft tissue infections	**Treatment duration**	Can treatment duration be shortened when treating skin and soft tissue infections?	2

(*continued on next page*)

Table 2 (*continued*)

Chronic obstructive pulmonary disease (COPD)	**Antibiotics in exacerbation of COPD**	Which COPD patients really benefit from antibiotics during exacerbation? Choice of drug?	2
Pneumonia	**Validation of treatment guidelines**	How often does PcV and PcG treatment fail in moderately severe community-acquired pneumonia? For treatment in outpatient care and hospital care, respectively.	2
Prosthetic infections	**Choice of antibiotic and treatment duration**	Optimised antibiotic treatment for prosthesis infections, drug selection, and duration of treatment.	2

5. Expected or preliminary outcomes

The expected outcomes of the hereby described model for identifying and prioritising research gaps by public funding and actions, are to improve the use of antibiotics for the benefit of both patients and society. As the vast majority of antibiotics used in clinical practice are older, off-patent drugs, there is a responsibility of the public sector to strive for improved use of current antibiotics and hence minimizing use of newer last-line antibiotics, emergence of resistance, negative side effects for patients and costs for society. The PHAS has fulfilled the governmental commission from 2014. So far, the Swedish model has identified and prioritised significant knowledge gaps and generated several published studies, which aim to improve optimized antibiotic use and ultimately result in slower development of resistance without compromising clinical efficacy [16-21, 23, 25]. Currently, preparations are ongoing for initiation of some of the prioritised studies from the recent survey, and hopefully additional researchers are inspired by the list. The future outcome is expected to yield additional important knowledge in the field following repeated surveys of knowledge gaps, and needs-driven studies.

6. Discussion and lessons learned

Knowledge gaps concerning clinical use of off-patent antibiotics identified by the healthcare professionals and the proposals of studies to fill these gaps are seldom in line with the priorities of private sponsors, but should rather be the remit of the public sector. The needs may vary by infection and resistance patterns but can also be broadly similar across different countries. The strength of the above-described process is the use of a structured and transparent collection and prioritisation methodology led by a public authority in collaboration with an external independent reference group. A facilitating factor is the long tradition of close cooperation between the PHAS and health care, and the strong engagement in prevention of antibiotic resistance at the local, regional, and national level. This also facilitates implementation of clinical guidelines. In addition, a prerequisite for performing cost-effective publicly sponsored studies was the willingness of primary health care centres, infectious diseases departments, and clinical bacteriology laboratories to participate in these needs-driven studies. A challenge for the public sector may be to engage the hospital clinics and primary health care centres, despite difficulties to offer a competitive financial compensation. A weakness of the described model is that in a small country like Sweden, the number of antibiotic experts is quite limited. This may, although indirectly, bias the prioritisation process and benefit researchers participating in the reference group, or their research fellows. The experience of the Swedish model is that surveys and studies regarding clinical needs in optimising antibiotic use, can be successfully performed through a national governmental initiative, ensuring a relatively smooth process in view of close cooperation with healthcare, financing responsibilities and legal considerations. Important in order to succeed with these intentions, is political engagement, a close dialogue and buy-in from the healthcare professionals, as well as between sister-authorities responsible for public health, research funding, regulatory issues and clinical guidelines. The model of independent surveys for knowledge gaps should preferably be implemented in the public sector as an instrument to maximizing societal value for public funding. To ensure sustainability, such a model for knowledge building should preferably be implemented based on long-term goals pronounced in national strategic documents and action plans. The effect of public research funding could however probably increase and generate even more powerful studies if several countries with similar resistance problems and clinical traditions coordinated and pooled resources and research activities collectively.

No previous reports were found on the concept of a publicly initiated process of identifying and prioritising clinical needs through a structured process, followed by publicly led clinical trials. The model has similarities with the successful process of the WHO's priority pathogen list which has a major impact on global research activities [28]. There are several valuable ongoing public-private initiatives aiming to develop and deliver new treatment alternatives for bacterial infections for which adequate studies are lacking [29, 30]. Nevertheless, independent publicly funded needs-driven studies on clinical use of existing antibiotics with a focus on limiting the emergence of drug resistance are more scarce, although their importance is highlighted by various national and international initiatives [31]. The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) [32] coordinates national funding to support transnational research and activities within the area of antibiotic resistance. Another example is the AIDA project, an investigator initiative founded by the EU programme FP7-HEALTH, running from 2011 to 2017 [33]. Further, the National Institute of Allergy and Infectious Diseases (NIAID) [30] which supports a number of studies on optimising the use of existing drugs. Also, the Global Antibiotic Research and Development Partnership (GARDP) [34] carries out clinical trials on a regular basis. All these initiatives are well functioning but, as far as we know, lack preceding independent systematic reviews of knowledge gaps.

7. Conclusions

The public sector has a potential to play a fundamental role in identifying and prioritising knowledge gaps, performing high-quality studies of medical need and at the same time assuring best clinical value for its funding. Through the development and implementation of the Swedish model, solid experience in identifying and prioritising knowledge gaps and initiating studies to optimise antibiotic use has been built up in dialogue with healthcare professionals. Public institutions or established organizations are very well suited to perform systematic public health driven reviews, combined with proposals on how to fill these knowledge gaps in coordinated national and international efforts. Accordingly, the experience from the Swedish model proves unique opportunities for meeting clinical needs and filling knowledge gaps on existing off-patent antibiotics.

CRediT authorship contribution statement

Gunilla Skoog Ståhlgren: Investigation, Formal analysis, Methodology, Project administration, Writing – original draft. **Malin Grape:** Conceptualization, Writing – review & editing, Funding acquisition. **Charlotta Edlund:** Methodology, Investigation, Formal analysis, Project administration, Writing – original draft.

Declaration of Competing Interest

None

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