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Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States

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ABSTRACT

Introduction: The pipeline of new antibacterials remains limited. Reasons include low research investments, limited commercial prospects, and scientific challenges. To complement existing initiatives such as research grants, governments are exploring policy options for providing new market incentives to drug developers.
Materials and methods: Reimbursement interventions for antibacterials in France, Germany, Sweden, US, and UK were reviewed and analysed by the authors.
Results: In France, Germany, and the US, implemented interventions centre on providing exceptions in cost-containment mechanisms to allow higher prices for certain antibacterials. In the US, also, certain antibacterials are granted additional years of protection from generic competition (exclusivity) and faster regulatory review. The UK is piloting a model that will negotiate contracts with manufacturers to pay a fixed annual fee for ongoing supply of as many units as needed. Sweden is piloting a model that will offer manufacturers of selected antibacterials contracts that would guarantee a minimum annual revenue. A similar model of guaranteed minimal annual revenues is under consideration in the US (PASTEUR Act).
Conclusions: The UK and Sweden are piloting entirely novel procurement and reimbursement models. Existing interventions in the US, France, and Germany represent important, but relatively minor interventions. More countries should explore the use of novel models and international coordination will be important for 'pull' incentives to be effective. If adopted, the PASTEUR legislation in the US would constitute a significant 'pull' incentive.

1. Introduction

1.1. Structural limitations of the antibacterial market

Antimicrobial resistance (AMR), and antibacterial drug-resistance in particular, represent a leading threat to public health in countries around the world. Over the past decade, public commitments for addressing AMR have grown rapidly, with governments and intergovernmental organisations launching large new initiatives in response. One area that has been prioritized among global and national concern is the lack of new antibacterial treatments that would be effective against resistant pathogens and the dwindling research and development (R&D) pipeline [1,2].

Numerous analyses have described the market failures that contribute to the lack of investment in R&D of new antibacterials [3–5]. Good stewardship requires that new antibacterials are only used when truly necessary. New antibacterials will thus be held in reserve to treat patients whose infections are resistant to first and/or second line treatment, minimising the number of units sold. For instance, the most recent antibacterials to be added to the World Health Organization (WHO) Essential Medicines List (ceftazidime-avibactam, meropenem-vaborbactam, and plazomicin) are all classified as ẗreserveäntibacterials in the WHO's

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AWaRe (Access, Watch, and Reserve) classification [6,7]. This highly selective and restricted use has an effect on revenues: median annual sales for originator antibacterials ranged US$24–75 million in 2011–2015, while other sectors are more profitable: for example, one study found that median sales for oncology medicines in 2017 were US$435 million [8,9].

Low sales volumes and the short treatment duration of acute infectious disease syndromes result in relatively low revenues for new antibacterials. In comparison to other sectors, limited returns on investment have been identified as major disincentives for pharmaceutical companies to invest in the development of new antibacterials [3–5]. Many large originator pharmaceutical companies have progressively withdrawn from antibacterial R&D over the past three decades [10], with new antibacterial R&D projects now led by small- and medium-sized (SME) biotech companies. Due to the grim revenue expectations for new antibacterials, we now face a new concern: some of these SMEs have declared bankruptcy, despite having brought new antibacterials to market. For example, Melinta, the company that brought the vaborbactam + meropenem combination to market, which has expected activity against carbapenem-resistant *Enterobacteriaceae*, a boronate beta-lactamase inhibitor, filed for bankruptcy in December 2019 [1,11].

Another worrying phenomenon is the increasing frequency of shortages of older generics, mostly injectable antibacterials, such as piperacillin-tazobactam or benzylpenicillin [12]. The fierce price competition combined with stringent production requirements for parenteral antibacterials has led to a significant reduction of suppliers, in particular of active pharmaceutical ingredients, and to highly optimized and thus more vulnerable supply chains.

Prominent analyses of the antimicrobial market have recommended using novel financing mechanisms to revitalise antimicrobial R&D, based on the principle of 'delinking' the sales of the end-product from the costs of R&D, so that investments in R&D are recouped through means other than sales of a product at a certain price per unit [3–5]. For pipeline drug candidates, a variety of 'delinked' financing mechanisms have been proposed, which can be summarised as 'push' financing (e.g. research grants or loans), 'pull' financing (e.g. prizes for products achieving certain milestones in development or a market entry reward upon securing regulatory approval). Non-profit product development partnerships, such as the Global Antibiotic Research and Development Partnership (GARDP) and the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), offer funding as well as scientific and regulatory assistance. Most recently, the pharmaceutical industry – in collaboration with the WHO, the European Investment Bank (EIB), and the Wellcome Trust – has launched the AMR Action Fund, which will invest in later phase development of antibacterial treatments (www.amractionfund.com).

1.2. Reimbursement interventions as policy tools to tackle antimicrobial resistance

Over the past years, health systems have adjusted reimbursement policies to disincentivise the misuse and overuse of antibacterials. A 2019 review of government policy interventions to reduce human antimicrobial use identified seven published analyses of interventions in pharmaceutical reimbursement, categorizing these as 'reimbursement penalty for patients', 'reimbursement penalty for prescribers', and 'restricted reimbursement' [13]. A 2020 review additionally identified 'restrictions on reimbursement of antibacterial prescription' and 'separating drug prescribing from drug dispensing in primary care to disincentivise profit making from prescribing' [14]. Overall, the interventions identified in these systematic reviews take the form of restrictions on antibacterial reimbursement with the aim of encouraging appropriate use, which is one of the five objectives of the WHO's Global Action Plan on Antimicrobial Resistance [15].

While the reimbursement-related interventions mentioned above would tend to reduce market size for antibacterials, more recently, health systems have begun to institute policies aimed at increasing reimbursement of valuable new antibacterials, in an attempt to ensure continued supply of antibacterials, in particular, reserve antibacterials, and to stimulate antibacterial R&D. We provide an overview and comparison of new reimbursement models that five health systems – France, Germany, Sweden, the UK, and the US – have implemented in recent years, or are planning to implement in the near future.

2. Materials and methods

A review of published literature was performed and relevant experts identified in each country through the authors' professional networks (listed in the Acknowledgments section). Experts were asked to identify relevant recent policy interventions in antimicrobial reimbursement.

Reimbursement interventions were then reviewed and analysed by the authors. Factors considered for each policy intervention were: the magnitude of the intervention (likely scale of effect on the antimicrobials market), capacity to incentivise R&D of novel antimicrobials, ability to ensure affordability of the end-product and good antimicrobial stewardship, eligibility/prioritisation criteria for antimicrobials, and scalability (e.g. to other countries).

This analysis provides a snapshot of recent developments, and a narrative discussion of potential advantages and disadvantages for each intervention, presented in dedicated sections titled *"Impact and implications"*. Our analysis is not a systematic review, and, as such, there was no formal search strategy and no formal analytic framework developed for this assessment.

3. Results

Novel approaches to tackling AMR through reimbursement policies in France, Germany, Sweden, the US, and the UK are outlined below. Following each outline, we discuss their potential impact and implications. The various policies and mechanisms are summarised in Table 1.

3.1. France

In France, the National Council of Industry and the government have signed a 'Strategic Contract for the Health Industry and Health Technologies', which describes reciprocal commitments between the government and industry [19]. Combatting AMR is one of the four central 'major projects' included in the Strategic Contract. The AMR project, among other things, aims to 'create favourable economic conditions for the development and commercialisation of solutions for the fight against AMR', with a deliverable of 'a proposal of new economic models for products to fight AMR and of measures to stimulate innovation and investments', scheduled to be completed by 2021 [19].

The French health system uses a diagnosis-related group (DRG) based system to reimburse hospitals, where each 'DRG' describes a type of condition or hospital admission. Certain high-cost medicines included in a 'DRG carve-out' list (*liste en sus*) are reimbursed separately [20]. The *liste en sus* includes a number of more recently approved antimicrobials – for example, fidaxomicin, bedaquiline, and delamanid. Criteria for inclusion on the *liste* include the medicine being used mainly for inpatients, added therapeutic value, and cost exceeding 30 % of the relevant DRG

Table 1
Summary of novel reimbursement mechanisms relevant to AMR.

Country	Name	Timeline	Mechanism type	Antimicrobials/pathogens targeted
France	Exception for antibacterials with ASMR level IV (minor)	In effect since 2015	Medicines with' moderate' or higher added therapeutic benefit are guaranteed a price not lower than the lowest price across 4 reference countries. This is extended to antibacterials with 'minor' added therapeutic benefit.	Antibacterials assessed as being ASMR level IV (minor)
	Exemptions in clawback scheme	In effect since 2015	Sales of certain medicines exempted from turnover liable to clawback	Antibacterials and other medicines used in combatting AMR
	Price renegotiation for medicines at risk of shortages	In effect since 2015	Companies may request permission for a price increase from the reimbursement authority, if continued commercialisation would otherwise not be viable	This mechanism has been used for antimicrobials, though details are confidential.
Germany	Changes in § 35 SGB V	In effect since 2017	*Ad hoc* exception of antimicrobials from internal price reference groups	Decided by reimbursement authority *ad hoc* taking into consideration resistance patterns
	Fair Health Insurance Law (Faire Kassenwettbewerbsgesetz)	In effect since March 2020	Automatic exception of 'reserve' antibacterials from internal price reference groups, accelerated reimbursement review process following EMA approval	'Reserve' antibacterials*
Sweden	PHAS pilot study	First procurement call planned for early 2020, pilot study to run through 2022	PHAS sets a minimum guaranteed annual revenue for selected originator antibacterials, in exchange for a guaranteed supply volume	"Critical" pathogens in the WHO Priority Pathogens List [16]
UK	Innovative models for the evaluation and purchase of antimicrobials	Product selection completed in 2020, HTA completed in 2021, commercial negotiations to be concluded in early 2022 [18]	Annual fee, negotiated based on AMR-specific HTA, delinked from volume supplied	Pathogens on the WHO Priority Pathogens List [16]; two antimicrobials to be selected in the pilot model – one approved in the last 1.5–3 years, and late-stage pipeline product expected to be approved by the end of 2020
US	GAIN Act	In effect since 2012	5 years of additional market exclusivity, faster regulatory review	Antibacterial or antifungal drug-resistant pathogens and other qualifying pathogens (QIDP pathogens)
	Updates in IPPS rule	In effect since October 2019	Increased reimbursement of cost to hospitals for procurement of newer antibacterials	Antibacterial or antifungal drug-resistant pathogens and other qualifying pathogens (QIDP pathogens)
	DISARM legislation	Proposed, still under discussion	Reimbursement of antibacterial expenditures separately from general in-patient expenditures	Antibacterial or antifungal drug-resistant pathogens and other qualifying pathogens (QIDP pathogens)
	PASTEUR Act	Proposed, still under discussion	Contracts granted to selected new antimicrobials guaranteeing minimum guaranteed revenues over 5+ years	To be defined, if the Act is passed, by a specially created Committee on Critical Need Antimicrobials
	Civica Rx	Contracts signed for manufacture of first antibacterials in May 2019	Contract manufacture of antibacterials to avoid shortages and price hikes and ensure more stable supply	Medicines susceptible to shortages, as identified and prioritized by Civica Rx members. To date, vancomycin (Watch) and daptomycin (Reserve)**

AMR – antimicrobial resistance. ASMR – *amélioration du service médical rendu* (added therapeutic benefit). DRG – diagnosis-related group. EMA – European Medicines Agency. HTA – health technology assessment. PHAS – Public Health Agency of Sweden. PPL – priority pathogens list. QIDP – qualified infectious disease product. TLV – *Tandvårds- och läkemedelsförmånsverket* (Swedish Dental and Pharmaceutical Benefits Agency).

* 'Reserve group' is to be defined by the Robert Koch Institute and the Federal Institute for Drugs and Medical Devices.

** WHO Essential Medicines List AWaRe classification given in parentheses.

tariff. There is no specific criterion concerning antimicrobials or AMR.

Elements of the health technology assessment (HTA) system in France follow a Framework Agreement between the Economic Committee on Healthcare Products (CEPS) and the pharmaceutical industry [21]. As part of the Framework Agreement, medicines with ASMR (*amélioration du service médical rendu*; added therapeutic value) evaluation at levels I (major), II (important), or III (moderate) benefit from being guaranteed a price not lower than the lowest price across the UK, Germany, Italy, and Spain. Medicines with ASMR levels IV (minor) or V (non-existent) do not enjoy this guarantee. An exception is made for antibacterials with ASMR level IV [21]. This mirrors, for example, the removal of the 'substantial clinical improvement' criterion from new technology add-on payment (NTAP) requirements (see *United States*, below).

Under French social security legislation, pharmaceutical companies must make 'contributions' to the social security budget if increases in their year-on-year turnover exceed a certain level (a type of clawback scheme). The sales of antibacterials as well as other medicines used in combatting AMR are excluded from the calculation of pharmaceutical companies' liable turnover [21,22]. This removes a potential disincentive for antibacterial sales.

The aforementioned Framework Agreement provides that if a company is planning to cease production or commercialisation for a product with no alternatives on the market, they may request permission from CEPS for a price increase. In this discussion, manufacturing costs will be considered, including costs associated with preventing environmental pollution. If a price increase is granted, the company must agree to adequately supply the French market, or the permission is rescinded [21]. This process has been described

as important for certain antibacterials in France, but specific information has not been disclosed.

3.1.1. Impact and implications

The extension of minimum price guarantees to antibacterials with 'minor' therapeutic benefit provides a safeguard for cases where the reimbursement evaluation process may be undervaluing an antibacterial based on the non-inferiority trials. DRG carve-outs are important in order to account for increased costs to hospitals of procuring newer 'reserve' antibacterials needed to treat resistant infections. They however need to be implemented carefully and limited to those products that offer significant added clinical value and are required to treat resistant infections.

The exception of antibacterials and other tools to fight AMR from the calculation of pharmaceutical turnover clawbacks removes a potential disincentive for manufacturers to sell antibacterials. However, it is likely only relevant if the manufacturer is close to a percentage threshold for the next tier of clawbacks.

3.2. Germany

In Germany, the reimbursement authority (Federal Joint Committee; *Gemeinsamer Bundesausschuss*) undertakes an 'early benefit assessment' to determine the magnitude of benefit offered by a new medicine compared to the current standard of care. Where the early benefit assessment finds that there is no added benefit, internal reference pricing is applied, meaning the reimbursement price cannot exceed the price of comparable existing medicines, which for antibacterials would in most cases be generic medicines. Medicines that are evaluated to have added therapeutic value over existing therapies are not subject to these reference pricing groups, and the level of benefit assessed by the authority affects pricing negotiations [23].

Legislation was passed in 2017 that invites the reimbursement authority to take into account resistance patterns when determining whether a new antimicrobial provides added therapeutic value, providing a route for reimbursement authorities to allow pricing negotiations for new antimicrobials that have only non-inferiority clinical data, rather than forcing them to be included in reference pricing groups [24]. The first product is currently undergoing assessment in light of the new legislation and the effect of the change is yet to be seen.

The same 2017 legislation enables the German reimbursement authority to pursue individual pricing arrangements for Reserve-group antibacterials (this group has, to our knowledge, not yet been defined in German law). This option has not been used so far. While this exception would not allow moving from paying for volume to paying for service, as in the UK model, it would allow for 'degressive' pricing models: for example, agreeing to pay a higher unit price for a pre-defined volume, and a lower unit price when and if this volume is exceeded.

Legislation passed in March 2020 exempts Reserve group antibacterials from the normal HTA process similar to those granted to orphan drugs: automatic exemption from certain price controls and shorter time to market. Reserve antibacterials are exempted from the early benefit assessment, as they automatically qualify as having therapeutic benefits in the context of pricing negotiations. This also means that they are exempted from being included in internal reference pricing groups [25,26].

Like France (see above), Germany uses a DRG-based system for hospital reimbursement and has a 'DRG carve-out' list of medicines for which additional payments are made on top of the DRG tariff. The list includes antimicrobials, predominantly antifungals [27]. In Germany, applications to award 'carve-outs' (*Zusatzentgelte*) for antibacterials targeting resistant infections have not been granted so far.

3.2.1. Impact and implications

Germany's *ad hoc* exemption of key antimicrobials from internal reference pricing groups provides a safeguard for cases where the reimbursement evaluation process could otherwise undervalue an antibacterial, potentially forcing a price so low that an originator does not launch or withdraws their product from the German market. If consistently employed by the reimbursement authority, this could increase incentives for antibacterial R&D by increasing expected revenues.

The recent legislation exempting reserve-group antibacterials from 'early benefit assessment' will provide more systematic safeguards and may make the earlier flexibilities redundant. It will thus be more likely to represent an incentive for antibacterial R&D, as drug developers could have greater confidence in the ability to make a profit even if sales volumes remain low for reserve antibacterials. Although the 'reserve' group is not yet defined, this system could favour the development of antibacterials that are effective for the treatment of drug-resistant bacterial infections.

In the practical application of these exceptions, it will be important to limit them to those new and 'reserve' antibacterials that add value to the current standard of care, in particular those that are likely to overcome cross-resistance based on a new mode of action, new target, or because they belong to a new class of antibacterials.

The same general advantages and disadvantages for DRG carve-outs, as outlined in section 3.3.1 above, also apply to the DRG carve-out list in Germany.

3.3. Sweden

The Public Health Agency of Sweden (PHAS) is undertaking a pilot study of a new reimbursement model over 2018–2022. The model is aimed at ensuring access to products that have market protections in force (e.g. patent protection), for which current demand volume may otherwise be too low to attract the proprietor to market the medicine in Sweden.

An open procurement call is planned, where companies will be invited to voluntarily submit candidate medicines for the pilot [28]. The pilot study will select antibacterials that have efficacy against a pathogen in the 'Priority 1: Critical' group of the WHO Priority Pathogen List (PPL) and have an acceptable safety profile [16,29,30]. PHAS will then set a minimum 'guaranteed annual revenue' for each selected antibacterial, based on the cost of a 'security stock' (an estimated safe reserve amount) at 50 % above the average European list price [29].

If the guaranteed annual revenue is exceeded through unexpectedly large volumes of sales, the relevant companies would be paid a bonus equal to the price of buying 10 % of the 'security stock' amount, in order to maintain attractiveness of the PHAS model to companies as an alternative to normal volume-based sales [28].

Pharmaceuticals are reimbursed regionally in Sweden. In the PHAS antibacterials model, regional health departments would pay the list price for the selected antibacterials, with the difference made up at national level if the guaranteed annual revenue is not reached through regional procurement [29].

For older medicines without market protections, where there is a danger of shortages due to low revenues causing manufacturers to exit the Swedish market, manufacturers can apply to the reimbursement authority (TLV) for permission to increase prices. PHAS has developed an algorithm for assessing which antibacterials are of 'special medical value', based on local resistance patterns, and has recommended that TLV takes this assessment into consideration with regard to granting price increases [17,30].

3.3.1. Impact and implications

Like the UK model, the PHAS pilot study represents a novel, partially delinked model for antibacterial procurement, which will provide valuable lessons.

The pilot model would ensure availability of originator antibacterials that may otherwise not be marketed in Sweden due to small market size. However, the procurement volumes will likely not be large enough in the PHAS model to represent a substantial incentive for antibacterial R&D (which also was not the intention of the pilot project).

In the PHAS pilot study, medicines are reimbursed at prices 50 % above European average list price. If the antibacterials would have been marketed in Sweden regardless, the PHAS model will have resulted in higher per-unit expenditures than the *status quo*.

3.4. United Kingdom

Since late 2013, the UK Government has been exploring innovative payment models for antimicrobials [31]. In July 2019, the UK Department of Health and Social Care (DHSC) announced a trial of a new pharmaceutical payment system for antibacterials, here termed 'the commercial model' [32]. Currently, the pilot model is limited to England.

The objective of the model is to arrange procurement of new, valuable antibacterials on the basis of a multi-year contract paid through a set annual payment (or 'fee'), for which the manufacturer would provide as many doses of the antibacterial as needed.

The commercial model will select two products from a pool of candidates. The pool of candidate products will be made up of submissions by originator pharmaceutical companies; any company is free to submit a candidate. One selected product will be an antimicrobial approved in the last 1.5–3 years, and the other will be a late-stage pipeline product expected to be approved by the end of 2020 [18]. Any company to be considered for the model must have a demonstrated commitment to relevant environmental standards, and performance on the AMR Benchmark, an index published by the Access To Medicine Foundation, could serve as an indicator of this [33,34].

The National Institute for Health and Care Excellence (NICE), which conducts cost-effectiveness analyses (HTAs) for most new originator medicines in the UK, will then undertake a full assessment of the two selected products. Standard cost-effectiveness methodology is limited in its ability to capture the broad benefit to society of having new, effective antimicrobials available, even if they are held 'in reserve'. For this reason, DHSC commissioned the development of a new cost-effectiveness evaluation methodology that is specific to new antibacterials [35].

Informed by NICE's assessment, National Health Service England will then enter into commercial negotiations with the proprietors of the two selected products to agree on payments, which will take the form of an annual fixed fee of up to £10 million per product. A proportion of the annual fee will be contingent on achieving certain performance requirements, including, for example, adherence to stewardship and environmental standards. Initial contracts will be for 3 years, with an option to extend to 10 years [18].

This maximum annual fee is based on a calculation what approximately England's "fair share" would be of the proposed US $2–4 billion financial incentive needed, per new antimicrobial, globally, to revitalise the antimicrobial pipeline. England represents approximately 2% of global pharmaceutical sales and 3.5 % of G20 GDP; applying these proportions to the estimated required global incentives results in a "share" of US$40–140 million (or about £30–100 million) over 10 years. The cap of £10 million per year per antimicrobial cap thus represents the top end of this range [5,36,37].

3.4.1. Impact and implications

The UK pilot model is the first that switches from procurement of antibacterials by volume to procurement of antibacterials as a service (or 'subscription'). The model would thus 'delink' the payments to manufacturers from the number of units sold. The principle of 'delinkage' has been recommended in numerous prominent analyses of the market failures affecting antibacterials [3–5]. As such, the model will yield valuable lessons both for future approaches to tackling AMR and for broader policy debates on incentives in pharmaceutical R&D.

In the UK model, the annual fee structure means the use of the procured products is not disincentivised by high unit prices, and use can be guided by clinical need alone. At the same time, the annual fee structure removes perverse incentives for manufacturers to encourage greater use volumes, which could result in inappropriate use.

The model includes HTA using methodologies that are tailored to the specific context of antimicrobials, with the aim of ensuring cost-effectiveness from a societal perspective. This is an advantage over many of the other mechanisms outlined in this analysis that do not include cost-effectiveness analysis.

In the long term, and if converted into a permanent or semi-permanent mechanism following the pilot phase, the model could provide a novel type of market incentive for drug developers. The effectiveness of this market incentive would depend on the size of the financial rewards compared to what would be available through 'normal' sales, as well as on how the selection of successful drug candidates is structured.

One important challenge is to ensure that only new antibacterials with true added clinical value are procured through this model, to avoid incentivising the development of 'me-too' drugs that offer marginal or no benefits over existing therapies. Its success is also contingent upon a sufficient pool of new products. This in turn relies on buy-in from pharmaceutical companies, as candidate medicines must be submitted by the proprietor pharmaceutical companies in order to be considered.

The model will likely result in greater overall costs than 'normal' procurement based on negotiated unit price. Until the pilot model has selected the first drugs and undertaken an HTA and negotiation process, it is unknown what the total cost of procurement within this model will be. The cap on annual costs mitigates this disadvantage, however.

3.5. United States

3.5.1. GAIN Act

In the US, 'market exclusivities' are granted to medicines based on certain criteria. For example, orphan drugs are granted a 7-year exclusivity period. During the "market exclusivity" period, the US Food and Drug Administration (FDA) may not approve a generic version, shielding the product from competition, and allowing the proprietor to leverage a monopoly to demand higher prices. Market exclusivity is granted irrespective of any patents that may also protect a medicine – thus it may be the market exclusivity, or the patent protection, that expires first, depending on the medicine in question.

The Generating Antibiotic Incentives Now (GAIN) Act of 2012 grants certain antimicrobials five additional years of market exclusivity, independent of any patent protection and added onto any other nonpatent exclusivity periods (such as those that are granted for orphan products), theoretically enabling higher prices to be charged for a longer period, generating greater total revenues. Antimicrobials are eligible for this 'GAIN exclusivity' if they have been designated a 'qualified infectious disease product' (QIDP) by the FDA. As of the end of 2019, antimicrobials that have received this GAIN

exclusivity include: dalbavacin, tedizolid, oritavancin, ceftolozane-tazobactam, ceftazidime-avibactam, isavuconazole, delafloxacin, meropenem/vaborbactam, secnidazole, plazomicin, eravacycline, amikacin (inhaled), omadacycline, rifamycin, lefamulin, cefiderocol, imipenem-cilastatin-relebactam, and pretomanid [38,39]. Apart from 'GAIN exclusivity', the Act also automatically gives QIDPs priority review with the FDA, meaning a faster target regulatory review duration, as well as making QIDPs eligible (if the applicant requests it) for 'fast track' designation, which offers other time-saving advantages in the review process. The FDA grants QIDP designation to antibacterial or antifungal medicines for the treatment of 'serious or life-threatening infection' with a certain list of 'qualifying pathogens', or for the treatment of an drug-resistant pathogens [40].

GAIN exclusivity is similar to orphan exclusivity, which is granted, for example, in the US, European Union (EU), and Japan.

3.5.1.1. Impact and implications. This mechanism can increase revenues for antimicrobial developers over the extended period of market exclusivity by enabling them to charge higher prices for a longer period in time, unless bacteria become resistant to the antibacterial in question before the end of the extended exclusivity period. This incentive also comes late in the drug development cycle, in principle, manifesting after the expiry of a 20 year patent term. This could provide additional incentives for antimicrobial development. However, this mechanism has no controls to ensure selection of best-in-class molecules, cost-effectiveness and access. In fact, some have criticised this mechanism for granting QIDP designations as too generous, with many of the products designated as QIDP since 2012 being modifications such as new formulations or indications, or compounds that do not have a new mechanism of action and limited evidence for added therapeutic benefit [41].

3.5.2. IPPS rule and DISARM Act

In the US, the 2019 revision of the Inpatient Prospective Payment System (IPPS) rule aims to improve the reimbursement of new antimicrobials.

The Centers for Medicare and Medicaid Services (CMS), a US government agency that provides health coverage to over 100 million patients, reimburses hospitals for expenses through the IPPS. An updated 'IPPS final rule' is published yearly, which sets out the details on how various expenses are categorised, which expenses are eligible for reimbursement, and to what extent they are reimbursed.

The IPPS system reimburses hospitals at a fixed amount for each DRG. For example, 'chronic obstructive pulmonary disease with major complication and comorbidity' is DRG code 190 [42]. It has been argued that this system was unfavourable to the uptake and, consequently, the development of new antimicrobials.

The DRG fixed payment was based on the assumption that existing generic antimicrobials would be used, which, in principle, is a useful approach to contain costs and prevent use of new treatments with low added value. Thus, using more expensive antimicrobials – some costing over US$10,000 per course – would exceed the amount covered by the DRG, jeopardizing the hospital budget, and disincentivising their use [43,44].

The IPPS rule update for fiscal year 2020 seeks to remedy these shortcomings. Two key changes were made.

Firstly, the 2020 IPPS rule added a subdivision to DRG codes to capture antimicrobial-resistant cases ('Z' codes). This means that, where hospitals add a 'Z' code to a patient's case, the hospital may receive additional reimbursement from Medicare or Medicaid, which in some cases may be substantial.

Secondly, the 2020 IPPS rule by tailoring the new technology add-on payment (NTAP) to better cover new antimicrobials. NTAPs allow hospitals to claim for reimbursements of certain new technologies. However, antimicrobials faced certain obstacles in qualifying for NTAP reimbursement. In order to qualify, technologies had to show 'substantial clinical improvement' over existing therapies, normally implying the need for a superiority trial. As antibacterials are often approved based on non-inferiority trials [45], only a few antibacterials had qualified for NTAPs. In the 2020 IPPS rule, an antimicrobial that is designated as a QIDP (see above, under GAIN Act) is exempted from the 'substantial clinical improvement' requirement.

CMS reimburses technologies eligible for NTAP at 65 % of the additional cost of the technology or 65 % of the cost of the overall treatment of the patient exceeding the DRG payment, whichever is lower. In addition, the NTAP rises to 75 % for medicines designated by the US Food and Drug Administration (FDA) as a QIDP [44].

A further proposal currently under consideration is to entirely separate reimbursement for important new antibacterials from DRG-based reimbursement, termed a 'DRG carve-out'. The Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act, currently under consideration in the US Senate, would create such a carve-out [44,46]. It is currently not known whether, and if yes when, the DISARM Act will become law. Reportedly, a DRG carve-out is also being considered for implementation in a future IPPS rule, independently of the DISARM Act [44] (although such a carve-out was not included in the proposed FY2021 IPPS rule [47]).

3.5.2.1. Impact and implications. If the IPPS rule changes result in more new antimicrobials qualifying for NTAP, this will create an additional reimbursement route for hospitals using recently approved antimicrobials and mitigate undesired effects of the fixed-rate DRG system. As the reimbursement is capped at 75 % of costs exceeding the DRG payment, some economic disincentive for hospitals remains.

It may also encourage earlier adoption of new antimicrobials in clinical practice. In the long term, whether IPPS rule changes provide improved market incentives for drug developers will depend upon whether the changes actually result in greater spending on high-cost new antimicrobials. The NTAP reimbursement route is integrated with the DRG-based reimbursement system, allowing DRG tariffs to be systematically adjusted based on NTAP claims.

However, earlier experiences with antibacterials qualifying for NTAPs saw that hospitals rarely claimed NTAP reimbursements, with no clear effect on the antibacterial revenues [44]. In many US hospitals, pharmaceutical costs come out of the hospital pharmacy's budget, while NTAP reimbursements are paid to the hospital's central budget. This means that economic disincentives may remain at the pharmacy level. Claiming NTAP reimbursement is also administratively burdensome, as it involves a separate billing route [44]. Inclusion of a technology in the NTAP generally only lasts 2–3 years, after which, if uptake of the technology has been high, the cost of the technology is added into the relevant DRG(s). If uptake has been limited, the NTAP 'expires' without a corresponding addition to the DRG, meaning that the cost of using the technology for a hospital effectively increases. Achieving high uptake is limited for novel antibacterials due to stewardship efforts. This was for example the case for fidaxomicin, whose NTAP expired in this manner [44].

Use of new 'Z' codes for drug-resistant cases is likely to be less administratively burdensome than NTAPs and is not contingent on the specific antimicrobials used qualifying for NTAP. However, neither the NTAP reimbursement route nor the new 'Z' codes has a formal mechanism to ensure the cost-effectiveness of the antimicrobials procured, although, as hospitals cannot pass on 100% of antimicrobial cost, there is some pressure for hospitals to negotiate prices.

One important challenge for new reimbursement mechanisms is to incentivise the development of truly novel antimicrobials (for example, with a new mechanism of action), rather than 'me-too' drugs that often offer marginal or no clinical benefits over existing therapies. The IPPS rule change, by removing the 'substantial clinical improvement' criterion for NTAPs, may overshoot in this regard. The proposed DISARM Act does not appear to have mechanisms to preferentially incentivise antimicrobials that represent true clinical advances, although the Act is still under discussion.

3.5.3. *PASTEUR act*

The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act, due to be submitted to US Congress, would establish a new federal funding stream for new antimicrobials, which would apply to federal payors in the US (e.g. Medicare, Medicaid) [48].

The Act would establish a Committee on Critical Need Antimicrobials to grant 'subscription contracts' to pharmaceutical companies that have developed a new antimicrobial and that meet certain conditions, including for example addressing priority R&D gaps and adding significant clinical value. The Committee would solicit applications and develop more detailed criteria for assessing eligibility for a contract. 'Subscription contracts' would then be granted to successful applicants, ranging in value from US$750 million to 3 billion depending on the characteristics of the drug, paid over a period lasting from at least 5 years to up to 10 years or until patent expiry. The exact methods for deciding the value of contracts within this range would be determined by the Committee. The Act would provide a budget of US$11 billion over 10 years for implementation of the model (sufficient for 3–14 total contracts, depending on contract value) [48].

Contracts would include requirements regarding availability, resistance surveillance, and ensuring appropriate use. While the contracts would require supply of a certain amount of the product (to be determined by the Committee), the contracts would not require the provision of an unlimited volume of an antimicrobial. Rather, any revenues from sales of the antimicrobial to federal insurance programs (e.g. Medicare) would be subtracted from the value of the contract. In other words, the value of the contract would provide minimum guaranteed revenues in the range of 750 million to 3 billion [48]. This is a key difference between this model and the UK model (above) or other 'subscription' models that have been used for hepatitis C medicines [49,50], where an annual fee is paid in exchange for an unlimited volume of the product.

3.5.3.1. Impact and implications. Full details on the PASTEUR model are not yet available, as key elements would be left for the Committee established by the Act to design, such as eligibility criteria and methods for determining contract value.

The value of contracts foreseen in the Act is substantial and would represent a significant incentive to antimicrobial developers as it would guarantee minimum sales/revenue. Under PASTEUR, individual hospitals may still pay the full price for the treatment, even if this is 'recouped' at the federal level (shadow pricing), meaning hospitals would still be discouraged from overuse. The ability of the model to effectively incentivise true therapeutic advances in a cost-effective manner will largely depend on the methodology developed by the Committee. Additionally, the PASTEUR model does not offer a mechanism for ensuring affordable pricing for patients under private insurance.

3.5.4. *Non-profit manufacturing*

Civica Rx is a non-profit generic drug company founded by seven health provider networks, which aims to address generic drug shortages in US hospitals. Since its founding, many more health provider networks and health insurers have joined the model. Civica Rx's model is to enrol provider networks and hospitals as 'members' and leverage the pooled demand to secure long-term supply contracts with manufacturers at affordable prices. Later, Civica Rx plans to acquire its own manufacturing facilities. Civica Rx also maintains a 'security stock' of medicines to ensure a stable supply for hospitals [51]. While Civica Rx is the only private initiative included in this analysis, the high reliance on private healthcare in the US, combined with the fact that Civica Rx's enrolled members currently represent 213,000 or 30 % of US hospital beds, and that Civica Rx supplies the Department of Defense, Veteran's Administration, and '340B' hospitals, mean that Civica Rx's role can be seen as quasi-public sector (comparable to work undertaken by the public sector in other countries) [52].

At present, Civica Rx provides vancomycin and daptomycin, 'watch' and 'reserve' antibacterials, respectively, according to WHO's AWaRe classification [53,54]. Civica Rx has recently signed an agreement for provisions of additional injectable antibacterials (specifics are not yet public) [55].

Separately, the Affordable Drug Manufacturing Act under consideration in the US Congress would establish a new Office of Drug Manufacturing, which would manufacture generic medicines in cases where there are shortages and/or prices are unaffordable due to a low number of manufacturers [56].

4. Discussion

After years of focusing on cost control and limiting the use of antibacterials to curb their inappropriate use, the countries covered in this review are taking a range of measures to address the faltering supply of new antibacterials. This, in itself, is an encouraging trend. The reimbursement interventions outlined in this analysis are relatively recent. Some are planned, but not yet implemented. As it is not yet possible to evaluate evidence on their relative effectiveness, this analysis is based on expected structural advantages and disadvantages.

4.1. *General shortcomings of current interventions*

Policy interventions in the reimbursement of antimicrobials can be considered a 'pull' incentives, as they increase the potential revenue for market authorization holders. If designed appropriately, they thus have the potential to incentivise the development of new and innovative antibacterial treatments.

Most of the interventions outlined in this review share three general shortcomings:

(1) **Most interventions form exceptions to general rules**. Reforms in Germany, France and the US are relatively small adjustments to national reimbursement systems to provide more tailored approaches for antimicrobials, or specifically antibacterials, mainly through creating specific exceptions to existing cost-containment measures such as the DRG reimbursement system.
(2) **Interventions differ from one market to another**. This increases the translational costs for companies. Companies will have to individually assess opportunities in each market and find their way through national mechanisms that take the form of exceptions to the general rules. This fragmentation may be particularly challenging for SMEs, which are currently driving the antibacterial development pipeline. This has to be considered against the fact that some of the newest antibacterials have not been registered in the European market at all, ostensibly due to the investments required to enter the market [57].
(3) **Financial impact remains unclear**. The fragmentation of the markets and different antibacterial-directed mechanisms

makes it difficult to assess the potential financial impact. Due to the arguably incremental nature of the interventions in the US, Germany, and France, we would expect the impact of those interventions on the incentives for antibacterial development to be limited.

4.2. Calls for delinkage and for increased coordination

The UK Review on Antimicrobial Resistance (2016) made two principal recommendations regarding financing antibacterial R&D: a global innovation fund for early-stage and non-commercial R&D, and globally administered market entry rewards (MERs) [4]. MERs consist of a large, fixed payment for innovative antibacterials that meet a predefined target product profile, 'awarded' upon market approval, for which the innovator would agree to supply the medicine at any volume necessary. The MER model is thus a type of 'delinked' model. The DRIVE-AB report (2018), co-sponsored by the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA), similarly recommended MERs, proposing that the G20 should implement and finance MERs for antimicrobials, and the European Commission should explore implementing a common European MER for antimicrobials [5]. With regard to ensuring access and affordability, both the UK AMR Review and DRIVE-AB proposed that, as a condition of receiving a MER, companies should be contractually bound to ensuring equitable access to the product (though neither prescribes a specific mechanism for this). Both reports put the benchmark size of an MER at around US$1 billion per antibacterial. DRIVE-AB recommended that such a mechanism could initially be piloted by 2–3 countries in partnership for 1–3 years and, when fully operational, the mechanism could be expanded to include financing from more partner countries. DRIVE-AB also recommended that, while MERs are still in development, HTA processes be improved to better capture the societal value of new antibacterials [5].

The interventions in reimbursement and procurement outlined in this analysis must be considered in the context of policy discussions over recent years, converging on the need to truly overhaul the antimicrobial R&D landscape. The financial incentives necessary for such an overhaul are likely to be greater than any one country can offer – estimates put the necessary worldwide funding increase at US$1−4 billion per year [5,36]. The limited national interventions outlined in this analysis – although laudable - pale when compared to the global need for new antimicrobials for drug-resistant infections. Internationally coordinated interventions in antimicrobial reimbursement would have a greater impact on drug developers' expected revenues; while such measures have been discussed in the G7 and G20 in the past, currently no such global initiative is underway.

4.3. Suitability of existing models for the next national, regional or global initiatives

The UK and Swedish pilots and the PASTEUR Act (the latter of which remains a legislative proposal as of writing) may serve as models for regional or global approaches. The initiative in the UK represents one approach to delinkage, wherein payments to companies are not based on the number of units sold, but on fixed annual payments or 'fees'. The Swedish PHAS model and the PASTEUR Act model are also delinked at the level of the government payor and from the point of view of the company selling the medicine: a set amount will be paid at national level and revenues will not depend on the number of units sold (unless the minimum guaranteed revenues are exceeded). In both models, individual units will still be bought from the seller at a unit price. If the minimum revenue 'floors' are exceeded by unexpectedly large sales, the market will no longer be delinked, as this scenario will be equivalent to a 'business as usual' market based on unit sales. This scenario is unlikely, however, and the policy aim will nevertheless have been achieved.

The UK model arguably represents a type of MER, as companies that can offer a product meeting the target product profile criteria will be paid a fixed amount over a set period of time, with the payments and duration negotiated up-front and not affected by usage patterns. The UK's model would result in a maximum £100 million (if the contract is extended to 10 years, and the maximum is paid each year). While this falls far short of the US$1 billion MER recommended by the reports cited above, if other G20 countries were to match this amount in proportion to their GDP, this amount would scale up to an MER of £3.5–4.0 billion (about US$4.4–5.0 billion) over 10 years [37]. The model proposed in the PASTEUR Act in the US would also arguably represent an MER, as companies would be incentivised to win the 'reward' guaranteed minimum revenues. Indeed, these guaranteed revenues of US$750 million to US$3 billion would represent a significantly larger incentive than the UK model, and may exceed the recommended magnitude mentioned above.

The UK and Swedish models broadly fit into DRIVE-AB's recommended plan of a smaller number of countries undertaking pilot models for MEAs, before other G20 countries join in. Models such as the UK or Swedish model, if replicated by other countries, could cumulatively represent a substantial increase in both the revenues available for antimicrobial developers and stability of market demand. A centralised or coordinated European-level reimbursement mechanism for antimicrobials would represent a far larger demand volume and potential revenues, providing a more substantial incentive to invest in the development of new innovative antimicrobials with significant added clinical benefits and would make it much more attractive for companies seeking marketing approval through the European Medicines Agency (EMA). At present, however, reimbursement remains a national competency in the framework of the division of tasks between EU and its member states. The increasing attention on medicines supply security due to the COVID-19 pandemic may also accelerate the development of European solutions in this space.

The German pricing system for reserve antibacterials does not by default represent a delinkage approach, but the German reimbursement authorities have the option of agreeing a high price for a small initial volume, with decreasing prices for larger volumes – such agreements could have a similar effect to fully delinked mechanisms such as MERs. Governments have also increasingly been exploring such reimbursement approaches outside of antimicrobials, for example, with 'subscription' agreements for hepatitis C medicines in Australia and the State of Louisiana [49,50].

The model pursued by UK, which fundamentally changes the way new antibacterials are procured, is a larger shift in implementation and requires greater 'set-up costs' but may in the long run address the problem more effectively. Other countries will benefit from the experiences of the UK pilot project, for example, in designing a novel HTA methodology and product selection procedure. Most high-income countries with state-run healthcare systems would likely be capable of undertaking similar projects (individually or together). Implementation could be more challenging for countries that do not have a centralized procurement system, but would be worthwhile exploring, even if it is for subsets of the market. The model envisioned in the US PASTEUR Act would also represent a fundamental and substantial change, if enacted.

Mechanisms that aim to remove financial disincentives to the use of new antimicrobials (e.g. DRG carve-outs) must of course be balanced with protocols for good antimicrobial stewardship, to avoid overuse of any new 'reserve' antimicrobials. Similarly, the need to adequately factor in resistance patterns when assessing the value of new antimicrobials in HTAs must be balanced

against the need to avoid incentivising the marketing of 'me too' antibacterials that do not offer added therapeutic benefit. In this context, countries should seek coherence in the criteria used to designate a qualifying antibacterial within any new reimbursement mechanism. The WHO PPL and AWaRe (access, watch, reserve) classification, as well as the WHO's annual assessment of the clinical antibacterial pipeline, which includes an assessment of innovation (new class, new target, new mechanism of action, and absence of known cross-resistance), can help in assessing the value of new antimicrobials and designating which drug candidates are high-value [1,2,7,16]. Both the UK and Swedish mechanisms outlined include procedures to select high-value antimicrobials for inclusion in the reimbursement mechanisms – both include criteria based on the WHO PPL [30,33].

4.4. Other challenges than reimbursement models

Another challenge is the paucity of clinical data underlying the marketing approval of new antibacterials, which are mostly approved based on non-inferiority trials [45]. For good reasons, reimbursement systems have been optimized over the years not to pay premiums for new treatments that are not superior to the standard of care, in order to avoid budgetary waste and, more broadly, to avoid incentivizing the development of 'me-too' products. However, antimicrobials represent a special case, as existing treatments are becoming ineffective and thus even products that are not superior (only non-inferior) may be needed to treat resistant infections; in particular, novel antibacterials that overcome cross-resistance (a new target, new mechanism of action or new class). Running clinical trials to demonstrate superiority in critically ill patients is also challenging and expensive [58]. At the same time, some commentators suggest that superiority trials should not be discounted as unfeasible; new trial designs could test superiority while still using an active comparator, and research networks could be established to make finding and enrolling trial participants easier [58].

In the broader context of AMR, it has also been suggested that – depending on the ultimate cost of new mechanisms such as the UK pilot model – large investments in tackling AMR may be better directed to objectives other than antimicrobial R&D, such as investments in primary care interventions and infection prevention and control [59].

As noted in the Methods section, we did not develop a formal analysis framework for assessing antimicrobial reimbursement policy interventions. However, development of such a framework could help in defining some key elements that would be required to ensure global coordination and increase the impact of reimbursement reforms.

5. Conclusions

Over the last years a number of countries have stepped up to revive antibacterial development and are revising their antibacterial reimbursement systems to set appropriate incentives. For the time being, however, only a few countries have taken action and the described reforms are still too limited. In the absence of consensus on a global pull mechanism at the international level (for example at the G7 or G20), reforms at national or ideally at regional level are the most realistic options at the moment for creating significant pull incentives to revitalize the antibacterial development pipeline.

Of the changes in antibacterial reimbursement outlined in this review, the pilot models in the UK and Sweden, and the PASTEUR Act under consideration in the US, are the most innovative and are most closely aligned to recommendations made in recent prominent reports on reviving R&D for AMR. Other adjustments in reimbursement mechanisms, while important, likely will have only minor market impact. Following the UK's initiative, more countries with well-resourced healthcare systems should undertake pilot projects that apply the principle of delinkage to antibacterial reimbursement.

Only by changing the way we purchase and value antibacterials can we adequately address the urgent need for the development of 'reserve' antibacterials, while reserving them for the patients who truly need them.

Author contributions

DG gathered and analysed data and prepared the first draft of the manuscript. PB gathered and analysed data and contributed to drafting of the manuscript. LM, MH, SP and IS assisted in analysis and contributed to drafting of the manuscript.

Declaration of Competing Interest

All authors declare no competing interests.

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