Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Global access to existing and future antimicrobials and diagnostics: antimicrobial subscription and pooled procurement

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The COVID-19 pandemic has underlined the importance of an efficient and equitable supply of and access to essential health products. These factors are equally pertinent to the antimicrobial resistance pandemic, in which access to a portfolio of existing and pipeline antimicrobials plus complementary diagnostics is crucial. This Viewpoint focuses on market shaping in low-income and middle-income countries (LMICs), where the need for effective antimicrobials and complementary diagnostics is most acute. We propose the creation of a subscription and pooled procurement model that consolidates the growing demand for a portfolio of antimicrobials and diagnostics in LMICs. Anchored by regional market leaders, these pooling mechanisms would guarantee consistent private-sector and public-sector access in participating countries, while creating conditions for long-term best practice in stewardship. Supported by data from South Africa and India, this proposal sets out an innovative approach to tackle the antimicrobial resistance crisis in LMICs.

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Introduction

Growing rates of antimicrobial resistance, driven by inappropriate antimicrobial use, are a global concern. Several factors contribute to inappropriate antimicrobial use, including over-reliance on empirical prescriptions because of inaccurate and unaffordable diagnostics, over-the-counter availability of antimicrobials, industry promotion, and insufficient knowledge of the consequences of overuse.[1,2] Substandard and falsified medicine sales and irrational fixed dose combinations are also nurturing resistance.[3] As antimicrobial resistance increases, governments and individuals (especially in low-income and middle-income countries [LMICs]) struggle to finance and procure efficacious antibiotics, many of which fall in the reserve category on the WHO Access Watch Reserve (known as AWaRe) list.[4]

Policy makers have struggled to attract—or retain—big pharmaceutical and biotechnology companies into the antibiotic market to address what WHO has described as a "clinical pipeline [that] remains insufficient to tackle the increasing emergence and spread of antimicrobial resistance".[5] As Steven Projan put it, there is also an "urgent need for accessible and affordable diagnostic products and the building of laboratory capacity in low-resource settings to support the responsible use of these agents".[6] Despite current discourse on delinking rewards from sales volume, and various push incentives (eg, subsidising research and development costs) and pull incentives (eg, creating viable demand in high-income countries [HICs]), more thought is needed on ensuring access in LMICs.

Various factors contribute to an unstable and often commercially unattractive market that is failing to ensure access and availability in LMICs. These factors include a high demand for inexpensive generic antimicrobials, price control in countries that set prices either too low or too high, and a fractured market that demands relatively low product volumes.[7] Today, most antimicrobials are manufactured as generics, and many producers are operating with thin profit margins, leading to insecurity of supply in both HICs and LMICs.[9,10] Growth in demand for antibiotics in some middle-income countries (MICs) is forecast to increase by 5–8% annually over the next 5 years. However, how to leverage growth in these so-called pharmerging markets, to ensure equitable global access to much needed antibiotics and diagnostics, remains an open question.[11]

This Viewpoint describes how antimicrobial subscription and pooled procurement (ASPP) could be implemented as a multinational or federal mechanism in which countries or states within a country, or both, leverage their combined purchasing power for a portfolio of newer and future antimicrobials and diagnostic products. Low-income countries (LICs) could participate with the help of subsidies from existing donor frameworks. Based on multi-year subscription contracts that are negotiated on behalf of these aggregated (ie, pooled) procurers, ASPP could reshape the LMIC market for essential antimicrobials and diagnostics. With targeted support built in for stewardship programmes, the proposed model would address the significant challenges currently faced by LMICs in ensuring access to and appropriate use of antimicrobials.

ASPP would complement the current efforts in HICs to stabilise essential medicine markets, through initiatives such as the social welfare pharmaceutical organisation Civica. Additionally, it would complement HIC efforts to incentivise antimicrobial research and development, through policies such as the US Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (known as PASTEUR) Act of 2021, which would provide "sizable, subscription-based government contracts for access to innovative, high-priority antibiotics" in the USA.[12] ASPP would expand the reach of this investment to ensure equitable global access beyond those who can currently afford to pay.

For more on **Civica** see https://civicarx.org/

Making the case: previous policy interventions and economic models

Many models to stimulate research and development for new antimicrobials have not addressed market shaping and access in LMICs. One exception is the 2019 model of Singer and colleagues,[13] who recommended an international antimicrobial resistance institute, funded by governments and foundations, to develop and manufacture antibiotics.[12] Akin to the collaborative approach used successfully in the human genome project, the idea has not gained traction.

Many pull mechanisms focus on creating an attractive market in HICs.[14] Towse and colleagues[14] proposed an insurance model that uses North American and European data to demonstrate how pre-tax estimated net present value could be brought from US$50 million to $100 million, to re-engage the pharmaceutical industry. This approach to partially delink volumes from reimbursement is significant. The researchers explain that $1680 for a 14-day course to treat a complicated Gram-negative infection in HICs could be lowered through "differential contribution rates as outlined in the differential pricing literature", and they suggest annual premiums based on income per capita.[14] However, they do not elaborate on how fractured demand could be aggregated. The "significant negative association"[15] between national income and the prevalence of antimicrobial resistance means that many LMICs will continue to be disproportionately affected by antimicrobial resistance and will have insufficient resources to shore up markets.[15]

Creating efficient markets in LMICs is essential, especially because the absence of an effective market limits the impact of any push funding and support for research and development. Drive-AB, a consortium of public and private partners from 12 countries, estimates that $1·75 billion per antibiotic is required in global pull funding to make almost all the projects under development profitable.[16] Current HIC efforts to create incentives for investors to overcome weak markets for antibiotics globally are important. However, given the need for new antibiotics, even if contributions were keyed to per capita income, the contribution needed from LMICs would quickly overwhelm public health budgets.

Novel payment schemes—like the subscription or so-called Netflix model—are used by HICs to reduce manufacturers' risks, increase market predictability, and ensure access to new products. Subscription models have encouraged greater alignment between the pricing and value of a health commodity, through health technology assessments. These assessments include the direct and indirect consequences of a technology for both individuals and health systems. Australia has negotiated subscription contracts to gain access to antivirals for hepatitis.[17] The UK is piloting a subscription model recognising the comprehensive benefits of new antibiotics and guaranteeing payments for a fixed period,[18] whereby Government payers agree to cover populations rather than paying for the volume of medicines purchased.[18]

Many solutions being proposed today focus on higher reimbursement rates in HICs.[19] This approach should increase engagement from drug developers for new products, but it does little to ensure access in LMICs. As a matter of urgency, push and pull mechanisms in HICs must be advanced, especially given the continued biotech bankruptcies, and so too should market shaping mechanisms that reflect the realities of and market opportunities in LMICs.[20] Access and market challenges are also acute for generic antimicrobials and diagnostic products in LMICs. Market shaping strategies therefore need to address access to a comprehensive portfolio of existing and future products.

How ASPP would work

An economic hybrid

ASPP would be operationalised through multiyear subscription contracts for a portfolio of antimicrobials and diagnostic products that are negotiated for participating countries. Diagnostic products would include point-of-care tests, routine laboratory reagents, and equipment for pathogen identification and susceptibility testing. Including diagnostics in the portfolio would help to ensure that antimicrobials are prescribed on the basis of diagnostic stewardship.

The portfolio approach sends a clear signal to manufacturers that products will be procured when quality, safety, efficacy, and pricing criteria set by procurers are met. ASPP will be a partially delinked economic hybrid. LICs would receive development assistance to maintain antimicrobial product portfolios and increase stewardship activities. This process would mirror the current support LICs receive to procure health commodities from UNITAID and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

MICs would self-finance in a similar way to how vaccines are paid for in the Pan American Health Organization Revolving Fund, in which member states pool national resources to procure life-saving vaccines. ASPP would do the same for a portfolio of antimicrobials and diagnostic products. Additionally, for branded products a nominal MIC licensing fee could flow back to patent holders. These fees would be lower than the licences typically negotiated by traditional proprietary pharmaceutical companies. ASPP will further support many principles of the African Continental Free Trade Area to focus on pooled procurement and a harmonised regulatory and quality framework.[21] It will also build on the success of the Africa Medical Supplies Platform, focused on COVID-19 product procurement. Antimicrobial contract prices negotiated by ASPP should not be considered a reference for HICs.

For the **Africa Medical Supplies Platform** see https://amsp.africa/

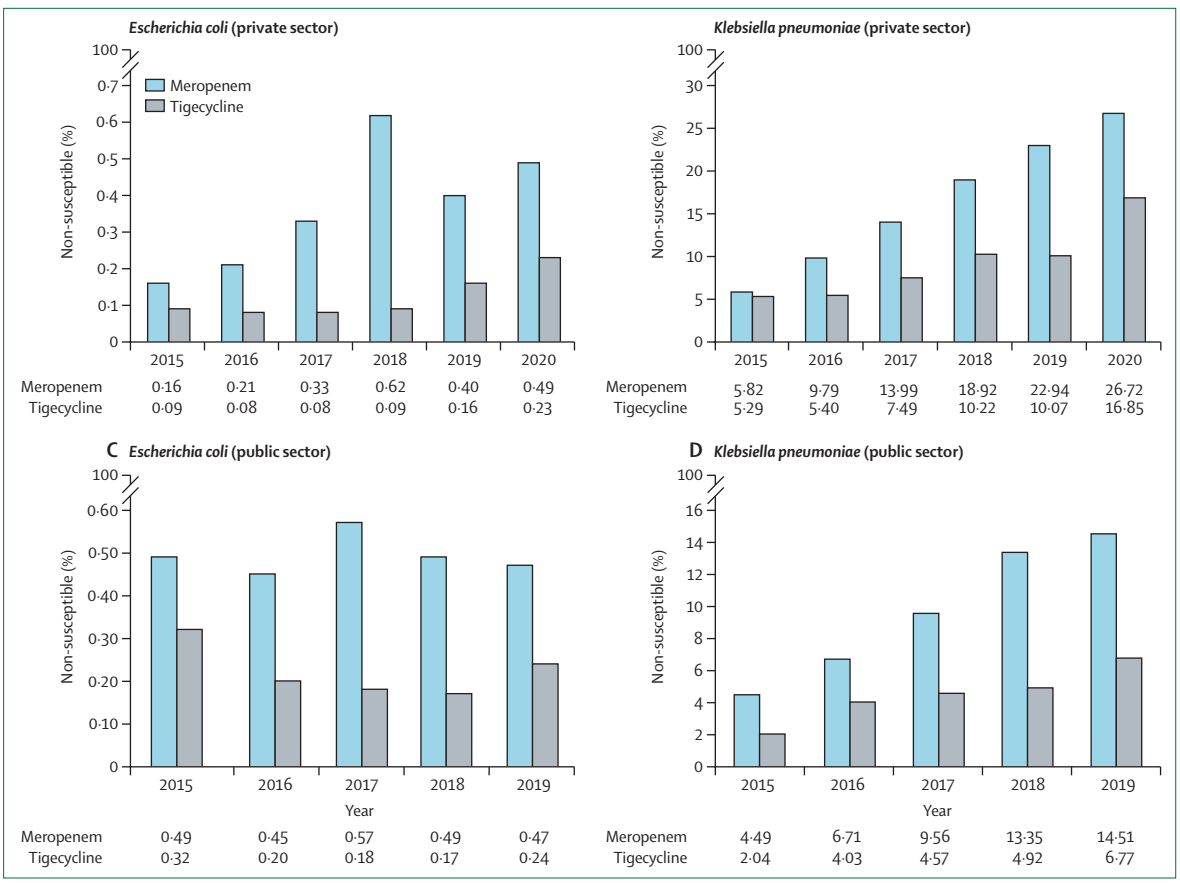


Figure 1: **Non-susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* to selected watch and reserve antibiotics in the public and private sectors from 2015 to 2019 or 2020 in South Africa**

Regional anchors

ASPPs would be regional and multinational procurement consortia that are anchored by key regional players. For example, one ASPP could be anchored by an Indian state for all of India and another by South Africa for sub-Saharan Africa. A regional executive committee with representatives from each country or state would provide governance and technical support. Each ASPP would need a legal and financial structure (secretariat) that would allow for negotiation with suppliers and for the ability to enter into legally binding, multiyear subscription agreements on behalf of consortium members. Payments could be guaranteed by a development bank. The coordinating secretariat would contract in support for forecasting and health technology assessments. Each regional ASPP would operate separately but could share information with other ASPPs. Consolidating and guaranteeing contracts as a bloc will enable stable demand and revenue for suppliers while also ensuring uninterrupted, affordable access.

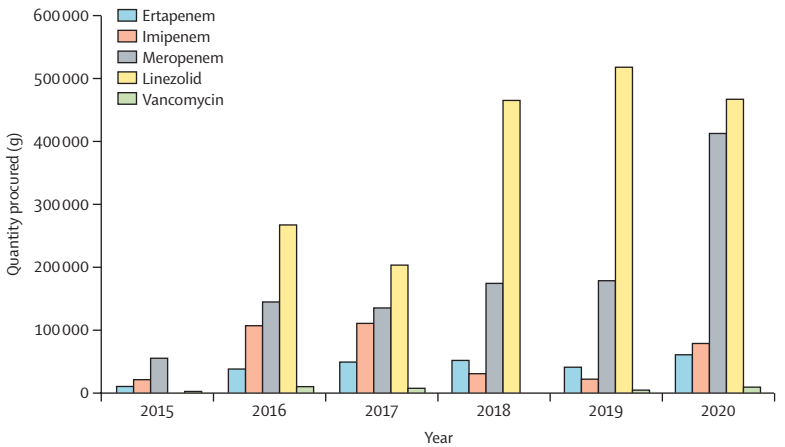
Membership of this scheme and the related provision of antimicrobials and diagnostic products could be explicitly tied to stewardship. This would support the call by WHO to "ensure that use of new products [is] governed by a public health framework".[22] This would require members to concomitantly procure diagnostic products that are suitable for use in resource-constrained settings, and it could be integrated into the terms of membership. From the authors' experience with the Longitude Prize, spending on diagnostic research and development is predominantly geared towards the needs of HIC markets. New diagnostic tests are usually not trialled in LMICs, and they often include features rendering them impractical to deploy, thus limiting global utility.

For more on the **Longitude Prize** see https://longitudeprize.org

In-country data: evidence of evolving needs

The case of South Africa highlights the importance of access to new antibiotics to address the dwindling efficacy of existing broad-spectrum, watch and reserve antibiotics, particularly for Gram-negative priority pathogens. Details of our case study on South Africa are in the appendix (pp 2–10). We found statistically significant increases in non-susceptibility to meropenem for *Escherichia coli* and to meropenem and tigecycline for *Klebsiella pneumoniae* in the public sector in South Africa from 2015 to 2019 (figure 1; appendix pp 8–10). Similar increases in non-susceptibility to these antibiotics for

See **Online** for appendix



	2015	2016	2017	2018	2019	2020
Ertapenem	10161	37798	48989	51574	40714	60514
Imipenem	20982	106697	110296	30380	21860	78462
Meropenem	55088	144333	134864	173996	178077	411911
Linezolid	0	266741	202984	464565	517129	466393
Vancomycin	2108	9860	7209	0	4378	9063

Figure 2: **Annual national procurement of selected watch and reserve antibiotics in the public sector from 2015 to 2020 in South Africa**

both *E coli* and *K pneumoniae* were evident in the private sector from 2015 to 2020 (figure 1; appendix pp 5–7). Gram-positive high priority pathogens did not reflect this trend except for the increase in non-susceptibility to vancomycin in *Enterococcus* spp in the public sector (appendix pp 5–10).

The statistically significant increase in procurement of watch (carbapenems) and reserve (linezolid) antibiotics further indicates increasing reliance on these antibiotics due to escalating non-susceptibility to narrower-spectrum access antibiotics (figure 2; appendix p 3).

In India, the Indian Council of Medical Research initiated the Antimicrobial Resistance Surveillance Network with four tertiary care hospitals hosting nodal centres, each focusing on certain clinically relevant organisms.[23] This network subsequently expanded to 16 regional centres by 2018. Data from 2016–18 suggest increasing prevalence of Gram-negative bacteria, with increasing resistance to carbapenems and colistin as well as increasing resistance to vancomycin in *Enterococcus* spp.[23] To understand trends over an extended period, we did a case study of one of the key nodal centres of this network, Christian Medical College, Vellore, India, which is described in the appendix (pp 2–3). For Gram-negative bacteria, the trend analysis of non-susceptibility to meropenem, tigecycline, and colistin from 2015 to 2020 showed statistically significant increase in *E coli* and *K pneumoniae* (appendix p 11). For Gram-positive bacteria, the trend analysis of non-susceptibility data to vancomycin and linezolid showed a mixed picture. Among *Enterococcus* spp, non-susceptibility to vancomycin increased until 2017, dipped in 2018, and jumped back up in 2019, whereas for linezolid there was an overall decrease, except in 2016 (appendix pp 11–15).

Antibiotic consumption data in the nodal centre from 2010 to 2019 showed a statistically significant increase in the consumption of meropenem, colistin, vancomycin, and tigecycline to a certain extent (appendix p 15). The increase in consumption of other antibiotics such as imipenem, ertapenem, and linezolid, was more variable, possibly due to varying factors including change in antibiotic policy and availability of medicines.

Overall, the rising consumption, along with increasing levels of resistance, highlights the crucial importance of watch and reserve antibiotics. Increased use of these antibiotics will raise the selection pressure for the development of resistance to these last-resort antibiotics, thereby further depleting treatment options in countries where infectious diseases remain among the leading causes of mortality. Access to and registration of new antibiotics, ideally with novel mechanisms of action, is therefore imperative.

Next steps: exploring viability

We believe that the markets for antimicrobials and diagnostics will stabilise and be sustainable if the demand for new antimicrobials and diagnostic products can be aggregated on a regional basis and delivered by international and regional suppliers through subscription contracts. Without the development of an innovative pooling mechanism, both existing and future pipeline products will not reach those who need them most.

The creation of ASPP would not only ensure that health-care facilities in LMICs will be able to access a portfolio of antimicrobials and diagnostic products, the mechanism would also ensure stewardship, which would be strengthened by the purchase of existing and new diagnostics designed for use in resource-constrained settings.

A number of key issues demand further exploration. First, the concept of regional ASPPs will need to be explored by regional working groups consisting of LMICs and donor countries that can commission a rigorous feasibility study. Financial scope will be determined by turnover, including margins for supporting secretariat costs, and will depend on the number of participating countries and donors, the number of antimicrobials and diagnostic products in the portfolio, and multiyear contract values. Experts in health technology assessment methodology will also be required because such assessments for products will need to be developed regionally. The feasibility study will require adequate funding to ensure that market and supplier issues are fully explored and that implementation scenarios can be stress-tested. There is also a need to secure partnerships with development banks that would act as the guarantor of contracts.

Second, several aspects of ASPPs require the cooperation of experienced partners. For example, WHO would be well placed to support and facilitate universal packaging, labelling, registration, pre-qualification, and

product introduction for new products. The collaborative procedure for product registration is a success story that can be built upon.[24]

Third, for new patented antimicrobials, the pooling mechanism could potentially negotiate licences for generic makers with support from the Medicines Patent Pool or the Global Antibiotic Research and Development Partnership. Although minimal licensing fees might not be sufficient to fund research and development, they could contribute a limited stream of income to biotechnology companies that are developing antimicrobials (with no-cost licences for LICs). Low-cost and no-cost licences will also need to be explored for patented diagnostic products.

Finally, any resistance from donors to support LICs to purchase antimicrobials and diagnostic products must be overcome. Support can be justified by the global nature of antimicrobial resistance and the relatively moderate cost of this intervention. Ultimately, as the current COVID-19 Vaccines Global Access (known as COVAX) response illustrates, action that is tailored to the needs of MICs and LMICs from the outset is essential to ensure that global health objectives are met.

Considering the urgent need to tackle the antimicrobial resistance crisis, we hope that the antimicrobial subscription and pooled procurement mechanism would provide a sustainable mechanism to increase access and save lives.

Contributors

DB initiated the project and conducted the investigation. DB worked on the conceptualisation and methodology of the manuscript together with SYE. OC assisted in the initial scoping, conducted a literature review and economic analysis, and drafted some sections. KM and SYE did data collection and data analysis for the South African case study. SJC and BV did the data collection and data analysis for the Indian case study. All authors reviewed and edited the manuscript.

Declaration of interests

We declare no competing interests.

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