GLOBAL AMR R&D HUB

Estimating Global Patient Needs and Market Potential for Priority Health Technologies Addressing Antimicrobial Resistance

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Contents

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Preface

Antimicrobial Resistance (AMR) continues to grow as a public health cause of concern. While significant efforts and investments have been made in the last few years to drive a global agenda and tackle the multi-faceted aspects of AMR, the challenge of bringing to the market new technologies and therapeutics addressing AMR remains as strong as ever. As a frontline clinician and a university professor, we witness those challenges and their effects on developers, patients and communities every day.

We believe that this study, one of the first of its kind globally, is essential to help global leaders, policymakers, philanthropists and scientists to quantify, predict and anticipate the global unmet patient need for key therapeutics and diagnostics addressing AMR. In addition, we hope that by showing the astonishing mismatch between global needs and commercial potential, this study will help mobilize the required action to both support innovation and ensure these necessary new products are accessible to those with the greatest need around the world.

Whether you are a policy maker, a funder, an advocate or a health professional, we hope this research will be useful for you. We also hope that studies such as this will continue to be commissioned in the future to expand on the existing knowledge on markets, investments, and priorities in this important but neglected area of public health.

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Study Summary

The Board of Members (BoM) of the Global Antimicrobial Resistance Research and Development Hub (Global AMR R&D Hub) sought to further understand the market attractiveness of new AMR-related health technologies that meet the highest priority unmet needs. The BoM initiated a quantitative study under the supervision of a global Expert Advisory Group (EAG), with broad geographic and technical representation across the One Health spectrum. They in turn commissioned the support of a specialist external contractor (groupH) to quantify the patient needs and market potentials in the areas they identified.

The EAG adopted a human patient-need led approach for its initial priorities, resulting in the identification of four priority health technologies – **two small-molecule therapeutics and two point-of-care (POC) diagnostics** – that were investigated in more detail by building epidemiological and commercial models, in order to provide an assessment of the patient need and market attractiveness.

The study outcomes reported here will be used to inform policy-makers of the scale of this part of the AMR challenge and to support current thinking on market intervention.

THERAPEUTICS: FINDINGS

Patient treatment needs in AMR do not lie in a single product or syndrome. Tackling AMR requires people, globally, having access to an uninterrupted and sustainable supply of therapeutics effective in treating multiple pathogens that may be involved in infectious syndromes occurring at a variety of body sites. In this study, the priority targets identified for new therapeutic advances were for **severely ill hospitalized patients with multi-drug resistant (MDR) bloodstream infections (BSI), and those with pneumonia**, caused by >2 'critical' priority pathogens as defined by the World Health Organization (WHO). WHO's critical pathogens are currently all Gram negative bacteria; their priority, in part, represents their complexity as a target for developers.

THERAPEUTICS: PATIENT NEED

All-cause pneumonia is currently associated with a larger disease burden than BSI (not least because it has non-bacterial causes as well), with almost 1.5x the estimated global cases. However, due to the higher prevalence of Gram negative bacteria in BSI (34%) than in pneumonia (16%) and the different pathogen proportions per syndrome, BSI is estimated to harbor the larger current (2020) and future (2040) burden of MDR than pneumonia by around twice – a finding corroborated by recent studies.

Of the six critical Gram negative pathogens able to cause the two syndromes – five of them are common between the two, with four of them contributing the greatest MDR burden in both syndromes. *Klebsiella pneumoniae* (the second-most prevalent pathogen in both at around 30%), *Escherichia coli* causing the greatest burden in BSI (43%) and *Pseudomonas aeruginosa* causing the greatest burden in pneumonia (40%). The latter pathogen together with *Acinetobacter baumannii* are more commonly extensively drug resistant (XDR). The relative rank, by syndrome contributions are forecast to remain the case for the next 20 years.

In terms of absolute patient burden, there were an estimated **3.7 million cases of MDR BSI** and **1.7 million cases of MDR pneumonia attributable to Gram negative pathogens worldwide in 2020**. In the absence of any intervention, patient numbers are forecast to rise to **5.5 million cases of MDR BSI and 2.8 million cases of MDR pneumonia by 2040**.

Both the absolute numbers and the proportion of MDR cases, in both syndromes, are expected to increase across all countries and income-group regions in the next 20 years. MDR incidence is currently slightly higher in BSI than pneumonia. Both MDR proportions and incidence rates grow with decreasing income status across both syndromes, demonstrating – at times starkly – how the burden of MDR infections will increasingly fall on upper-middle income countries (UMICs), lower-middle income countries (LMICs) and low-income countries (LICs). While the current burden in these income groups is heavily dominated by a few countries, for example India, the forecasts show that by 2040 other countries within the LMIC/LIC group are expected to contribute more equally (46% to 53%) to the overall income-group burden of 3.3 million estimated cases of MDR BSI by 2040. This regional levelling out is similarly seen also for pneumonia (52% to 57%).

The data show that drug-resistant infections constitute a truly global challenge. For the two syndromes and critical bacterial pathogens that were the focus of this study, high-income countries (HICs) will experience a combined case-burden of >0.5 million by 2040, driven by a doubling of MDR BSI cases. Average MDR proportions are forecast to rise from 23% to 38% (BSI) and 19% to 32% (pneumonia) in the coming 20 years. By 2040, the average rate of BSI infections that are MDR is expected to be a third in HICs; this means that in 20 years, treatment with currently available therapies will be more challenging[1] for 1 in 3 patients. Even at present there are estimated to be HICs with MDR proportions already exceeding 50% in BSI and 30% in pneumonia.

As the BSI therapeutic is likely to be the route to a new treatment for neonatal sepsis, the demographic analysis – albeit based on limited data – suggests that while children and neonates currently have higher BSI incidence rates in UMICs and in LMICs/LICs, the faster rate of population growth in the older adult (>65 years) category will likely shift the future (2040) incidence and therefore burden towards the older age group – more similar to what we see in HICs presently. In contrast, for pneumonia the highest incidence of respiratory tract infections – across income regions – is in

[1] Treatment failure is better represented by extensively drug resistant (XDR) measures, but data were considered too limited to use this measure in this study

older adults (>65 years), followed by young children (0 – 4 years). Due to higher population growth, the former will also likely remain the most significant driver of future MDR Gram negative pneumonia patient numbers.

THERAPEUTICS: MARKET POTENTIAL

The 'market potential' of a product is a measure of attractiveness for private sector developers and was expressed in this study in terms of peak year sales. The priority unfulfilled needs for antibiotics identified in this study were a therapeutic for the treatment of BSI (Therapeutic 1, Tx1) and pneumonia (Therapeutic 2, Tx2). Each therapeutic was estimated to generate less than $200 million[2] (**$184 million for BSI** and **$127 million for pneumonia**) in sales revenue at their market peak in 2036, following a first launch in the US in 2025. Under the current market model, this revenue is determined by the volume and price that payors in the market are able, or willing, to pay/reimburse. These estimates are broadly in line with similar estimates previously carried out and confirm a now solid body of evidence – from studies and anecdotally – that antibiotic markets are unattractive investments for private companies and investors, both in absolute terms and relative to other therapeutic areas. What this study suggests is that at the apex of the public health need (the products modelled here), the market may be failing most acutely and therefore struggle to deliver these most needed products to society. This situation, combined with the long development time of new drugs, signals that action is warranted increasingly urgently.

[2] $ refers to US dollars throughout the report

'Peak year sales' is a simple measure that companies use in the early stages of product development to inform their investment decisions around which medicine candidates to progress – it is simply the 'return' aspect of the 'return on investment' equation. Factoring in conservative investment (or cost) estimates for R&D of between $200 million – $300 million (per product), simply demonstrates how unfavorable the economics currently are. Additionally, these costs do not account for the further investments, post launch, to secure the additional indications and testing necessary to reach both the populations profiled and specific high-need patient populations, i.e., for our BSI therapeutic to reach its critical neonatal sepsis population group.

At peak modelled sales of our therapeutics, the BSI and pneumonia antibiotics capture, on average, a **7.4% and 5.3% patient share**, respectively, of a projected, branded, intravenous (IV) Gram negative market currently worth ~$500 million in sales from 70+ countries worldwide. Private investors and companies can also look to this total market as an indicator of commercial possibility. The relatively weak commercial assessment is explained both by the profiles themselves and the market response to them, whereby they would be late entrants and, given data deficits, they would struggle to differentiate themselves from the competition. These calculations (base-case) represent market realities despite both antibacterials having a good clinical profile and being 'needed' by clinicians to treat their patients.

The global uptake of our therapeutics was modeled as a function of the roll-out by

region coupled with patient shares, and it assumes that a multinational pharmaceutical company – with the requisite global distribution network – would support multi-market entry. This broad global availability, the basis of these calculations, can no longer be relied on given that **only two of eight Gram negative active therapeutics, launched since 2014, are currently available outside the US**. At peak year sales in 2036, around **70% of the therapeutic revenues are estimated to originate in HICs and 30% in the rest of the world**. When looking at the patients associated with these revenues, our forecasts indicate a worsening access gap whereby the antibiotics that work are **not available in the parts of the world at the scale where the need is dominant and growing most rapidly**. This represents a concern for the whole world given the transmissibility of AMR and related infections and the pivotal role effective antibiotics play across modern medicine.

These revenue estimates were made as the current most likely scenario, based on a stable existing market. However, the estimates are sensitive both to changes in the environment and also to the assumptions that were used. Possible favorable and unfavorable impacts on the baseline market potentials were explored, in the current patent-based system, through the existing market levers of price and/or volume.

When the model assumed that 30% of the market (as opposed to 5 – 7% under the base case) could be captured by one of our therapeutics – perhaps through a superiority data claim – revenues for both therapeutics were forecast to exceed $700 million. In contrast, **a shrinkage of the whole market** (in patient terms) – perhaps due to more stringent stewardship – by 36% at peak in 2036 from 2019 patient numbers, saw a contraction of the revenues for our therapeutics of **around 66% to $61 million (Tx1 BSI) or $44 million (Tx2 pneumonia)** at peak year in 2036 – indicating that under such a scenario such products would never be brought to market and therefore patients.

Looking at price as a lever, a scenario where all currently purchasing countries increased their valuations and willingness to pay for these therapeutics, **prices would need to increase in the range of 380% – 550% to reach $700 million**. In a second scenario, with only **10 currently purchasing countries** – from the high-income G20 pool of countries – it showed that a much **higher level of price increases of 520% (Tx1 BSI) to 900% (Tx2 pneumonia)** would be necessary to improve the overall global attractiveness of these products for developers.

DIAGNOSTICS: FINDINGS

Enhanced and more widespread diagnoses – and the improved understanding these provide – would bring benefits across the AMR response, as we have so dramatically witnessed through the current Covid-19 pandemic. The priority diagnostic needs identified for this work were (i) a rapid POC device to differentiate bacterial from non-bacterial infection (Dx1), a critical tool for our ability to move beyond empiric treatment, and (ii) a diagnostic device that can perform pathogen identification and antibiotic susceptibility testing in one device (Dx2) – important as we try to move towards more targeted treatment of bacterial infections.

DIAGNOSTICS: PATIENT NEEDS

In 2020, five years before the modeled launch of the hypothetical diagnostics, Dx1 (bacterial vs other etiology) is expected to have a **global patient need of 436 million people**. Due to the need for this diagnosis to be made early in the patient journey, i.e., when the patient first presents to the healthcare system, this need is estimated based on eligible patients from the number of primary care consultations. This patient need, however, is around 20 times higher than the **22 million patients conservatively estimated to be eligible for the second prioritized diagnostic – Dx2 (ID/susceptibility)**. Such a device would enable a more specialized physician to be informed exactly what the causative bacterium is and what medicines the various bacteria are susceptible to. As we move towards 2040, such a device would be critical for supporting the uptake and use of the more narrow-spectrum agents increasingly in development.

In 20 years' time (2040), when these hypothetical diagnostic devices would have been on the market for 15 years, the patient need has been forecast to have risen **to around 800 million and 30 million patients for Dx1 (Bac. vs other) and Dx2 (ID/susceptibility), respectively**. For Dx1 (Bac. vs other), the majority (57%) of the need in 2040 is required in the LMIC and LICs with the remaining 43% fairly equally distributed across HICs (20%) and UMICs (23%). For Dx2 (ID/susceptibility) by 2040 85% of the forecast patient need – and utility – will lie outside HICs, with UMICs and LMIC/LICs more similarly distributed at 39% and 46% respectively.

DIAGNOSTICS: MARKET POTENTIAL

Under current market conditions, in value terms, both diagnostics are much more similar, with global annual revenues in 2030 estimated to be **around $300 million** for each. Although 10 years later (2040), or 15 years since their launch, global revenues for Dx1 (Bac. vs other) are forecast to grow 47% to reach **$403 million**, a much higher level of growth than for Dx2 (ID/susceptibility), with projected growth of 25% to reach **$394 million**. At ~$400 million for each, these are modest returns indeed for a diagnostic developer successfully realizing the development of such valuable health technologies that could transform our AMR response.

The hypothetical nature of these products, the scarcity of data available for modeling and greater uncertainty around the assumptions, have made the base case less certain. Hence, a 'more favorable' market scenario was modeled (in terms of uptake and reimbursement). Under this favorable scenario, revenues from 2030 sales of Dx1 (Bac. vs other) were **8 times higher (at $2.1 billion) and for Dx2 (ID/susceptibility)** around **1.6 times higher (at $496 million)** than under the current status quo. This scale difference represented by the more favorable scenario largely remains until 2040, with the developer of Dx2 (ID/susceptibility) gaining lower revenue growth (to $600 million) than for Dx1 ($2.8 billion). More notable under this more favorable scenario is the estimated growth in reach of these products, enabling an increase in patient diagnoses with Dx1 (Bac. vs other), of nearly 14 times (to achieve 233 million patient diagnoses in 2040), but a less marked 2.75-

fold increase with Dx2 (ID/susceptibility) to reach 8.8 million patient diagnoses in 2040. The less marked increase could partly be due to its relatively greater success already under the base-case or current situation, with the 'use-case' (device adoption) indicating it could reach ~10% of the projected hospital need in contrast to that for Dx1 (Bac. vs other), which was projected to barely reach 2% of its target patients in primary care settings, due to an overall less positive use case with clinicians likely to still favour quick empiric treatment.

The study's breadth and concrete nature have enabled reflection on the key data/knowledge gaps that were revealed during the conduct of this work, future directions for this initial, foundational, study and recommendations for policy action.

Policy Insights & Recommendations

Priority AMR Patient Needs

- Our study identified the priority targets for new therapeutic advances in antimicrobial resistance (AMR) as those for severely ill hospitalized patients with multi-drug resistant (MDR) bloodstream (BSI) and pneumonial infections, caused by >2 'critical priority', Gram negative bacterial pathogens, as defined by the World Health Organization (WHO).
- These most critical needs have been estimated as a current challenge and one that is set to increase globally over the next 20 years in all countries across all income groups. By 2040, cases – for only these two syndromes and critical causative pathogens – are forecast to impact 8.3 million people across 80% of the world, meaning current treatment options will increasingly be ineffective.
- High-income countries (HICs) are forecast to see both their absolute number of patients with MDR BSI double by 2040 and the rates of growth in BSI infections that are MDR climb to a third on average. At present there are estimated to be HICs with MDR proportions already exceeding 50% in BSI and 30% in pneumonia.
- Overall, the growing burden of MDR Gram negative bacterial infections is forecast to be disproportionately borne by patients in low and middle-income countries i.e., outside traditional innovation-financing countries.
- A handful of individual countries currently bear a disproportionate AMR burden in all income-groups. In lower-middle income (LMICs) and low income countries (LICs), particularly, while India's absolute country burden currently dominates and is forecast to climb, its declining burden as a proportion of its income group suggests a 'catching up' by other countries at similar level of development.
- The two priority needs in terms of diagnostics are (i) reducing empiric prescription – *Diagnostic 1* and (ii) moving towards more targeted treatment – *Diagnostic 2*; around 80% of the need for these diagnostics was identified as falling outside HICs.
- The highlighted patient burden of AMR cannot be met by new products alone and serves as a timely reminder of the importance of the Global Action Plan and the supporting of implementation of National Actional Plans to strengthen – particularly cost-effective – public health interventions across the breadth of the AMR response.

AMR Therapeutic Market

- Analysis of the small-molecule candidates currently in the clinical pipeline indicates that the priority therapeutics, as defined for this study, are unlikely to reach the market in 2025 as modeled. However, should this happen, they were forecast to generate peak sales revenues (in 2036) of $184 million and $127 million for BSI and pneumonia, respectively. These revenue forecasts indicate the magnitude of the current market 'pull' as being low – likely too low to cover the product development costs – and a challenging investment case for traditional private actors.
- This most recent quantification, corroborates previous studies over the last decade as well as the insufficiency of the current clinical pipeline. Further public/philanthropic support for these markets is warranted, given the public health importance and the weak investment case, which is compounded by multiple other challenges around data generation and licensing in the countries and patient groups facing the highest need.
- Current pre-licensure support for product development (push) needs to be flanked by strong action on the post-licensure (pull) side of the market – the focus of this study. This will ensure that current push

investments are able to yield the full breadth of their patient and societal benefits. New technologies reaching market approval with significant clinical utility for priority needs, should be supported with larger and more sustainable rewards to reflect their full social value so new products continue to be both developed and available across the breadth of global need quantified in this study.

- Should such priority therapeutics reach the market, they are likely to struggle – under current market conditions – to be registered and available in a critical mass of priority countries. Three factors brought into focus through this study highlight these global access risks and vulnerabilities in the current system and call for both earlier more embedded access planning together with urgent dialogue with a broader constituency of stakeholders including the international donor community. The first is the scale of the mismatch between the forecasted need and the likely geographic availability of new therapeutics and diagnostics highlighted, the second is the emerging trend of diminishing availability of new antibiotics in all countries outside the USA and finally – perhaps an underestimated risk for the public sector – are the access implications of the current dominance of small developers combined with the reliance on the global commercialization and distribution apparatus of only two remaining multinational pharmaceutical companies.
- Scenarios explored in this study, indicate both the necessity, and limitations, in the ability of traditional policy levers available under the current market system – price, volume and patents – to increase the market potentials sufficiently. The specific features of these markets, such as the stewardship imperative, slow uptake, low and fragmented global volumes and cheap and plentiful[3] older antibiotics suggest that supplementary support and /or implementation of new models will additionally be required.

AMR Diagnostic Market

- Improved and more readily available point of care diagnostics – and the enhanced understanding this imparts – would bring benefits across the AMR response.
- Two emerging trends are observed: (i) an increase in the number of narrow-spectrum antibiotic candidates in the pipeline and (ii) a higher and growing burden of critical AMR outside HICs. Both are adding urgency to the need for increased diagnostic capability in countries, particularly for the roll-out of newer antimicrobials.
- The uptake of critical new antibiotics such as those modelled in this study or those narrow-spectrum agents in the pipeline, could be collectively and usefully supported by diagnostics that cover a range of bacterial identification and broad-susceptibility panels (a profile similar to our Diagnostic 2 – ID/susceptibility). The susceptibility panel data could be captured to improve AMR surveillance. The public health costs and benefits warrant further investigation.
- The two priority diagnostic needs identified showed only very modest market potential under current market and reimbursement conditions, reducing the likelihood of private sector development and global roll-out.
- The demonstrated impact – in terms of number of patients diagnosed globally – of a more favorable reimbursement environment (including donor support) particularly for Diagnostic 1 (bacterial vs. other etiology) warrants global development stakeholders and donors being more closely engaged in the AMR dialogue.
- The transformative global diagnostic uptake precedent seen through Covid-19 is a positive learning experience to be harnessed.

[3] if increasingly redundant

Recommendations

This study was conducted based on the current market context for AMR technologies (antibiotics and diagnostics) defined as being of critical priority to the AMR response and the authors recommend:

1. That widespread and immediate use of existing policy levers i.e., national-level reform of pricing and reimbursement (ideally backed by broader value-assessment frameworks) are required, as current sales revenues from AMR technologies are insufficient to support private investment. This intra-country action would leave individual health systems to discriminate and value individual AMR technologies according to their own needs, priorities and available policy-levers.

2. That such national efforts should be supplemented with additional pull support measures in order to reach the scale of return on investment to be attractive to private developers and investors and ensure critically important new products are both sustainably developed and also licensed in a broad number of countries with accompanying stewardship measures to ensure their longevity.

3. To substantially progress the dialogue on possible global access, distribution and supply chains efficiency mechanisms due to the growing reliance on smaller developers and the geographic location of the projected future AMR burden – outside HICs.

4. Three areas for action to further strengthen rewards that warrant further investigation are:

   - Options to stabilize the priority antibiotic market segment (priority pathogen-targeting or Gram negative) beyond individual products should be investigated, thereby sending an urgent signal to private investors/companies/capital markets and securing a whole market segment of high public health importance
   - Considering if and how voluntary cooperation on demand-aggregation mechanisms (pooling volumes through procurement or similar) can help ameliorate the challenges of low and geographically thinly-spread demand across many individually unattractive markets
   - Mobilization of donor-support and exploration of supra-national coordination of procurement and widespread distribution options particularly for diagnostics and especially for LICs and LMICs

Glossary

Term	Definition
Analogue	An analogue is a close comparator – an existing thing or situation which is then adapted and applied to something that does not exist or has little data (i.e., a hypothetical) to support it
Core Countries	Countries for whom detailed analysis was performed for quantification
Compound Annual Growth Rate (CAGR)	The change in an investments value over a set period of time (yearly). This is used in the modeling conducted here to adjust for uncertainty in the future
Estimate	An approximate calculation of the value, number, quantity, or extent of something [e.g., expected revenues, costs for developers, patient needs]
Forecast	Estimating what the situation will be in the future
Forecast Model	A simplified version of reality that allows us to observe, understand, and make predictions about (economic) behavior
Healthcare Professional (HCP)	The term used to describe a physician or community health worker that typically would diagnose and treat a patient across healthcare settings
Incidence	The number of new cases that *develop* during a specified time period
Loss of exclusivity (LOE)	When a patent on a product expires
Market attractiveness	Measure of the financial appeal of a market to private sector actors
Market potential	A measure of maximum, estimated, attractiveness – or how much actors are expected to pay for and value a new health technology (most often expressed in peak revenue or peak sales)
Multi-drug resistance (MDR)	Resistance to one or more antibiotics in three or more distinct antibiotic classes
Net present value (NPV)	The value of all future cash flows. A measurement of the difference between present value of cash inflows versus the present value of cash outflows over a period of time
Peak patient-share	A measure of the proportion of patients for whom the product is likely to be considered both clinically beneficial over other options and cost-effective and therefore prescribed
Peak revenue	The highest revenue for a manufacturer from a product during its life cycle
Prevalence	The number of disease cases present during a particular time
Proportion	A part of share of the whole population
Projection	An estimate or forecast of what the situation will be in the future based on present trends
Peak year sales (PYS)	The highest revenue for a manufacturer from a product during a calendar year
Scale-up	Is a simple measure of extrapolation, applied here to different countries deemed to have similar attributes but which are not assessed on an individual basis
Standard of Care (SoC)	The treatment that has the evidentiary and clinician support making it the most appropriate for a particular disease in a specific setting
Total Addressable Market (TAM)	The total available revenue opportunity for a product were it to secure 100% market share
Uplift	A term used in modeling – often in the context of analogue analysis – that enables a detailed understanding of one situation to be used as the basis for extrapolation to similar situations

Acronyms

Acronym	Term
AB	Antibiotic
AMR	Antimicrobial resistance
AST	Antibiotic susceptibility testing
BoM	Board of Members
BSI	Blood stream infections
CAGR	Compound annual growth rate
CAP	Community-acquired pneumonia
DTR	Difficult-to-treat resistance
Dx	Diagnostic
EAG	Expert Advisory Group
GBD	Global Burden Disease
GN	Gram negative
GP/PCP	General practitioner (GP) /Primary care physician (PCP)
HAP	Hospital-acquired pneumonia
HCAP	Healthcare-associated pneumonia
HCP	Healthcare personnel/professional
HIC	High-income country
iAB	Intra-abdominal infection
ID	Identification [pathogen]
IPC	Infection prevention and control
IV	Intravenous
IVD	In-vitro diagnostic [device]
LIC	Lower-income country
LMIC	Lower-middle income country
LOE	Loss of Exclusivity
MDR	Multi-drug resistant
MIC	Middle-income country
MNC	Multi-national company
MOA	Mechanism of action
MRSA	Methicillin-resistant *Staphylococcus aureus*
NPV	Net present value

PK/PD	Pharmacokinetic and pharmacodynamic [model/profile]
POC	Point-of-care test
R&D	Research and Development
Rx	Prescription medicine
SoC	Standard of care
SME	Small medium enterprise
SSTI	Skin and soft tissue infection
TB	Tuberculosis
TPPs	Target product profiles
Tx	Therapeutic
UMIC	Upper-middle income country
UTI	Urinary tract infection (cUTI; complicated urinary tract infection)
VAP	Ventilator-acquired pneumonia
WASH	Water, Sanitation and Hygeine
WHO	World Health Organization
XDR	Extensively drug-resistant
YoY	Year-on-year

1. INTRODUCTION

1.1 Origins and background

One of the challenges hampering a more unified and coordinated global action in the field of Antimicrobial Resistance (AMR) product development is a lack of systematic evidence or data to quantify the need for specific products, as well as their market potential, expressed in monetary terms. Assessing any mismatch between patient needs and forecasted revenues is pivotal for understanding the public health challenge and for indicating the scale of the support and intervention required.

The Global AMR Research and Development Hub (Global AMR R&D Hub) was established following a call from G20 leaders – during Germany's 2018 presidency – for a new international R&D collaboration hub "*to maximize the impact of existing and new antimicrobial basic and clinical research initiatives as well as product development*".

The Global AMR R&D Hub aims to improve and enhance R&D activities and policies across the One Health spectrum. In 2019, one of the Board of Members' (BoM) first actions was to establish an Expert Advisory Group (EAG) to undertake market analysis on the need for and revenues of selected technologies.

Addressing AMR requires several types of innovations in the form of new technologies offering especially therapeutic, diagnostic and preventive solutions. Therapeutic technologies such as antibiotics are exposed to the inexorable dynamic of AMR. Therefore, it is essential to create a product development and deployment landscape that is innovative and sustainably able to introduce new products that replenish or even broaden our therapeutic arsenal, as old products lose efficacy. The pipeline from discovery to licensure of new drugs and the associated timelines (currently up to 15 years), has to respond and adapt to future resistance profiles and population needs – decades into the future. This is clearly a challenge which requires systematic analyses of these needs, as well as of the likelihood they will be translated into revenues for product developers.

Diagnostic technologies such as rapid tests are widely acknowledged as key tools to support the rational use of antibiotics and preserve their value. However, there is limited evidence of the actual size of the needs for these type of products in healthcare systems and of the revenues that they can provide to developers. In fact, it is only by assessing to what extent patient needs can be translated into actual demand and revenues that we can understand how economically attractive any AMR-related product is for developers.

Development of health technologies builds on academic foundations and large swathes of public money before, largely, being 'translated' into clinical development and commercialization which is largely undertaken by private companies. Economically unattractive but highly needed products would accordingly motivate further public interventions to stimulate development. Assessing economic attractiveness for particular technologies requires modeling the functioning of the markets into which they are expected to be introduced.

1.2 Modeling health technology markets

Modeling health technologies is commonplace within companies and increasingly within the donor community. In the field of AMR, one of the first warning bells about the challenges in antibiotic markets, was sounded through the Swedish Presidency of the European council in 2009[4]. In the interim 15 years or so, a number of subsequent studies and reports [5,6,7,8,9,10,11,12] have aimed to investigate both the challenge and proposed solutions. From the UK AMR Review[6] and the EU IMI's DRIVE-AB[12] to the German G20 presidency of 2018[7,8], while adopting different approaches, many of these studies produced similar findings and made concrete suggestions for paths forward.

A model is a structured way of thinking about the dynamics of a situation. The Covid-19 pandemic has familiarized us with modeling in the field of public health and infectious diseases, from the simplest epidemiological models that help us understand how a virus may affect populations into the future, to more complex scenario-based models that help simulate the varying effects of public health interventions. These models let us use the know-how gained to make plausible assumptions and predictions about potential future scenarios and outcomes despite the inevitable unknowns and uncertainties. Modeling for public health requires understanding patient or societal needs and their fulfillment whereas in the private and philanthropic sectors economic factors have more prominence. Similar approaches for understanding which patient needs and technologies to support and prioritize are increasingly being adopted by all actors.

Drug discovery and development are a special case of investment in the context of greatest uncertainty. In addition to estimating costs and revenues (returns) one has to also factor in the risk that a drug project will be terminated before launch[13]. This type of modeling is commonplace among many business actors making decisions based on a hazy future.

As with many projects across all technological domains, the attractiveness of a product for a developer in the private sector is reflected by its return on investment (ROI), which in turn depends on the revenues it can generate compared to the costs to develop or obtain it. Market modeling and analysis helps stakeholders to assess the expected return and value of pharmaceutical candidates and other medical technologies so as to inform R&D investment decisions years before a product is finally ready for market launch. This type of modeling also helps developers compare the return and values of alternative investments, such as drugs in different therapeutic areas, when they have to select only one or a few options.

[4] (Mossialos et al., WHO 2010)
[5] (Sertkaya et al., 2014)
[6] (Review on AMR Final Report, 2016)
[7] (GUARD Report, 2015)
[8] (GUARD Report, 2017)
[9] (Daniel et al., 2017)
[10] (OECD, 2017)
[11] (Wellcome Trust, 2020)
[12](DRIVE-AB Report, 2018)
[13] (Svennebring & Wikberg, 2013)

2. METHODOLOGY

2.1 Overview of approach

The aim of quantifying both the patient need and market potential to meet those needs required both epidemiological and commercial modeling.

Market potential is a measure of attractiveness – or how much actors are expected to pay for and value a new health technology – and can be determined in a number of ways. Typically, both large pharmaceutical and Small and Medium Enterprises (SMEs)/ biotechnology companies and their private financiers (venture capitalists and other private investors) use either 'peak sales potential' or 'net present value (NPV)' measures.

As the simpler measure, peak sales are more typically used by established pharmaceutical companies during early stage, strategic planning. They can also be a more meaningful measure to assess known, established markets. Additionally, it is often considered the most important parameter for deciding whether to move a research project into development and comprises two components: the height-of-peak sales and the time required to achieve peak sales[14].

Peak sales are one component of the more comprehensive NPV-based assessments. As projects progress further through development, or when a project is thought to significantly differ (from average projects) with regard to time, cost or risk, NPV is more commonly applied. This uses probability distributions to model development risk, costs, potential outcomes and respective consequences. A risk-adjusted NPV calculation is the more complex calculation but, in addition to sales, takes into account costs, timings and associated risks. An example of how these two measures differ is provided in the **Info Box**[15] above, which illustrates – for the same project – how the outcome may differ.

Example of the difference between peak sales and net present value

'Taking a project with a peak sales potential of $250 million, the equivalent risk adjusted NPV falls from $38 million to $9 million and for projects with a peak sales potential of $100 million, the risk adjusted NPV turns negative to -$9 million. These are tangible examples of the impact of risk on the attractiveness of a market.'[15]

In smaller or more niche therapeutic areas, broader measures are also sometimes used. Some investors and companies tend to employ 'total addressable market (TAM)' as a measure of the overall revenue opportunity available to a product or service if 100% market share has been achieved.

Due to the hypothetical nature of the need profiles and the broad geographic scope of the project, peak revenue was considered a simpler and hence more meaningful measure of market attractiveness in this instance (see **Info Boxes** on 'Rationale for approach' below). For the diagnostics, the even more hypothetical nature of the products themselves combined with a substantially less

[14] (Fischer, Leeflang & Verhoef, 2010)
[15] (Nickisch, Greuel & Bode-Greuel, 2009)

robust knowledge and data foundation, led to a single conservative bottom-up global estimates with 'Use Cases' at their core to determine both patient needs and market potentials.

2.2 Overview of process

An overview of the process adopted to conduct this work is shown in **Figure 1** and summarized in this section. The work was carried out in five phases during 2019-2021. Three of the phases (1, 2 & 5) were conducted by the EAG. For the core quantific ation work (phases 3 & 4), the EAG outsourced this activity to a specialist company to perform. Terms of Reference were drawn up and a public invitation to tender in accordance with UVgO (Unterschwellenvergabeordnung) was successful in securing a specialized contractor (groupH). The EAG and groupH worked closely during phases 3 & 4, with the former providing steerage and oversight as the quantification phases were being performed and the latter bringing their specialized know-how to the work. The Secretariat of the Global AMR R&D Hub supported the parties and the process throughout. In the fifth and final phase, the EAG were closely involved in drafting and finalizing this report.

Rationale for approach to Therapeutics

Due to the global nature of the task and the limited availability of data, an approach was adopted that prioritized simplicity while using best-available evidence for its baseline. Hence for the therapeutics, two, separate, static models were selected. The quantification of the patient numbers used a bottom-up epidemiological model and the quantification of the market potential used a top-down model based on the existing market for Gram negative antibiotics. Uncertainty of the commercial estimates is explored by modeling alternative scenarios.

Rationale for approach to Diagnostics

In the absence of a repository, or source, of commercial data on diagnostic markets (as exists through IQVIA with therapeutics), combined with the absence of robust epidemiological data to inform patient numbers. An approach based on combining best-available patient number estimates with consideration of the 'Use Cases' (see pg. 37) – immediate diagnostic context – for each diagnostic was considered the most feasible given both the substantial data gaps and the hypothetical nature of both diagnostics. Uncertainty of the commercial estimates is explored by modeling alternative scenarios.

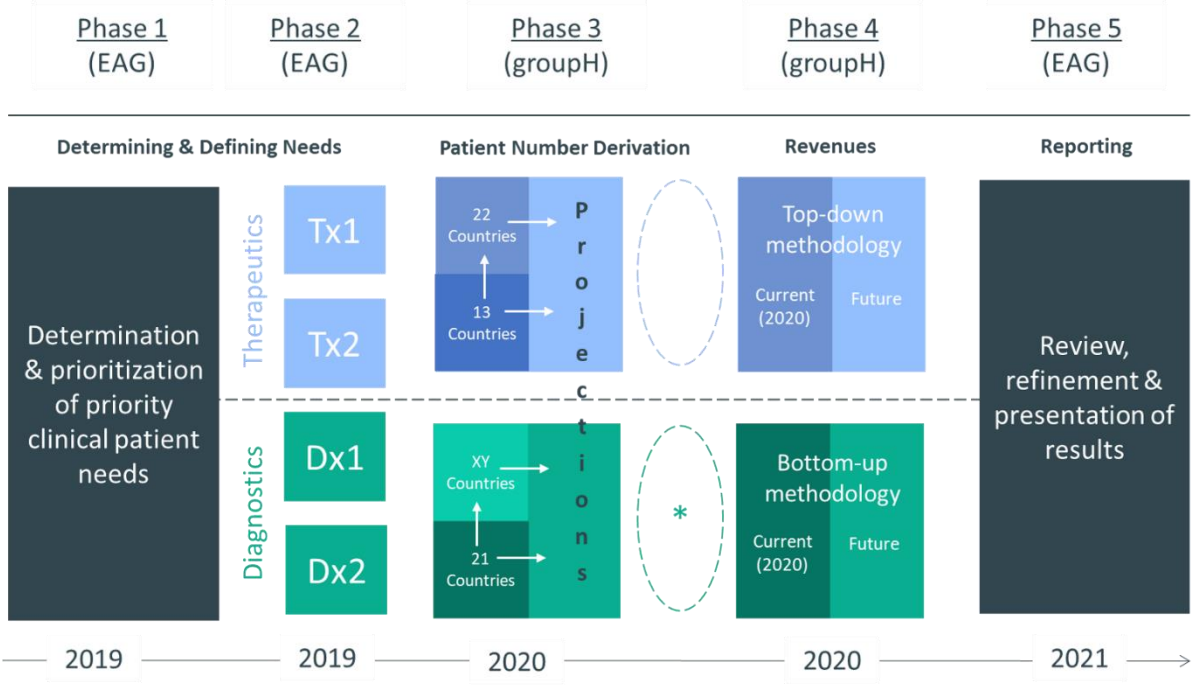

Figure 1: Overview of process & approach to the work.*Section 3.3.*

Phases 1 & 2: Determining the needs to be quantified (pg. 25-27).

A literature review was the basis for drawing up an initial short-list of global clinical needs by syndrome, pathogen and product. A survey then elicited EAG members' input and priorities, and this was combined with contributions from board members and other emerging work in the field. The four resulting 'need profiles'[16] (two **Diagnostics** and two Therapeutics) were agreed upon.

Phase 3: Quantifying patient need (pg. 28-39).

Therapeutics

For the two therapeutics, an epidemiological, bottom-up approach was taken to estimate the current global patient needs for these products. Detailed analysis was conducted at the national level for 13 countries, with four countries for each of the three selected World Bank income groups. The countries chosen (**Table 2**) and the criteria for their selection can be found in **Appendix 1**. These granular data were then used to create a 'syndrome analogue' enabling the extrapolation or 'uplift' (see **Info Box** on pg. 31) of the estimated patient numbers in an extended set of 22 countries.

Figure 3 illustrates the step-by-step process used to estimate patients with multi-drug resistant (MDR)-severe (syndrome) caused by Gram negative bacteria, starting with overall syndrome incidence. Those patient case estimates were then projected at five-year intervals (2020, 2025, 2030, 2035, 2040), by applying resistance proportions and syndrome cases to population growth forecasts.

[16] These are not target product profiles (TPPs) but were developed only so far as was considered necessary to delineate a 'market'

Diagnostics

To quantify the need for the diagnostics, patient numbers were calculated through a bottom-up process. Similar to the analysis conducted for the therapeutics, it used a core pool of 21 countries (**Table 4**) based on the selection process found in **Appendix 1**[17].

Calculating the patient needs (**Figure 7** & **Figure 8**) was based on estimates of patient consultations in the setting where the diagnostic would primarily be accessed (primary care for Diagnostic 1 and hospital care for Diagnostic 2) applied to country-level syndrome estimates from the epidemiological modeling. A 'scale-up' factor was defined for each of the three income groups, based on the countries in each. This factor was then applied to further countries by income group until an estimate of current 'patient cases in need of such a diagnostic' in 80% of the world's population was reached.

Phase 4: Quantifying market value (pg. 40-57).

Therapeutics

The market potential for the two therapeutics was calculated top-down using peak revenue as the measure of market attractiveness. A sub-set of the current market comprising nine branded agents formed the basis for the revenue calculations.

For both therapeutics, a market launch date of 2025 was assumed. A product analogue (see **Info Box** on pg. 31) was built capturing how the product was likely to perform in relation to its class competitors. The expected sales figures generated by country were then estimated and aggregated by income group. These estimates were projected using 2010-2019 consumption trends to generate expected future trends and market drivers, becoming more conservative as the projections go further forward over time.

Four alternative scenarios were explored (see 'Therapeutics: Scenarios' on pg. 46), two for the pricing parameter and two for the volume parameter, as below:

- *Scenario A*: Positive pricing scenario
- *Scenario B:* Moderately favorable pricing scenario
- *Scenario C:* Positive volume scenario (individual product)
- *Scenario D:* Negative volume scenario (at market-segment level)

Diagnostics

The study was limited by the absence of an established global market, the 'aspirational' nature of the defined diagnostic and a relative dearth of data in the diagnostics field (compared to therapeutics). The diagnostic revenues were calculated bottom-up, building the market from the patient numbers derived in phase 3 (**Figure 7** & **Figure 8**). Commercial parameters and assumptions were applied to the country-level patient numbers[18] (derived from phase 3) at an income group[19] level to determine peak patient-share revenues for each test[20]; these current revenues were then broken down by country on a population basis. Aggregated income group population data were used to define a 'scale-up' factor

[17] 13 of which overlapped with those selected for the therapeutics analysis
[18] The number of 'all-cause hospitalised patients with BSI, HAP, VAP and CAP' by country are subject to instrumental 'site viability' considerations and financing assumptions following the rationale of the 'local use case' and research and analysis of analogues
[19] Except the US
[20] And associated instruments

for each grouping and then summed to provide an estimate of current global revenues.

The estimates were then projected into the future, at the same five-year intervals, using population growth forecasts (Diagnostic 1) for the >65-year-olds for each country. For Diagnostic 2, the total projected numbers of hospitalized syndrome cases (from the therapeutic epidemiology in phase 3) was used for projections.

Two commercial scenarios were modeled (see **Table 10**) as below:

- *Scenario 1*: Current situation
- *Scenario 2*: Hypothetical situation (assuming favorable changes to policy, reimbursement & uptake context)

Phase 5 (verification and reporting)

Interim data sources, assumptions and findings were presented to the EAG at regular intervals. Feedback was collated and addressed by groupH within the bounds of the study's scope, budget and available time. EAG members had the opportunity to provide input on emerging findings, report drafts and recommendations. At times, sub-groups were formed to enable more in-depth discussions among those of similar expertise and many EAG members made themselves and their networks available for interviews as part of the secondary research that supported the modeling (see **Appendix 2** for examples).

2.3 Determining priority needs

A step-by-step process was undertaken as outlined in **Figure 2**.

Step 1: Scope. As defined by the Global AMR R&D Hub's BoM, the scope of the EAG's work was set out as follows:

- *Pathogens*: Causative pathogens as listed on the World Health Organization (WHO) Global Priority Pathogen List of Antibiotic-Resistant Bacteria[21] and *Mycobacterium tuberculosis* (listed pathogens) only
- *Sectors*: Could include treatment, prevention or diagnostic products from other sectors in the veterinarian and environmental fields that might have a direct impact on human infections caused by the listed pathogens
- *Product types*: Treatment, prevention or diagnostics, as detailed in **Table 1**
- *Product Target*: While some products will be pathogen-specific, others may target syndromes caused by multiple pathogens
- *Product Profiles*: Detailed market-potential analyses based on fully developed target product profiles (TPPs) are not within the scope of this study and are hence subsequently described as 'need profiles'

Step 2: Literature review. To identify and prioritize products where, globally, there was the greatest unmet need, a literature review was undertaken that identified diseases caused by the listed pathogens.

[21] (Global Priority Pathogen List, WHO 2017)

Figure 2: Overview of the process undertaken by EAG to derive the priority needs for quantification.

Step 3: Scoping analysis. The rough incidence and mortality (where available) and an assessment of the landscape and pipeline of products for the syndromes identified was conducted. The review informed EAG discussions and the development of an online survey. Steps 2 and 3 led to the development of a list of identified syndromes, pathogens and products (**Table 1**).

Step 4: Targeted survey. An online survey was drawn up to gather expert opinions from EAG members and others regarding what products for which disease syndromes were most needed to help address drug-resistant bacterial infections. The survey asked respondents to prioritize the list of disease syndromes drawn from the literature review, identify which pathogen they considered most important for each syndrome, and what product (therapeutic, diagnostic, or preventive) was, in their opinion, most needed.

Step 5: Testing prioritized products. The results of the survey were summarized and themes and recommendations grouped under key themes. These were further discussed by the EAG, taking into consideration the scope provided by the Global AMR R&D Hub's BoM, the broader market landscape and the AMR community.

Step 6: Product outlines developed. The EAG agreed on a preliminary list of three priority areas:

- Bloodstream infections (BSI) - diagnostic for all and therapeutic for MDR Gram negative infections
- Preventive (multi-disease) - for enteric infections with a focus on *Salmonella* and *Escherichia coli* (human and animal)
- Pneumonia - diagnostic for all and therapeutic for MDR Gram negative infections

Step 7: Product outlines refined. The three priority areas were amended based on feedback from the Global AMR R&D Hub's BoM and other experts in the field (approached by EAG members and the Secretariat), and revised again to align with and incorporate relevant WHO findings published after the work of the EAG had begun[22]. The final list of products identified by the EAG as representing the greatest unmet needs were:

[22] This included the landscape of diagnostics against antibacterial resistance and related target product profiles for diagnostics identified as priorities, and also the target product profiles (TPPs) for the antibacterial agents needed.

1. Diagnostic to determine whether an infection is bacterial or not - **Dx1 (Bac. vs other)**
2. Diagnostic for rapid pathogen identification and resistance testing - **Dx2 (ID/susceptibility)**
3. Therapeutic for MDR Gram negative BSI listed on the WHO Global Priority Pathogen List[21] (with a focus on the critical pathogens) **- Tx1 (BSI) - a small-molecule antibiotic**
4. Therapeutic for MDR Gram negative infections listed on the WHO priority pathogen list (with a focus on the critical pathogens) that cause pneumonia - **Tx2 (pneumonia) - a small-molecule antibiotic**
5. Multi-disease vaccine for enteric diseases with a focus on *Salmonella* and *E. coli* (human and animal)
6. Preventative for *M. tuberculosis*

Due to time and resource constraints, only the **first four products** identified were taken forward for the first phase of this work as presented here.

Pathogens*	Syndromes	Potential Products
• *Acinetobacter baumannii*, carbapenem-resistant (C) • *Pseudomonas aeruginosa*, carbapenem-resistant (C) • Enterobacteriaceae carbapenem-resistant, 3rd generation cephalosporin-resistant (C) • *Enterococcus faecium*, vancomycin-resistant (H) • *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant (H) • *Campylobacter spp.*, fluoroquinolone-resistant (H) • *Salmonella spp.*, fluoroquinolone-resistant (H) • *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant (H) • *Streptococcus pneumoniae*, penicillin-non-susceptible (M) • *Haemophilus influenzae*, ampicillin-resistant (M) • *Mycobacterium tuberculosis*, rifampicin resistant	• Pneumonia • Urinary tract infections (UTI) • Bloodstream infections (BSI) • Neonatal sepsis • Gastroenteritis • Skin and wound infections • Enteric fever • Cervicitis • Vaginitis • Urethritis etc. (sexually transmissible infections, STIs) • Tuberculosis • Meningitis	Treatment ○ Both prophylaxis and treatment options will be considered ○ Novel compounds and methods will be examined These may include but are not limited to peptides, viruses, antibodies, bacteriophages and hydrolytic enzymes Prevention ○ Including vaccines and other novel methods which may include microbiome interventions. ○ Antiseptics and disinfectants are out of scope Diagnostics Novel methods, both in the laboratory and at point of care (POC), will be in scope. These may include but are not limited to immunoassay, PCR, next-generation sequencing, mass spectrometry and rapid POC testing and other novel methods

Table 1: List of pathogens, syndromes and products explored in Steps 3 & 4 of the prioritization process. *C – Critical; H – High; M – Medium. *denoting the WHO Global Priority Pathogen List[21] category. M. tuberculosis is a global priority pathogen.*

2.4 Quantifying global patient need

Therapeutics country selection

The current global patient need for both therapeutics - Tx1 (BSI) and Tx2 (pneumonia) - were calculated based of a core pool of 13 countries, selected by the EAG using criteria (**Appendix 1**) that aimed to ensure global representation. These national-level data were then extrapolated to a further 22 countries (see **Table 2**).

These 35 countries together represent 80% of the world's population and this is therefore considered a 'global estimate'.

As an indicator of need and revenues across levels of socio-economic development, three country groupings were determined based on World Bank income groups, as follows: high-income countries (HICs), upper-middle income countries (UMICs), and lower-middle income countries/lower-income countries (LMICs/LICs), plus the US (which is variably included or separated from the HIC group).

Due to data challenges and much lower levels of access to medicines in LICs, the decision was made to combine the LMIC and LIC groups.

Global: 80% of the world's population

Readers should be aware that 'global' in the context of this report refers to **80% of the world's population**.

The 35 countries (core plus uplift) detailed in **Table 2** & **Table 4** altogether represent 80% of the world's population. The decision to forego the final 20% of the world's population as part of the quantification (epidemiological and diagnostic commercial components) was taken for pragmatic resource considerations and a wish to prioritize the quantification approach based on best-available data, which differed for the epidemiological and commercial streams of this work, i.e., very weak data availability compounded by an expected small contribution of this data to the overall quantification. Additionally, this would facilitate better alignment with the therapeutic commercial data set – which captures close to 100% of the available branded market, representing 72 countries worldwide – from which sales are not known or reported from these countries.

List of Countries Used for Patient Need and Therapeutic Revenue Modeling			
Income Group	**Sub-set**	**Patient Need (epidemiology) Calculations**	**Revenue (Commercial) Calculations**
HICs	Core country pool	USA, Italy, Japan, Saudi Arabia, UK	Argentina, Australia, Austria, Belgium, Canada, Chile, Croatia, Czech Republic, Finland, France, Germany, Greece, Hong Kong*, Hungary, Ireland, Italy, Japan, Korea, Kuwait, Latvia, Lithuania, Netherlands, New Zealand, Norway, Poland, Portugal, Puerto Rico, Russia, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, UEA, UK, Venezuela
	'Uplift Countries'	France, Germany, Spain, South Korea	
UMICs	Core country pool	Brazil, South Africa, Thailand, Turkey	Belarus, Bosnia, Brazil, Bulgaria, China, Colombia, Dominican Republic, Ecuador, Jordan, Lebanon, Malaysia, Mexico, Peru, Romania, Serbia, South Africa, Thailand, Turkey
	'Uplift Countries'	China, Russia, Mexico, Iran, Colombia Argentina	
LMICs/LICs	Core country pool	Egypt, India, Kenya, Vietnam	Bangladesh, Central America (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama), Egypt, India, Indonesia, Pakistan, Vietnam
	'Uplift Countries'	Nigeria, Pakistan, India, Bangladesh, Ethiopia, Philippines, Congo, Tanzania, Uganda, Myanmar, Algeria, Ukraine	

Table 2: List of countries and their role in developing patient and revenue estimates for both therapeutics. **For pneumonia only.*

Therapeutics: Deriving patient estimates (2020 – 2040)

The reductive methodology for estimating MDR patient numbers for our syndromes, bacteria and resistances of interest are depicted in **Figure 3**. All data sources used for the epidemiological modeling can be found in the **References for modeling** section, in **Figure 5** & **Figure 6** and evaluated in Section **3.5 Data Assessment**.

Annual cases for BSI and pneumonia in the 13 EAG-selected countries were derived from nationally reported statistics for each syndrome. If not available, data from the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) for the related conditions of sepsis and lower respiratory tract infection were used.

Country-specific etiology studies were used to apportion the percentage of each syndrome attributable to each of the following Gram negative pathogens: *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Serratia marcescens* and *Enterobacter cloacae*.

MDR vs. XDR How did we define AMR?

While extreme drug resistance (XDR; resistance to all but two or fewer antibiotic classes) is the better measure of untreatable infections and therefore the true unmet need for new antibiotics, data are more available and reliable for MDR (resistance to one or more antibiotic in three or more classes) and was therefore used for this study. One of the key differences is the exclusion – by the latter definition – of key carbapenem resistances prevalent in the critical category of WHO's priority pathogen list (see **Table 1**).

N.B. The study initially calculated XDR/DTR, in addition to MDR, but data from the former were subsequently removed due an unknown level of overlap between the two.

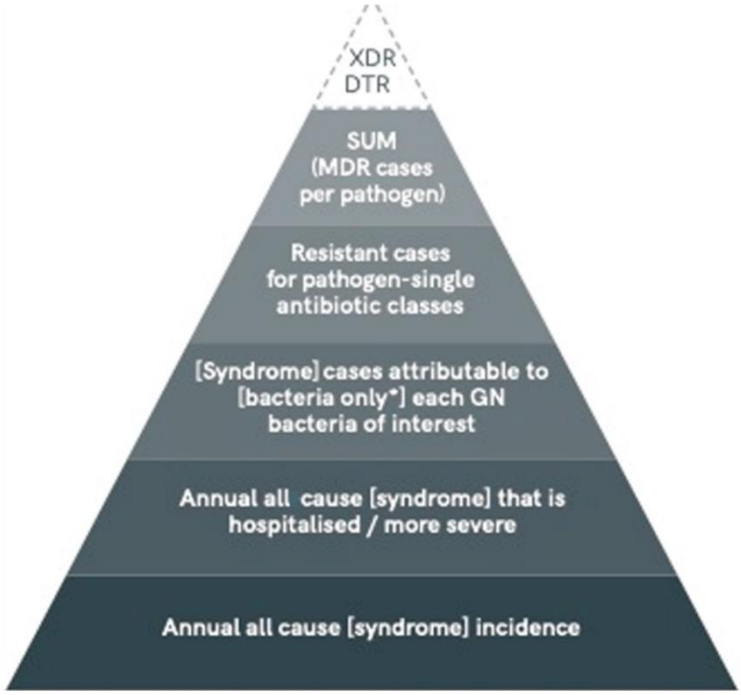

Figure 3: Generalized overview of process used for current epidemiological estimates. **Pneumonia can have non-bacterial causes.*

Analogue-Use in Modeling

Both the epidemiological and commercial modeling in this study made use of analogues. An analogue enables extrapolation by taking the characteristics of a known then adapting it or directly applying it to an unknown (something that does not exist or for whom data are sparse). Analogues are therefore a tool to facilitate making assumptions, by converting a known into a similar or closely related unknown. Product, syndrome and country analogues were used during the course of this work.

For each country, in the core pool, MDR proportions for each individual Gram negative pathogen were applied to the derived number of syndrome cases attributable to each pathogen, then totaled to give the annual patient numbers for MDR Gram negative BSI and pneumonia. Demographic (age) data relating to each syndrome was sourced from nationally reported statistics (**Appendix 4c**). If not available, age data was sourced from IHME GBD data for the related conditions of sepsis and lower respiratory tract infections. These data were used to derive cases and incidence rates for the different age groups.

Global patient numbers (current and projected) were calculated using syndrome-specific analogues built from the data derived from analysis of the 13 countries. 22 additional countries were selected based on population size, which when taken together with the 13 analyzed countries to represent the majority (80%) of the world's population (see **Info Box** on pg. 28)[23].

Projected (to 2040) MDR Gram negative BSI and pneumonia patient numbers for each of

[23] NB: going beyond 80% requires inclusion of a large number of additional countries, many of which lack the MDR data required to calculate patient numbers.

the 13 selected countries were calculated from two parts: 1) projections of total Gram negative BSI and pneumonia cases, and 2) projections of proportions of MDR Gram negative pathogens.

With regard to 1) projected cases; these were calculated on a country-by-country basis using current incidence rates for each age group applied to US Census Bureau (See **References for modeling**: Population statistics) projected population growth / decline. The proportion of cases attributable to each Gram negative pathogen was applied to projected annual cases to enable calculation of BSI and pneumonia attributable to each Gram negative pathogen out to 2040 (see **Figure 4**). With regard to 2) projected resistance proportions; these were calculated on a country-by-country and pathogen-by-pathogen basis from MDR data trends in Pfizer's ATLAS[24] or JMI's SENTRY[25] surveillance databases. These databases were used due to a lack of MDR and extensively drug resistant/difficult-to-treat resistance (XDR/DTR) data available from nationally-reported AMR data.

Identified trends were applied to current MDR proportions and projected forward linearly. If historical data lacked any trend, growth rates from a similar country (with similar MDR proportions and antibiotic usage) were used.

In general, growth of MDR pathogens was modeled to slow once higher resistance proportions (of ~60%) were reached and then plateau at resistance proportions of ~80%. All sources used to calculate current and future MDR Gram negative BSI and pneumonia patient numbers can be found in the **References for modeling** section. The data sources and assumptions used to derive the (MDR Gram negative BSI and pneumonia) patient number estimates and forecasts through the process previously highlighted are found in **Figure 5**, **Figure 6** & **Table 3** and in more detail in **Appendix 1** and the **References for modeling** section. Best efforts were made to cross-check and overcome the challenges of data gaps and deficiencies and develop reasonable and plausible assumptions. The impact of this on the numbers is explored further in the Section **4. Discussion**.

[24] (Antimicrobial Testing Leadership and Surveillance (ATLAS), Pfizer)
[25] (SENTRY Antimicrobial Surveillance Program, JMI Laboratories)

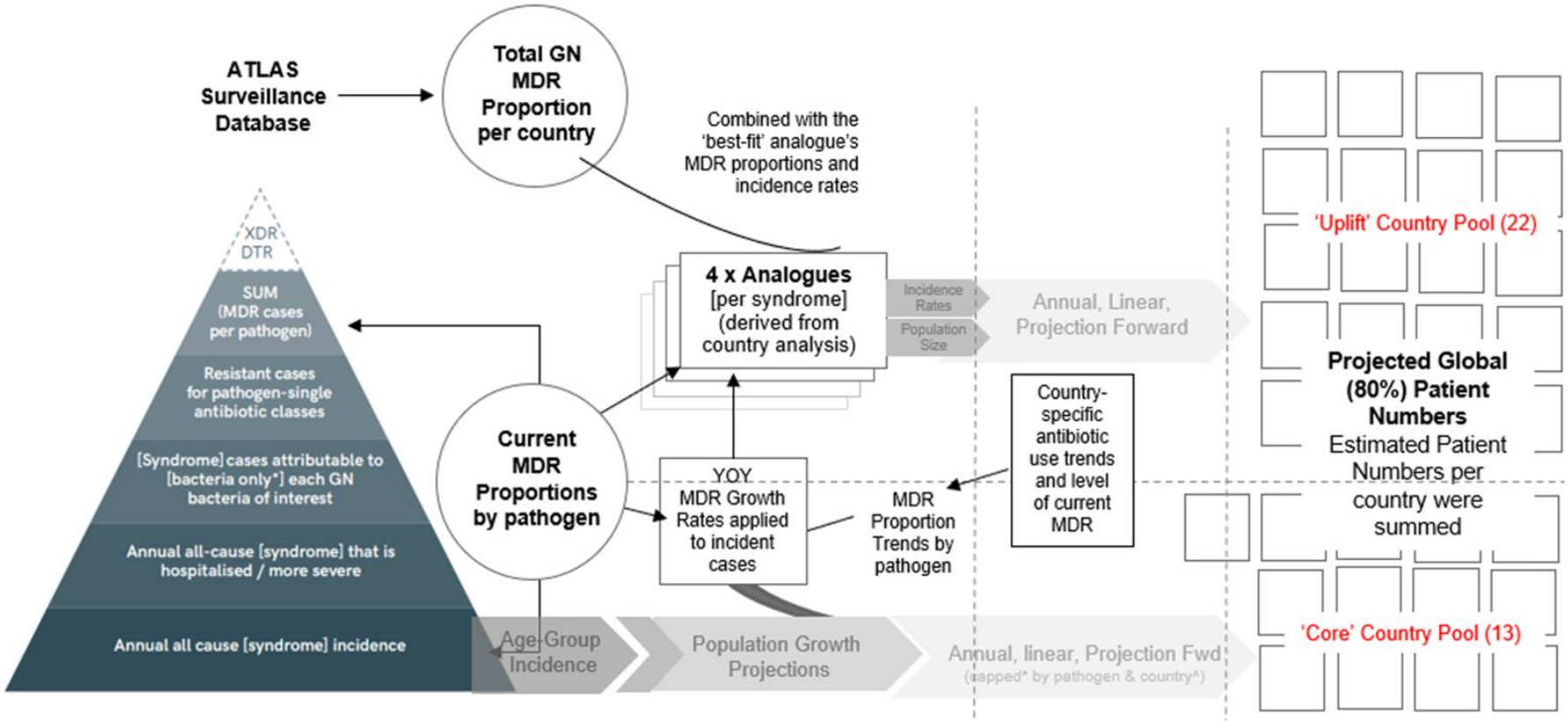

Figure 4: Overview of process and data sources used for epidemiological forecasts. **Pneumonia can have non-bacterial causes. YoY = Year-on-Year.*

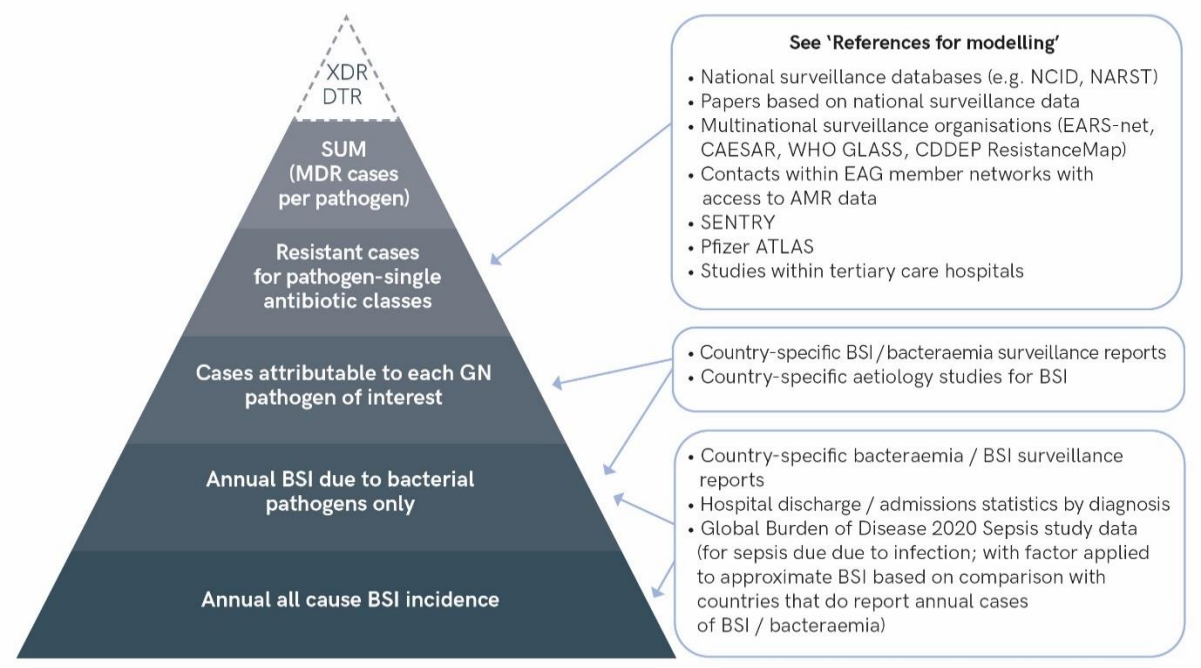

Figure 5: Data sources used to calculate epidemiological estimates of global need for Tx1 (BSI). **Pneumonia can have non-bacterial causes.*

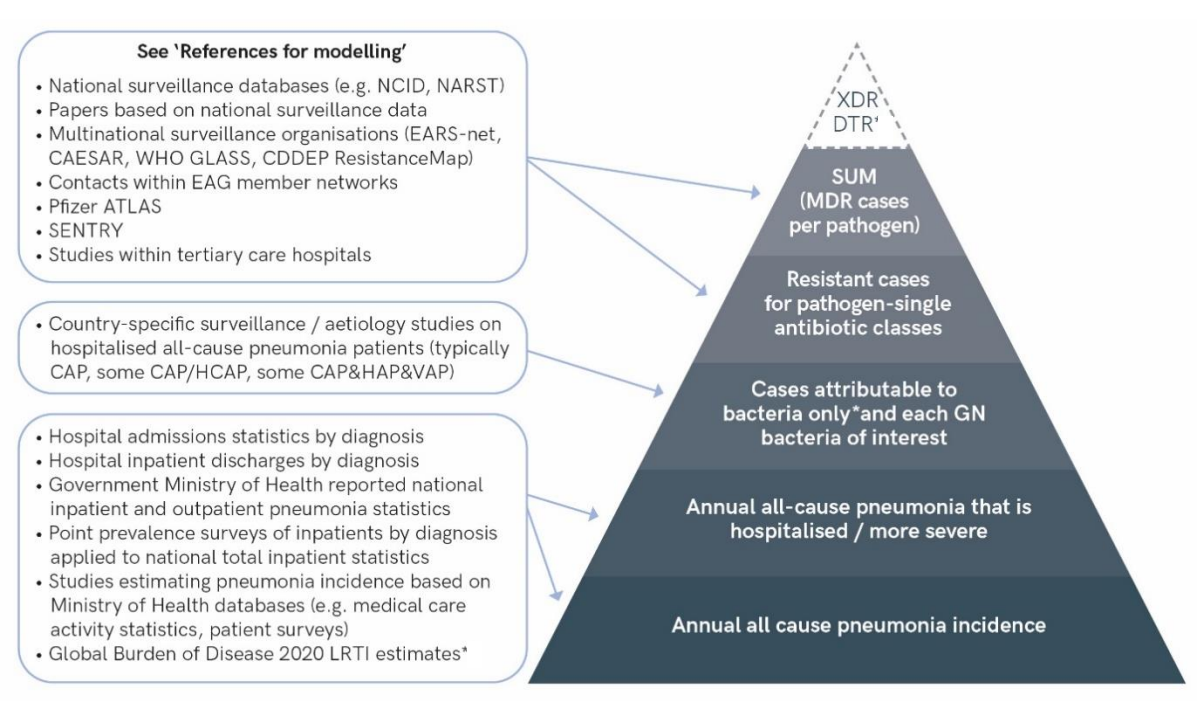

Figure 6: Data sources used to calculate epidemiological estimates of global need for Tx2 (pneumonia). **Pneumonia can have non-bacterial causes.*

Model Input Parameter	Certainty Estimate*	Source / Derivation/ Comments
Current incidence of all cause syndrome		**Pneumonia**: Incidence data lacking for some HICs/UMICs and most LMICs/LICs. No data available that gives an indication of pneumonia incidence due to HAP/VAP/CAP/HCAP **BSI:** Bacteraemia AMR surveillance exists in many countries, but often quantification of country-level incidence is absent
Current incidence of Gram negative syndrome		**Pneumonia**: Incidence data lacking even in HICs where there is inaccurate coding in hospital data for pneumonia that is due to Gram negatives. Pneumonia aetiology data for age groups especially <5 yrs and neonates lacking; current studies focus on more major causes of pneumonia in this age group i.e. viruses, *Streptococcus pneumoniae* **BSI:** Lack of robust data for Gram negative incidence quantification but generally good characterisation of Gram negative BSI for some regions from available papers. For <5yrs and neonates aetiology studies are available but not quantification of incidence
Current MDR proportions for individual Gram negative pathogens		MDR proportions extracted from SENTRY and Pfizer's ATLAS as many countries lacking robust national MDR proportions for all Gram negative pathogens. Data extracted from SENTRY & Pfizer's ATLAS may not be representative of the national AMR situation as a whole and in some cases is incomplete (only historic years data or low number of isolates)
Projected population growth by age groups		Projections by age groups sourced from the US Census Bureau
Projected incidence of Gram negative syndrome		Derived Gram negative syndrome incidence rates per 100,000 population by age group applied to population projections from US Census Bureau. Proportions attributable to the individual Gram negative pathogens held constant
Projected MDR proportions for individual Gram negative pathogens		Current and historical MDR proportions used to project YoY growth rates forward linearly for each pathogen; growth modelled to slow on reaching higher MDR rates or country-specific MDR proportion caps and then plateau No secondary research data available on this topic. Current estimates are based on best practice industry assumptions and analysis Extensive country-specific primary research with epidemiologists or microbiologists required to understand YoY MDR growth rates expected for each Gram negative pathogen out to 2040
Projected MDR proportion caps		Individual countries assigned a peak MDR resistance proportion cap based on current MDR and antibiotic consumption trend as indicators for antibiotic stewardship, to help shape realistic 2040 MDR resistance proportions No secondary research data available on this topic. Extensive country-specific primary research with epidemiologists or microbiologists required to understand and quantify peak MDR resistance proportions expected for each Gram negative pathogen
Overall	**Medium - Low**	

*collectively across US, HICs, UMICs and LMICs/LICs

Key: High Medium Low

Table 3: Tx1 (BSI) and Tx2 (pneumonia) patient projection assumptions summary and qualitative certainty estimate.

Diagnostics: Country selection

The current global patient needs for both Dx1 (Bac. vs other), and Dx2 (ID/susceptibility), were calculated on the basis of a selection of 21 countries (see **Table 4**, below), split relatively equally across the three World Bank income groups. The 21 countries include the 13 EAG-selected, representative countries for each income region that were also the basis for the BSI and pneumonia epidemiology. Additionally, a further eight countries were selected based on the premise that for country-access to be sought for these relatively sophisticated diagnostics, certain preconditions would likely be necessary (for donor support or national roll-out of uptake) – for instance, there would be high need for them combined with a minimum level of health system maturity/AMR attention. The process and analysis used to select the countries is detailed extensively in **Appendix 1** and includes: 1) burden of disease (MDR, severe Gram negative pneumonia), 2) health expenditure per capita, 3) AMR surveillance data availability, and 4) stewardship levels. Finally, the estimations based on these countries were then scaled up to represent 80% of the global population.

Final List of Countries Used for Diagnostic Modeling			
HICs	USA	**USA**	The regional groups have been scaled-up to include those countries contributing to 80% of the world's population. Scale up **5%**
	EU-5	**Italy, UK,** France, Germany, Spain	
	Other HICs	**Japan, Saudi Arabia**	
UMICs		**Brazil, South Africa, Thailand, Turkey, Argentina, China, Russia,**	Scale up **13%**
LMICs/LICs		**Egypt, India, Kenya, Vietnam,** Nigeria, Pakistan	Scale up **33%**
Total		21 countries	

Table 4: List of countries, by World Bank income group used in the diagnostics calculations. *HIC groups are sub-divided to accommodate different commercial assumptions within the World Bank income groups. The core pool of 13 countries (**dark blue**) from the epidemiological work were supplemented by eight additional countries (light blue).*

Diagnostics: Deriving patient estimates (2020 – 2040)

The diagnostic 'patient need' (or estimated number of patients eligible globally) was not epidemiologically derived based on febrile illness as the EAG had hoped (see **Info Box** and **Appendix 4c**). Instead, the quantification combined patient estimates with the healthcare setting where the diagnostics would primarily be accessed (the 'clinical setting') and considered 'clinically useful (clinical decision)'. The calculation of patient numbers for diagnostics is hence referred to a 'patient eligibility'. The detailed analysis and assumptions for deriving the estimates can be found in **Appendix 3**.

The process for deriving the patient eligibility for Dx1 (Bac. vs other) is shown in **Figure 7**. An estimated number of primary care consultations per country per year was derived for each of the 21 countries by adjusting various healthcare infrastructure parameters. These 'health system' proportions were combined with patient presentation incidence data on patients 'symptomatic for possible infection' to arrive at an estimate of 'total patients eligible', which is a percentage of primary care consultations for where the diagnostic would likely be considered 'clinically useful'.

For Dx2 (ID/susceptibility) (see **Figure 8**), the baseline input figures for the model were the number of hospitalized BSI and pneumonia patients (with hospital-acquired pneumonia [HAP], ventilator-acquired pneumonia [VAP], or community-acquired pneumonia [CAP]) for each of the 21 countries, from publicly available sources.

Febrile Illness (See Appendix 4c)

Incidence of febrile illness as an epidemiological basis for assessing patient need for Dx1 (Bac. vs other) was not considered feasible for the following reasons:

- Febrile illness is not a clearly defined indication included in the IHMR GBD study
- Febrile illness overlaps with malaria and other acute, non-bacterial, conditions excluded from the 'need profile'
- Fever is only present in a minority of acute bronchitis cases
- Definitions and data availability are weak and variable (see **Appendix 4c** for assessment)

Use Cases in Modellling

Use cases describe interactions between users and systems and also the behavior of a system in satisfying users' goals (or needs). In this work, use cases are a way of describing the immediate clinical context in which a diagnosis occurs. Specifically, they were used to capture how the user (clinician or patient) would interact with the healthcare setting (system) to receive a diagnosis – or not – per product per income-group settings.

From here, local use cases per income group were developed (See **Info Box** above) in detail for both Dx1 (Bac. vs other) and Dx2 (ID/susceptibility) in order to identify the percentage of consultations in each of the income-group settings where the diagnostics would be clinically beneficial. Applying this percentage figure to the respective country-level inputs at the income-group level enabled determination of the 'total number of patients' with a clinical rationale ['eligible for Dx]' for use of each test.

This approach will likely underestimate the full extent of patient need, which will probably include other hospitalized primary and secondary infections beyond BSI/pneumonia as well as a potential sepsis screening for inpatients and those in an ambulatory care setting.

These patient eligibility estimates were projected by applying estimated population growth rates per country at five-year intervals based on the US Census Bureau. For Dx1 (Bac. vs other), the projections were based on the >65-year-old population to reflect their dominance in growth trends. No further parameters were adjusted for the future projections. The process of moving from 'hypothetical demand' (eligibility) to 'actionable/realizable demand' (patients estimated to actually be diagnosed this way) and the 'revenue calculation' from these sales is described in the Section **2.5**, which uses these patient numbers as the baseline.

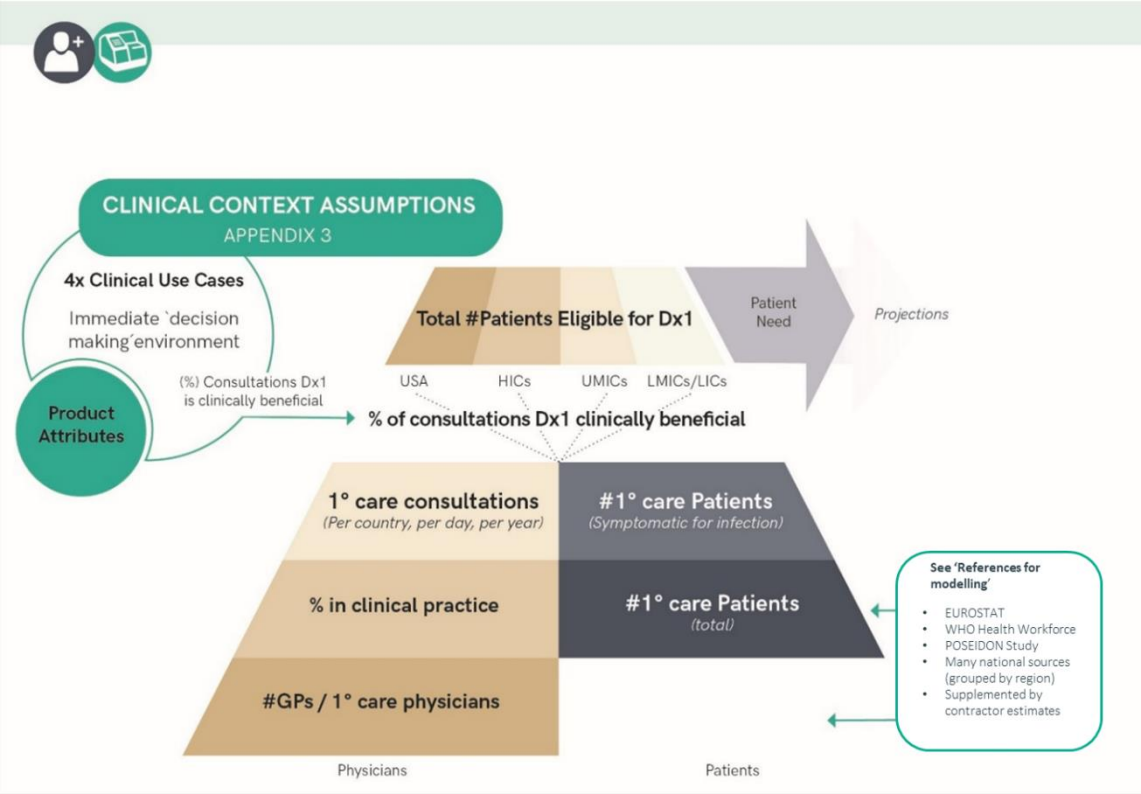

Figure 7: Overview of the methodology to determine the patient need (numbers) for Dx1 (Bac. vs other).

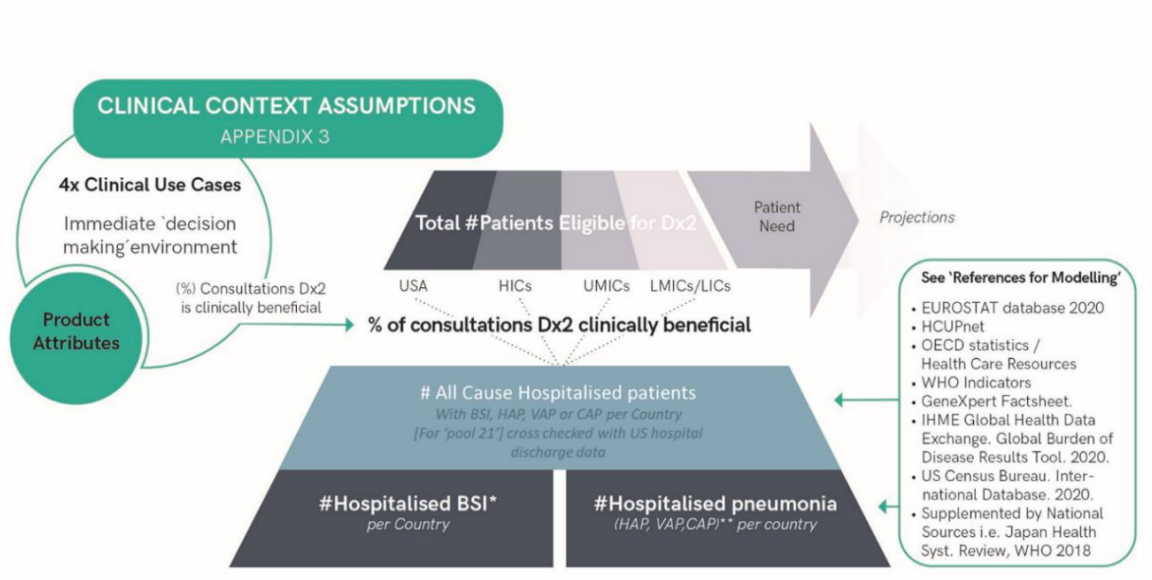

Figure 8: Generalized overview of the methodology to determine the patient need (numbers) for Dx2 (ID/susceptibility).

2.5 Quantifying global patient demand/access

The method for deriving the revenue estimates and forecasts is outlined in Section **2.6**. In a supplementary step, the revenues were converted back from $ US to 'units' or patient numbers to indicate the number of patients those sales represent. This 'actionable demand' calculation was performed by equating one cartridge[26] to one patient (for the diagnostics[27]) and, for the therapeutics, using standard dosing conversions of their closest analogues. Specifically, the IQVIA volumes (standard units/ vials) were converted to 'patients' using average vials per patient per day and average days per treatment course per year for an average 70kg patient (see **Table 5**) according to the FDA's prescribing guidelines and in house estimates. This enabled an assessment of 'demand', or the number of patients actually treated with one of the products, as opposed to 'patient need' (see Section **3.3**).

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PRODUCT	VIALS PER DAY	DAYS PER YEAR
MARKET DEFINITION		
Avycaz/Zavicefta	**3**	**10**
Baxdela	**2**	**8**
Fetroja	**6**	**10**
Recarbrio	**4**	**9**
Tygacil	**2**	**10**
Vabomere	**6**	**10**
Xerava	**3**	**9**
Zemdri	**2**	**5**
Zerbaxa	**4.5**	**10**
UPTAKE ANALOGUES		
Cubicin	**1**	**14**
Zyvox	**1**	**14**

Table 5: Data underlying conversion of revenues to patient numbers.

[26] NB: the unit of a diagnostic device that is specific to an individual patient, the reader/instrument remains across patients
[27] For the diagnostics: 1 unit = 1 test = 1 cartridge = 1 patient

2.6 Quantifying global market potential

Therapeutics: Approach to revenue determination

In contrast to how patient numbers were derived, the revenues were calculated using a top-down approach, based on data available from the current products on the market. This leads to a discrepancy in the countries used for the derivation of the 'need' versus those used for the 'revenue' as can be seen in **Table 2**. However, this was justified based on the wish to prioritize the quantification approach based on best-available data, which differed for the epidemiological and commercial streams of this work.

An overview of the process used to derive the revenues for the two therapeutics is shown in **Figure 9**. The total current, global, existing market revenue (sales of on-patent intravenous [IV] Gram negative antibiotics in 72 countries) from IQVIA's MIDAS database was used as the starting point. These data were converted to *'total number of patients on branded Gram negative antimicrobial treatments'* by income group and geography by converting from IQVIA's 2019 standard units and using assumptions of average vials per day and days per patient from published prescribing guidelines for each brand (see **Table 5**). We further assume that the number of patients is equivalent to the number of branded Gram negative treatment courses per year. From here, detailed commercial assumptions (see pg. 43) are applied at an income-group level to the above estimates of patient numbers, to derive the 'peak patient share (%)' for each product.

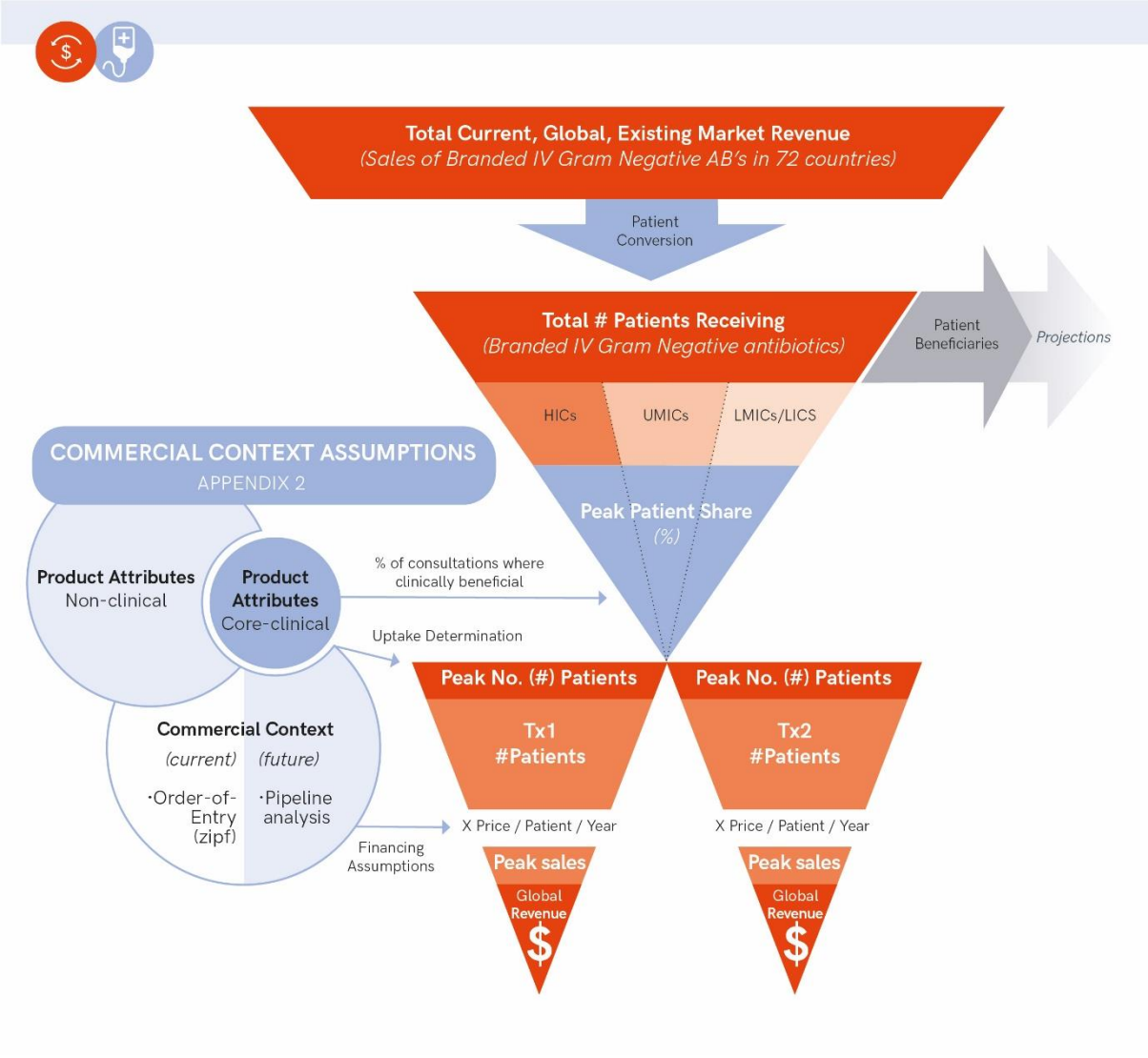


Figure 9: Overview of the model to determine the therapeutic revenues.

Therapeutics: Commercial assumptions

Detailed evaluation (**Appendix 2**), supported by the modeling team's knowledge of anti-infective markets, was undertaken to generate commercial assumptions (**Table 6**). These can be broadly grouped into analysis of product attributes and market context. In an initial step, the first of these 'product attributes' has been based on 'analogue analysis' – comprising a review of the need profiles relative to other products already available on the market. Once the closest fit for each parameter has been determined from available analogues, the data gathered regarding that analogue can be adjusted to apply to the model. The outcome of this product analysis is used to derive and estimate the peak patient share expected to be captured by each of the therapeutics. Peak patient share (%) is a measure of the proportion of patients for whom the product is likely to be considered clinically beneficial, over other options, and therefore prescribed. In commercial terms, it represents that part of the market that could be 'captured' by these new products. The second component, the market context analysis, assesses the broader commercial and competitive context into which the defined products would launch (in 2025). The probable level of competition (now and in the future as a factor in the product pipeline) is anticipated in terms of 'order of entry' (modified Zipf's law[28]) and the future diagnostic, policy and pricing environment.

See Appendix 2 for full analysis underscoring the Analogue Analysis	**Tx1 (BSI) / Tx2 (pneumonia)**
Product attributes	Pfizer/AbbVie's Avycaz/Zavicefta (ceftazidime/avibactam) is considered the best clinical analogue match for Tx1 (BSI) and Tx2 (pneumonia) in terms of breadth of Gram negative pathogen activity, MDR/XDR in-vitro activity, route of administration, target-patient segments (hospitalized patients, second line, all age groups, non-inferiority to current therapies in at least one approved indication) and labelled indications.
Commercial attributes	Both our therapeutics were considered to be 'later entrants' and having a narrower label than the most suitable analogues. This applies to Avycaz/ Zavicefta (ceftazidime/avibactam) when looking at criteria such as number of countries launched and 'being close to or past peak sales' (due to its US launch in 2015). Later Gram negative entrants such as Fetroja (cefiderocol), Recarbrio (imipenem, cilastatin, and relebactam) or Zemdri (plazomicin) have struggled to be relevant analogues due to their recent launch and/or US-only availability. Zerbaxa (ceftolozane/tazobactam) and Tygacil (tigecycline) fall short in terms of their breadth of therapeutic and in-vitro activity vs Tx1 (BSI) and Tx2 (pneumonia) need-profiles. For the uptake and time-to-peak assumptions, supplementary analysis was added from Gram positive-targeting products (i.e., Zyvox and Tygacil), due to their more mature life-cycles.

Table 6: Summary of the therapeutic analogues that were identified and analyzed in the generation of the assumptions.

[28] Zipf's law explains distribution of resource among individual/products in a way where the amount of resource one gets is inversely proportional to its rank.

Therapeutics: Revenue derivation

Once the income-group-level commercial assumptions have been applied to determine the peak patient share (%) for each therapeutic, these are converted into peak patient numbers per product. These figures represent the expected realizable demand, or number of patients who could be realistically expected to gain access to these therapeutics. Finally, pricing and population growth assumptions are applied based on the IQVIA market analysis and population projections by income group to determine the revenue.

Multiplying the peak number of patients per product with the estimated peak 'Price per Patient per Year' results in 'Peak Revenues'. The 'Price per Patient per Year' is based on analogues and price differentials to the US market as seen in the existing branded Gram negative market. First revenues are generated per income group per year, this is then fractioned-out to a country forecast based on the 2019 country share. What results from the model is a calculation of 'revenue per country, per World Bank grouping per year'. As a last step the Total Revenue by income group is summed (see country selection in **Table 2**) to represent a 'global revenue'[29].

Projecting and forecasting the revenues into the future, is done by taking the number of patients of the current IQVIA market in each region and projecting them forward from 2019 to 2040 using lifecycle growth rates at five-year intervals.

Future five-year growth rates converge towards 0% the further away from the present moment to reflect an increase in uncertainty and an overall conservative approach to forecasting. The project Compound Annual Growth Rates (CAGRs) tend towards stabilization in the later part of the forecast horizon with a smaller percent growth on a larger population base.

CAGR-Use in Modeling

CAGR's are used to measure a rise or fall in value (typically of an investment asset) overtime. Future CAGRs were used in the modeling to capture estimated future dynamics – of patients in the market being prescribed an antibiotic – based on what is known today. As the model was static and was not able to account for uncertainty, this was addressed by adjusting the CAGR's so they gravitated towards zero the further away from the present moment. This was to avoid unintended cumulative effects that can occur when successive growth rates over many years can have a large cumulative, and potentially misleading, impact.

[29] IQVIA MIDAS data were considered to represent 100% of the available global market (see Section **2. Methodology**)

Overview of Assumptions Underlying the Quantification of the Revenues

- ❖ The data, research and analysis to inform the development of the assumptions below is detailed in **Appendix 2**
- ❖ The more detailed and also product-specific assumptions can also be found in **Appendix 2** and are recapped for convenience in the respective results sections
- ❖ The assumptions feature in the Section **4. Discussion** and are qualitatively evaluated - for their robustness - in Section **2. Methodology**

Both therapeutics (Tx1 BSI and Tx2 pneumonia) are assumed to:

- Follow an established prescription drug (Rx) business model by a multinational pharmaceutical company with a global commercial apparatus
- No drastic change to current policy environment in the next 20 years (forecast period)
- Assumed to come to market with a non-Inferiority label, initially not licensed in the *Indication of key Interest* (defined in the need profiles) and assumed to be restricted to later-line use
- The therapeutics will both launch in 2025, into the existing market place, currently comprising 9x branded Gram negative antibiotics
- Non-cannibalization is assumed (they do not directly compete) despite similarity of their profiles
- Data suggest a pronounced order-of-entry effect (low shares captured by later entrants)
- Tx1 (BSI) and Tx2 (pneumonia) are assumed to be mutually exclusive (they do not directly compete for the same patients)
- Their premium branded price at launch is based on current analogues in different income regions.
- Uptake is based on first in class product and assumed to be linear following launch and is based on historical trends for both Gram negative and positive analogues
- Patent expiry or Loss of Exclusivity (LoE) is to occur globally in 2037 (12 years after US launch)
- Market growth rates are assumed to flatten into the future. From negative growth rates in the last decade, market growth is forecast to become positive (off the back of recent launches) but to flatten steadily into the future driven by a fall in the US
- We assume that the number of patients being able to afford a branded, novel Tx for Gram negative infection by income group will continue to grow at a slow, but steady average rate of 3% per year

Therapeutics: Scenarios

This 'base-case' situation – assumed through the modeling – was explored using a number of 'alternative scenarios'. A 'What If' or Threshold analysis – using an upper ($700 million) and a lower ($400 million) revenue threshold – was then performed to attain a sense of the extent that Price/Volume parameter changes would need to change to achieve these alternative therapeutic revenues.

The scenarios explored are detailed below:

A: Positive Pricing Scenario, where all currently purchasing countries increased their prices by a factor of 2.2 (Tx1) or 3.2 (Tx2) to generate $400 million or by 3.8 (Tx1) or 5.8 (Tx2) to generate the upper threshold of $700 million.

B: Moderately Favorable Pricing Scenario**,** where only 10 of the currently purchasing HICs increased their prices to generate the upper and lower thresholds (see **Table 10** for details).

C: Positive Volume Scenario, where an increased share of 30% of the eligible market (vs. 5-7% under the base case) was captured for both Tx1 and Tx2.

D: Negative Volume Scenario, where the eligible (branded Gram negative) market contracts due to stewardship or other negative market forces, such that at peak in 2036 there are 36% fewer eligible patients than in 2019 (as opposed to 84% more eligible patients for the base case).

Therapeutics: Data & assumptions assessment

Table 7 summarizes the seven key assumptions that were used in the commercial modeling together with a qualitative assessment of their robustness. In many cases the assumptions were built based on extensive experience of the modeling team specifically in anti-infectives markets together with extensive analysis of the existing market that is provided in full in **Appendix 2**.

The underlying market data for therapeutics is seen as relatively robust overall. IQVIA data, in particular the unit data, is the industry standard and relied upon by manufacturers. In addition, the data was cross-checked with selected manufacturer reported revenue data and found within +/- 5% of variation.

Assumptions behind Tx1 and Tx2 future patient shares and prices follow established pricing and uptake analogues, whose existing patient shares also align well with an Order-of-Entry approach (modified Zipf's law)[28] to estimating future peak patient shares in stable markets with products of comparable efficacy.

Estimating the number and clinical profile of future market entrants often represents the most uncertain part of any projections. The model's base case assumes a 'steady-state' branded market whereby products suffering LoE are replaced by launches of novel branded products.

Model Input Parameter	Certainty Estimate (for parameter across income groups*)	Source / Derivation/ Comments
Underlying Branded Gram negative Market / Patients		IQVIA market audit data from 2010 – Q2 2020, coverage and data quality overall good with a lower coverage for LMICs/LICs but with relatively minor impact
Launch Year Loss of Exclusivity (LoE)	N/a. (determinants set by project team/EAG)	High-level assumptions; sequential launch lags modelled as: US + 1 + 2 and +4 years; LoE assumed to occur 12 years following US launch (2037) in all regions; US and Rest of the World erosion curves
Pricing Inputs (per patient per year)		Tx pricing based on analysis of market data, assuming price parity to current analogues for purpose of modelling and avoiding artificial price inflation; assuming no significant change in access/reimbursement • USA: Based on basket of 4 (Avycaz, Vabomere, Recarbrio & Fetroja) in 2020 • Other HICs and UMICs: Based on basket of 2 (Avycaz/Zavicefta & Vabomere) in 2020 • LMICs/LICs: Based on Tygacil & Avycaz/Zavicefta pricing difference in 2020
Peak Share Assumptions (% Pts)		Avycaz used as baseline analogue adjusted by order-of-entry and other income-group determined factors such as # of competitors in the market: 1. 25% market share the theoretical limit for an early entrant (like Avycaz in US), targeting later-line (MDR) with broad label and assumed continued ~6 - 8 competitors in market; Tx considered a late entrant assuming up to 12% patient share 2. Assumed 'non-inferiority' label for Tx (no 'clinical superiority' over Standard of Care (SoC) assumed) 3. Assumed restriction to later-line use (in line with cost & stewardship consideration) Other HICs, UMICs, LMICs/LICs: Progressively higher share assumed for ex-US geographies because of smaller number of ex-US competitors (smaller market sizes apply ex-US)
Time to Peak Share / Adoption-Uptake Curve		Linear uptake curve assumed based on Avycaz in US market (4 years), subsequent regions longer time to peak due to sequential launches, other HICs (after 5 years), UMICs & LMICs/LICs (after 7 years)
Market Projections (2020 – 2040)		Market projections were based on historical 5-year CAGR trends for HICs, UMICs, and LMICs plus general growth expectations for each income group. CAGRs are flattening the further into the future
Competitive Environment		A comprehensive pipeline analysis was conducted, but the exact number and profiles of future launches remains speculative. We assumed a steady state of # of competitors in the branded Gram negative market going forward
Overall	**Medium**	

*collectively across US, HICs, UMICs and LMICs/LICs

Key: High Medium Low

Table 7: Tx1 (BSI) and Tx2 (pneumonia). Input assumptions summary and qualitative certainty estimate.

Diagnostics: Approach to revenue determination

The number of patients eligible for each of the diagnostics was determined based on product analogues (**Table 7**) and clinical use cases for both diagnostics (see pg. 37). The broader context surrounding that clinical decision is what is modeled in this second stage, which aims to quantify revenues and realizable demand. The bottom-up approach used for calculating patient need is continued here. The derivation of the revenues ('commercial case') for the two diagnostics Dx1 (Bac. vs other) and Dx2 (ID/susceptibility) followed the same process, as shown in **Figure 10** , with the percentage of the total number of patients eligible for Dx (as outlined in **Figure 7** & **Figure 8**) as the baseline. The analysis used to inform the detailed commercial assumptions is available in **Appendix 3**. From the 'eligible patient' starting point and for the following steps, the detailed commercial assumptions are applied at an income-group level to the estimated patient numbers, diagnostic site numbers and expected consultations (uptake).

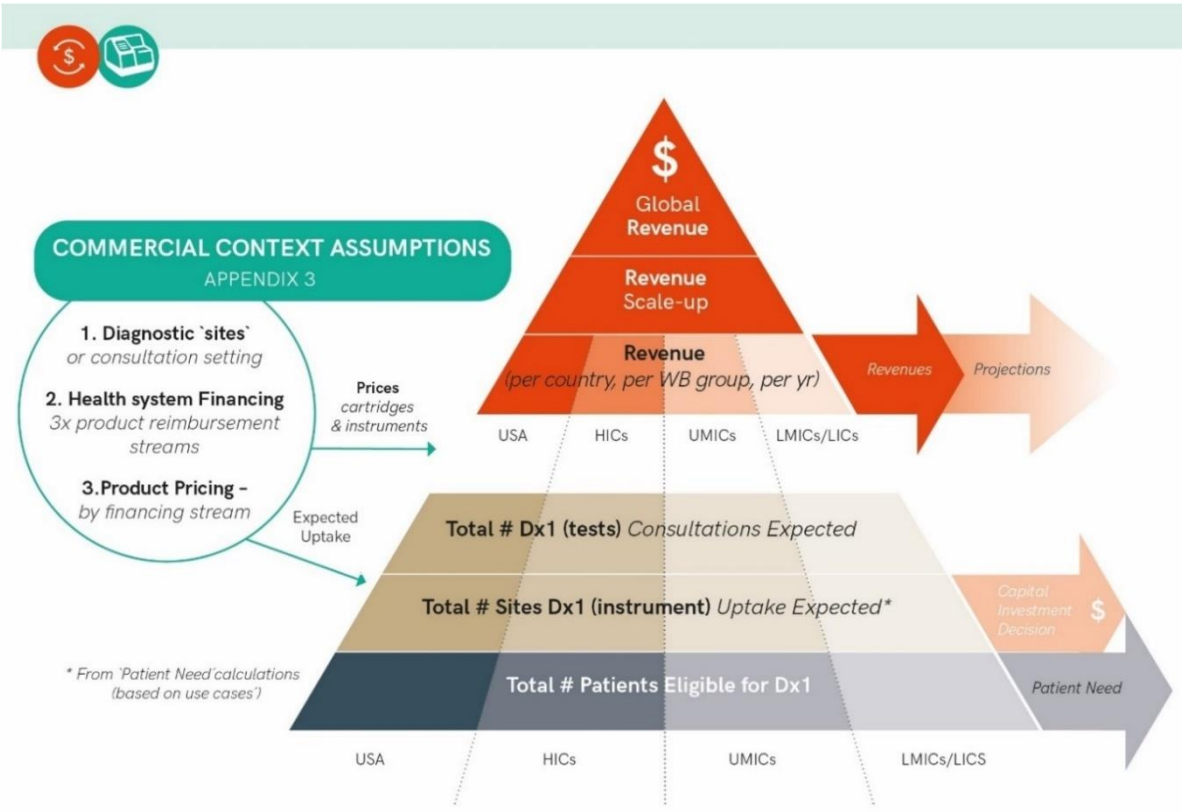


Figure 10: Overview of the methodology used by the model to determine the revenues for both diagnostics.

Diagnostics: Commercial assumptions

The 'commercial context' assumptions that are used to incorporate the diagnostic pricing and uptake data into the model can be briefly summarized as comprising a product analogue analysis and a health system context analysis. The former (**Table 8**) was based on a comprehensive review of the currently existing diagnostics in the market place. The small selection of products deemed to be the closest fit to the diagnostic profiles defined by the EAG were then taken forward for a more detailed analysis based on at least 6 criteria within both technical and commercial domains (see Analogue Analysis in **Appendix 3**).

As previously noted, the profiles, as defined, are largely considered to be much further away from being a realizable development output than those of the therapeutics, which makes this analysis more speculative and uncertain. The profiles focus on the healthcare delivery setting where the diagnostic decision would be made (**Table 9**), the financing streams (**Figure 11**)[30] used to characterize the origin and nature of the reimbursement and pricing assumption (for the instruments and cartridges), and finally the launch year and roll-out timings (collectively considered as the uptake). All of these components, when combined by income group, lead to the generation of assumptions on pricing and uptake of the diagnostics for the 21 countries.

Dx1 (Bac. vs other) analogue/s	Dx2 (ID/susceptibility) analogue/s
▪ Better technical analogue: **MeMed BV** – three protein markers, qualitative, algorithm, result read by instrument (sensitivity 91%, specificity 94%) ▪ Better commercial analogue: **RPS FebriDx** – two markers, rapid diagnostic test (sensitivity 80 – 95%, specificity 76 –94%)	▪ Better technical analogue: **BioMerieux Biofire pneumonia panel** (pneumonia) ▪ Better technical analogue: **T2 Biosciences bacteria panel and resistance panel** (BSI) ▪ Better commercial analogue: **Cepheid GeneXpert MTB/Rif** is an analogue for modest success in roll-out of a complex technology in LMICs (heavily subsidized)

Table 8: Summary of the diagnostic analogues identified and incorporated into the commercial assumptions.

[30] (Escadafal, Incardona & Fernandez-Carballo & Dittrich S, 2020)

Defined healthcare delivery settings – Dx1 (Bac. vs other) (Mainly primary-care based)	**Defined healthcare delivery settings – Dx2 (ID/susceptibility)** (Mainly hospital-based[31])
▪ Small General Practitioner (GP)/Primary care physician (PCP) ▪ Large GP/PCP ▪ Urgent Care ▪ Other	▪ Very large (or 800+ beds) ▪ Large (or 400-799 beds) ▪ Medium (or 151-399 beds) ▪ Small (0-150 beds) ▪ Other
Groups and Financing Streams for both Dx1 (Bac. vs other) and Dx 2 (ID/susceptibility)	
Groups as basis for financial coverage & pricing	**Defined financing streams**
Groups used for US	▪ Commercial ▪ Medicare/Medicaid ▪ Out-of-pocket
Groups used for non-US HICs (including EU5)	▪ Private ▪ Public ▪ Out-of-pocket (or other)
Groups used for UMICs and LMICs/LICs	▪ Domestic – Private ▪ Domestic – Public ▪ Domestic – Out-of-Pocket ▪ International funding

Table 9: Summary of the healthcare delivery settings (top) and financing streams (bottom) defined for the two diagnostics.

[31] The authors note that this terminology is mainly applicable to HIC settings. For LMICs/LICs, we may not talk about GP/PCP settings but their equivalents (such as outposts or hub-and-spoke structures staffed by nurses or health workers). Similarly, the authors note that what is large, medium or small varies by country with LMICs/LICs (e.g., India), where average hospital sizes are much smaller.

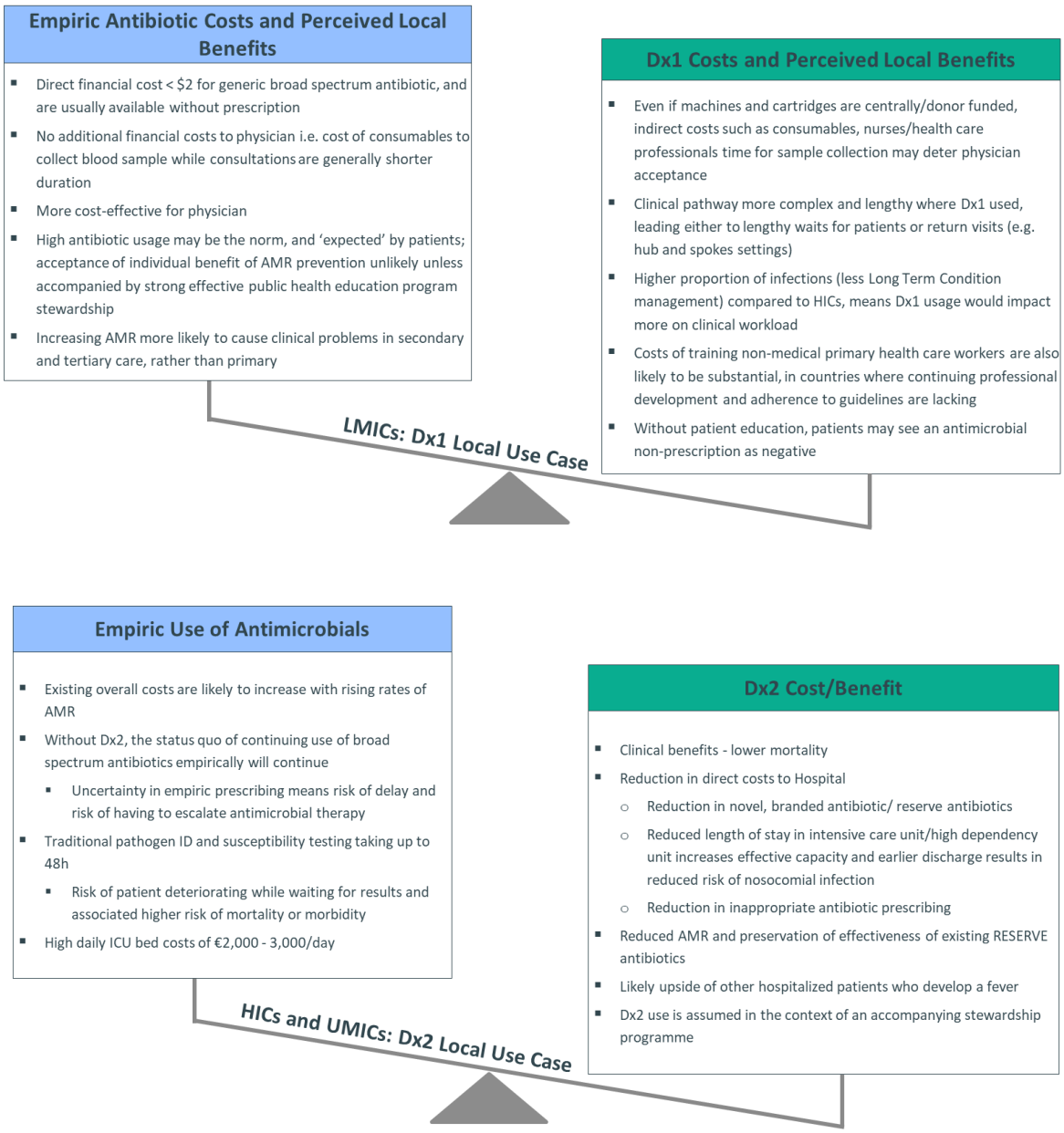


Figure 11: An example 'Diagnostic Use Case' for each diagnostic. Dx1 in LMICs (above) and Dx2 in HICs & UMICs (below). *NB: Separate 'Use Cases' were developed for each diagnostic per income group setting and can be found in full in* ***Appendix 3****. Source: groupH research & analysis, interviews & (Escadafal et al., 2020)[30].*

For each income group, different financing streams were defined (**Figure 11**), based on research and analysis (**Appendix 3**) in order to characterize the financial coverage of such a product (reimbursement or other) and to associate the instrument and cartridge pricing assumptions. The financial assumptions differentiate between the possible price levels at which the instrument and the test would be reimbursed in different geographies or income groups. In contrast to HICs and UMICs, overall revenue in LMICs/LICs is not driven primarily by the local use case but by a set 'international donor' budget that has been added as a fourth financing method. The size of this budget is informed by budgets put in place in the past for tuberculosis (TB) and other priority public health causes.

Diagnostics: Revenue derivation

Four possible healthcare settings (sites) for each diagnostic (as per **Table 9**) per income-group are defined, taking the site numbers (total sites) as the starting point to determine what proportion of them would be likely to invest capital costs to purchase the instrument. This results in an assessment of the total number of sites where instrument uptake is expected. From a modeling perspective, this is captured and referred to as 'site viability' for Dx2 (ID/susceptibility) or its opposite, a 'drop-out rate' for Dx1 (Bac. vs other), describing the percentage of sites where installing an instrument is not anticipated to be viable. The income-group-level commercial assumptions are applied to the total number of patients eligible for Dx and the resulting total number of Dx tests/expected consultations (uptake). The model calculates revenue per World Bank income group per year. As a last step, the total revenue for instruments and tests by income group, representing a total of 21 countries, is scaled up (see '**2.4** Diagnostics: Country Selection' and **Table 4)** to represent 80% of the world's population, arriving at a global revenue for each diagnostic.

The revenues for the two diagnostics are forecast into the future for 20 years until 2040. For Dx1 (Bac. vs other), this was done by using population growth forecasts for >65-year-olds for each country at five-year intervals, based on the rationale that this age group will disproportionately drive primary care consultations. For Dx2 (ID/susceptibility), the forecasts were performed by summing together the projected hospitalized syndrome cases (from the therapeutic epidemiology in phase 3). The 2020 context of primary care consultations in 21 countries has been projected forward for Dx1 (Bac. vs other) based on a number of factors. It was assumed that the number of primary care consultations is developing in five-year intervals in line with the projected growth in >65-year-olds, according to the US Census Bureau, up to 2040 for each geographic area.

Site viability and financing assumptions, including pricing, have been kept constant from 2020 to 2040 (as described before for both diagnostics), which likely adds to the conservative nature of the estimates.

Overview of Assumptions Underlying the Quantification of the Revenues

- ❖ The data research and analysis to inform the development of the assumptions below is detailed in **Appendix 3**
- ❖ The more detailed and also product specific assumptions can also be found in **Appendix 3** and are recapped for convenience in the respective results sections
- ❖ The assumptions feature in the Section **4. Discussion** and are qualitatively evaluated for their robustness in Section **2. Methodology**

Both diagnostics (Dx1 Bac vs other and Dx2 ID/susceptibility) are assumed to:

- Both launch in 2025, into their respective market places
- Instruments are assumed to be purchased only once for each setting
- Are mutually exclusive (they do not compete for the same patients)
- Sales have plateaued but not peaked in the modeling period. No patent expiry or LoE assumed.
- Instrument and test pricing for LMICs/LICs is guided by sponsored price assumptions as per need profile. For all other income groups, we assume pricing in line with existing product analogues supplemented by groupH estimates
- Uptake & adoption assumptions are the same for both diagnostics. Linear uptake curve ranging from 5 years after launch (USA/EU5), to 7 years (other HICs) to 8 years (UMICs) and 10 years (LMICs/LICs)
- Instrument and test prices fixed for the forecasting period to those of 2020 for simplicity. Guided by the need profiles (which were seen as ambitious). Variable pricing assumptions per sector (private, public). No other price increases or decreases assumed
- Peak revenue = market size, this assumption was due to the uncertain/speculative nature of the further competitive environment (despite pipeline analysis having been conducted)
- Market projections based on population growth trends 2020-2040 in >65 years for each region

Diagnostics Scenarios

Data deficits were considerably greater for the diagnostic modeling than for the therapeutic modeling, with an almost complete absence of data for diagnostic use in the LMIC/LIC income groups. In situations where data are weak but generally available, a sensitivity analysis or 'Monte Carlo simulation' are typical tools used to explore the impact of uncertainty in more detail. However, in this instance the model uses scenarios as the primary means for displaying the large degree of uncertainty over the model outputs. For both diagnostics, two possible scenarios were developed.

In practice, these scenarios affected only those commercial assumptions pertaining to financing, pricing and uptake. **Table 10** describes the two scenario's that were explored for both diagnostics. The first scenario is a baseline scenario (Scenario 1) to capture the current situation or status quo. A second scenario tries to capture a hypothetical situation (Scenario 2) where favorable changes occur in the policy and financing context, leading to both higher reimbursement and use in patient care as well as system uptake/adoption across the three income groups.

	Scenario 1 (current situation) No substantive changes to reimbursement and uptake above current status quo	**Scenario 2 (favorable situation)** Hypothetical scenario; Broad Reimbursement in HICs and Donor Funding for LMICs
Description	A less positive scenario: broadly assumes no substantive developments in Dx reimbursement and use within clinical practice, system uptake and no adoption/use (globally) over and above the current status quo	A hypothetical scenario: broadly assumes positive – or favorable - developments with respect to future Dx reimbursement and use in patient care, system uptake/adoption and consequently for manufacturers developing innovative diagnostics, as described in the need profiles (Section **3.1**)
Diagnostic 1 Dx1 (Bac. vs other)	• Only very limited use of Dx1) in the primary care setting (similar to current situation) • Very limited use of Dx1 in LMICs/LICs • No general, broad reimbursement of rapid diagnostic test, inc. Dx1, in HICs and UMICs in primary care • Neither broad normative support by WHO (in terms of adoption to Essential Dx Lists etc.) nor donor support for LMIC/LIC adoption	NB: Applies to Dx1 and Dx2 • Using the Dx is seen as 'good clinical practice'. • Not using Dx1 is seen as malpractice or even negligence • Dx1 may not be mandatory or viable in smaller primary care settings, even in HICs, due to required capital investment • Testing will generally be reimbursed in both HICs and UMICs • AMR becomes a more broadly prioritized and supported public health topic (including normative support and integration within WHO tools) • Third-party donor support for uptake and roll-out in LMICs/LICs at a level similar to TB, HIV and malaria
Diagnostic 2 Dx2 (ID/susceptibility)	• Dx2,due to its break-through attributes and positive use case, is reimbursed in tertiary care and national-level hospitals even in a less positive scenario • Dx2 therefore still attracts adoption in larger hospitals in HICs and UMICs, but remains limited to these settings • Very limited use in LMICs/LICs (only in selected, large, national-level hospitals) • Neither broad normative support by WHO (in terms of adoption to Essential Dx Lists etc.) nor donor-support for LMICs/LICs adoption	

Table 10: Detailed overview of Scenario 1 and 2 used for the diagnostic modeling.

Diagnostics: Data & assumptions assessment

Table 11 and **Table 12** provide a summary of all assumptions concerning the inputs applied in modeling the market for the two diagnostic products, as well as a qualitative assessment of the certainty of the various input parameters. Compared to the model for therapeutics (see **Table 7**), most input parameters for the two diagnostic tools have more uncertain data (see the presence of only one green indicator in **Table 11**).

While it was possible to find fairly certain and reliable data about the number of users of the Dx1 (Bac. vs other), especially for HICs and UMICs, the corresponding data about Dx2 (ID/susceptibility) was more difficult to identify across all geographies because this product has a more complex expected pattern and context of use. The input parameter with the highest degree of uncertainty for both diagnostic tools is the competitive environment as there are currently no products available on the market with exactly the technical features of these two tools, especially for Dx2 (ID/susceptibility), the profile of which is very aspirational.

The pricing assumptions, which importantly impact revenues, include the price both for purchasing the instrument and for performing each test by using consumables or cartridges provided by the product developer. Dx2 (ID/susceptibility) is expected to have a higher price both for the instrument and per performed test, except for some market contexts in LMICs/LICs where it is fully paid by sponsors such as donors and where prices correspond to those of Dx1 (Bac. vs other).

Model Input Parameter	Certainty Estimate (for parameter across income groups*)	Source / Derivation/ Comments
Primary Care Data		# of GPs per country from various publicly available sources (WHO, Eurostat and government sources) with contractor assumptions on % in clinical practice and # of consultations per year. Figures more reliable for HICs and UMICs and well structured settings, less reliable in LMICs/LICs
Market Segmentation (Primary Care Settings)		Variable distribution of consultations by primary care setting (small/large practice or urgent care), similar distributions of 55 – 60% in large GP practices for HICs & UMICs, for LMICs/LICs consultations are more concentrated in the individual healthcare worker setting at ~60%. Settings scaled down by '% without capacity for investment' due to capital investment requirement. High dropout rates >90% for small practices even if test is reimbursed. Dropout rate LMICs/LICs > UMICs & HICs
Scenarios	N/a.	Scenario 1: Current market situation = higher dropout rate in primary care setting (and other adjustment in funding assumptions depending on scenario), Scenario 2: Broad reimbursement = lower dropout rate
Launch Year		2025 launch across all regions and countries. No LoE and no instrument replacement assumed
Pricing Inputs (Cartridges and Instruments)		Variable pricing for private (Source: Contractor estimate) and public / sponsored markets (Source: Contractor estimate and EAG Dx1 need profile). No price inflation assumed • LMICs/LICs sponsored markets $5 per test/$5,000 per instrument, private $25 per test/$10,000 instr. • UMICs/HICs sponsored / public markets $10 per test/$10,000 per instrument, private $25/test/$10k instr.
Peak Share Assumptions (% Consultations)		Consultations where Dx1 would be clinically beneficial between 3% (HICs & UMICs) and 8% (LMICs/LICs) based on income group specific clinical use cases
Time to Peak Share / Adoption-Uptake Curve		Linear uptake curve ranging from 5 years (USA/EU5) to 7 years (other HICs) to 8 years (UMICs) and 10 years (LMICs/LICs) to reflect rollout across constituent countries within each region (Source: Cepheid GeneXpert MTB/RIF for LMIC, HICs/UMICs & Contractor estimate)
Projections up to 2040		Market projection based on population growth trends 2020 – 2040 in ≥65 year olds for each region
Competitive Environment		A comprehensive pipeline analysis was conducted, but the exact number and profiles of future competitors with similar profiles remains very speculative. Hence, peak revenue ~ market size
Overall	**Medium**	

*collectively across US, HICs, UMICs and LMIC/LICs

Key: High Medium Low

Table 11: Diagnostic 1. Input assumptions summary and qualitative certainty estimate.

Model Input Parameter	Certainty Estimate (for parameter across income groups*)	Source / Derivation/ Comments
# of hospitalized BSI and pneumonia patients	🟡	Country-reported data and modelled estimates (US all-cause pneumonia sourced from HCUPnet i.e. hospital discharge statistics, and US all-cause BSI from GBD Sepsis Study - which uses hospital admissions and death records)
Market Segmentation (Hospital Settings)	🟡	Variable distribution of patients between hospital settings divided into 800+ beds, 400 – 799 beds, 151 – 399 beds, 0 – 150 beds for US and EU5 and 'Very large', 'Large', 'Medium', 'Small' for HICs, UMICs and LMIC/LICs. Majority of patient volume in medium-sized settings in US and HICs.
Scenarios	N/a.	Scenario 1: Current market situation = higher dropout rate in primary care setting (and other adjustment in funding assumptions depending on scenario), Scenario 2: Broad reimbursement = lower dropout rate. Due to generally positive Dx2 Use Cases viability rates = 45 – 70% in HICs and 10 – 40% for Sc. 2 and 10 – 50% in HICs and 1 – 10% in LMICs/LICs for Sc. 1
Launch Year	🟡	2025 launch across all regions and countries. No LoE and no instrument replacement assumed
Pricing Inputs (Cartridges and Instruments)	🟡	Variable pricing for private (Source: Contractor estimate) and public / sponsored markets (Source: Contractor estimate and EAG Dx2 need profile). No price inflation assumed • LMICs/LICs sponsored markets $5 per test/$5,000 per instrument, private $120 per test/$50,000 per instr. • UMICs/HICs sponsored / public markets $60 per test/$50,000 per instrument, private $120/test/$50k instr.
Peak Share Assumptions (% Dx2 beneficial)	🟡	% of patients where Dx2 would be clinically beneficial at 90% (US, EU5, HICs, UMICs and LMICs) based on income group specific clinical use cases
Time to Peak Share / Adoption-Uptake Curve	🟡	Linear uptake curve ranging from 5 years (US/EU5) to 7 years (other HICs) to 8 years (UMICs) and 10 years (LMICs/LICs) to reflect rollout across constituent countries within each region (Source: Contractor estimate + Xpert case study)
Projections up to 2040	🟡	Market projection based on patient growth trends 2020 – 2040 for each region
Competitive Environment	🔴	A comprehensive pipeline analysis was conducted, but the exact number and profiles of future competitors with similar profiles remains very speculative due to the ambition of the need profile. Hence, peak revenue ~ market size
Overall	**Medium**	

*collectively across US, HICs, UMICs and LMIC/LICs

Key: 🟢 High 🟡 Medium 🔴 Low

Table 12: Diagnostic 2. Input assumptions summary and qualitative certainty estimate.

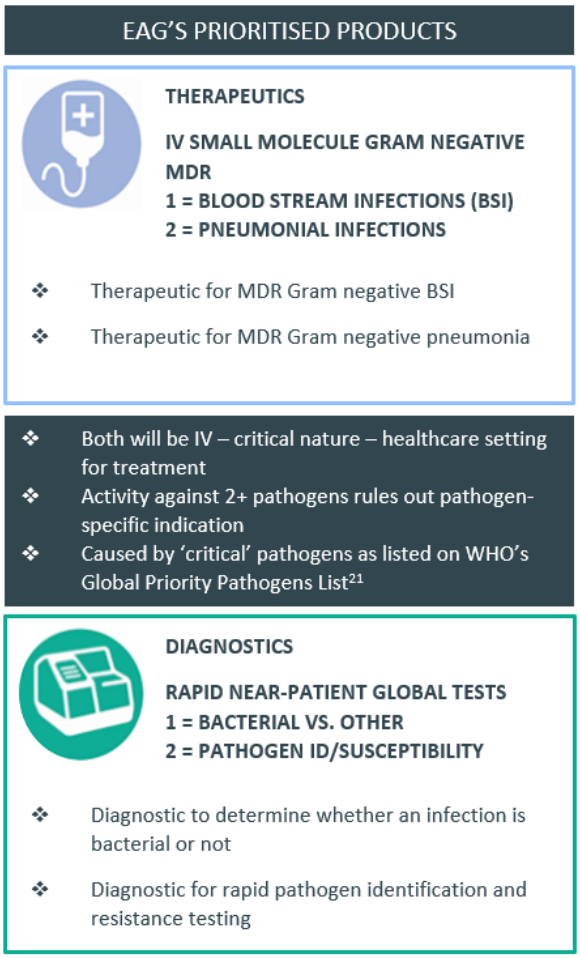
3. RESULTS

3.1 Global patient need: AMR priority product needs

3.1.1 Population needs (by syndrome and pathogen)

As defined by the Global AMR R&D Hub's BoM, the scope of EAG's work was limited to estimating the market potential of products (therapeutics, preventives and diagnostics) that address diseases and/or syndromes caused by pathogens listed on the WHO's Global Priority Pathogens List of Antibiotic-Resistant Bacteria and *M. tuberculosis* (focusing on the 'critical' pathogens)[21].

AMR, unlike Covid-19 or Hepatitis, is not a single disease caused by a single pathogen and extends horizontally across all pathogens regardless of the spectrum of infectious diseases caused. Antibiotic resistance can result from multiple resistance mechanisms, within a variety of bacterial pathogens, whose presence at different sites in the body may result in a number of different infectious syndromes or diseases. Treatment of infections caused by resistant bacteria is more complicated and expensive than treatment of infections caused by susceptible pathogens for a number of reasons. Effective treatment may be delayed and it is often prolonged, in some cases there is no effective treatment option available.



After a 7-step process of desk research and expert consultation (see Section **2.3**), the **Info Box** above (& **Table 13**[32]) shows the final list of prioritized, global needs defined by the EAG that, for this initial phase, are prioritized by human needs through a patient-led approach.

The need profiles developed aim to reflect some of the highest and most acute unmet needs for new products in the field of AMR while stopping short of being full target product profiles (TPPs) of which the WHO hosts an online repository[33]. Despite this, it is acknowledged that the unmet or unfulfilled therapeutic needs in this space are much

[32] (BioPharma Dive, News Brief June 27, 2018)
[33] (WHO TPP Library)

broader. Additionally, **Appendix 4** provides important context regarding the status of current data and knowledge regarding the human burden of bacterial infections and AMR nationally, regionally and globally. The work conducted here – while a valuable addition to the field – must be interpreted within this broader context of the limited data foundation on which it has been built.

	Tx for MDR Gram negative infections that cause BSI	**Tx for MDR Gram negative infections that cause Pneumonia**
Target Convergence *(all Gram negative & on WHO's PPL as 'critical')*	Susceptibility to at least 2 of the following: • *Escherichia coli* • *Klebsiella pneumoniae (Enterobacteriaceae)* • *Acinetobacter baumannii* • *Pseudomonas aeruginosa*	Susceptibility to at least 2 of the following: • *Escherichia coli* • *Klebsiella pneumonia (Enterobacteriaceae)* • *Acinetobacter baumannii* • *Pseudomonas aeruginosa*
Divergence	• *Enterobacter cloacae*	• *Enterobacter spp.* • *Serratia marcescens*
Likely Label / Path to Market	BSI is not currently considered a lead indication, so would get indicated for: • Treatment of [syndrome] due to [bacteria], including cases with bacteremia • Bacteremia could be the leading term (but have to demonstrate superiority over SoC for cases with bacteremia of mixed origins) *	• 1st indication would probably be complex UTI or intra-abdominal infection (iAB) • Going straight to HAP/VAP is theoretically possible but would be an extraordinarily challenging proposition

Table 13: Comparison of the final selected therapeutic needs by causative pathogen and likely path to licensure.
**Achaogen was unsuccessful in showing superiority of Plazomicin over SoC in BSI of mixed origins. Source: Global AMR R&D Hub & (BioPharma Dive, News Brief June 27, 2018)[32].*

3.1.2 Summary of product outlines (to meet identified needs)

The profiles outline what is most needed from small-molecule therapeutics for MDR Gram negative syndromes and is not limited to products that are existing or currently in clinical development. Likewise, the diagnostic profiles outline what is needed from a diagnostic and are not limited to products that are existing or currently in clinical development. Both have criteria specifically requiring appropriateness in low-resource settings. The full profiles are accompanied by an 'industry perspective' on these.

DEVELOPER PERSPECTIVE ON THE DEFINED THERAPEUTICS

> *Small molecule, 'traditional', antibiotics active against Gram negative bacteria represent one of the most challenging sub-set of all the antibacterials to develop. The first hurdle is getting the drug to the tissue of interest. This is a greater challenge with the potential pneumonia target (Tx2) and the lungs than it is for the blood stream infection target (Tx1) since the drug is already in the blood. Discovery efforts also have to overcome the notoriously difficult cell-wall (from where the nomenclature derives) as well as other mechanisms of AMR in Gram negative bacteria. Several strategies have been reported to fight and control resistant Gram negative bacteria like the structural modification of existing antibiotics, and novel chemical structures with new mechanisms of action those resistant bacteria are sensitive to. However, two primary challenges of the antibacterial discovery process remain: (i) proper target selection; and (ii) improvement of chemical libraries. It is clear that antibacterial development in the future will require a wide range of biological, chemical, computational and pharmacological disciplines working towards a common goal to progress 21st century medicines. Based upon the substantial costs, long development time, risks, and limited commercial potential associated with attempting to bring such innovative new Gram negative therapeutics to market, this would be a very challenging program for investors and companies to support.''*
>
> ***Patrick Holmes, Science and Innovation Policy Lead, Global Policy & Public Affairs, Pfizer Inc.***

OUTLINE 1: Therapeutic for MDR Gram negative BSI – Tx1 (BSI)

The profile is to outline what is most needed from a therapeutic for MDR Gram negative BSI and is not limited to products that are existing or currently in clinical development.

- Therapeutic: An innovative antibiotic that quickly achieves and maintains therapeutic concentration in the blood and satisfactory pharmacokinetics/pharmacodynamics (PK/PD) data for common primary infection sites
- Intended use: Treatment of BSI caused by MDR and XDR Gram negative pathogens. With a view that this would subsequently lead to a treatment for neonatal sepsis caused by MDR and XDR Gram negative pathogens. See note below – development pathway – on likely discrepancy between intended use and indicated use (or label)
- Target population: All age groups, initially the product would be developed in adults but with a condition that it is tested and registered in children as soon as possible. Patients who have been hospitalized with failure on empiric treatment and/or with proven microbiology
- Route of administration: Both IV /infusion and oral (where possible)
- In-vitro activity: Innovative antibiotic with activity against at least two of the following MDR *E. coli, K. pneumoniae, P. aeruginosa, E. cloacae* and *A. baumannii,* against defined resistance mechanisms.
- Efficacy: Non-inferior activity compared to current therapies

DEVELOPER PERSPECTIVE ON THE THERAPEUTIC POPULATIONS

> *The challenges of developing innovative Gram negative therapeutics lies not only in passing their membrane, having the right target and avoiding the many resistance pathways, it is also the ability of these new therapeutics to efficiently reach the human target tissues/organs in which Gram negative infections are life threatening. Currently the most common – and therefore likely, for the identified profiles – pathway to licensure would be through large cUTI trials (due to their feasibility) simply to get the drug to market despite it being unlikely to ever be used in this indication. Developing novel therapeutics directly in the key target indications of pneumonia and BSI, while more difficult and more expensive is what we collectively need to work towards. Scientists, industry and regulators must work together further optimizing endpoints and study designs that allow for an efficient trial setup to bring urgently needed medicines as quickly as possible via critical indications to the specific patients in most need. To reach the neonatal sepsis population that could be possible were we to fulfill the Tx2 profile, this target remains someway off. First, we must reach adolescents and children prior to the infants. This would likely require at least 2-5 additional years of studies and substantial additional investment. We need to offer efficient medicines especially to this most vulnerable population and while this is likely not economically viable, the return from adult indications in the G20 must cover these investments.''*
>
> ***Marc Gitzinger, Board VP BEAM Alliance and CEO BioVersys AG.***

Outline 2: Therapeutic for MDR Gram negative infections that cause pneumonia – Tx2 (pneumonia)

The profile is to outline what is most needed from a therapeutic for MDR Gram negative infections that cause pneumonia and is not limited to products that are existing or currently in clinical development.

- Therapeutic: An innovative antibiotic with different mechanism of action (MOA) to Tx1 (BSI) with good penetration into epithelial lining fluid and with rapid attainment of the therapeutic concentration in the lungs and PK/PD data for patients with BSI
- Intended use: To treat pneumonia caused by MDR and XDR Gram negative pathogens. See note below – development pathway – on likely discrepancy between intended use and indicated use (or label)
- Target population: All age groups. Patients who have been hospitalized with proven microbiology and/or failure on empiric treatment
- In-vitro activity: Innovative antibiotic with activity against at least two of the following MDR *P. aeruginosa, K. pneumonia, A. baumannii, Enterobacter spp., E. coli,* and *S. marcescens*
- Route of administration: Both IV and oral, if possible, in nebulized form if not cost prohibitive.
- Efficacy: Non-inferior activity compared to current therapies

Note on Regulatory Pathways to Antibiotic Licensure (see also **Table 14**)

Given currently available – and foreseeable – development and regulatory pathways for therapeutics, two main pathways are considered for how a developer would attain licensure for these products as defined in the need profiles. There is a high-chance that in clinical reality – across income groups – that the products would likely, often, be prescribed off-label (see below)[34]. However, the development and approval of the defined products to meet the patient populations delineated in the need profiles (pg. 61 & 62) will most likely occur as below:

For Tx1 (BSI):

- **Site-specific Indication**: BSI is normally a consequence of another infection that starts in a specific tissue. As such this syndrome is not currently considered a lead-indication *per se* rather one of the site-specific indications (UTI, iAB, pneumonia) is its likely route to initial licensure.
- **Bacteremia:** '…including cases with bacteremia', while a more difficult label addition, this is a possibility for how a developer would reach this population. For 'bacteremia of mixed origins' (which could be the lead term) one would have to show superiority over SoC, which is not currently considered viable.
- **Pathogen-specific indications**: While a regulatory possibility, the multi-pathogen goal and the challenges in recruitment make this unfeasible for our therapeutics.
- **Neonatal sepsis**: Reaching neonates (< 1-year old's) would only be done subsequently and sequentially (adult – adolescent – child – infants) following initial licensure. A pediatric investigation plan (PIP) details the pediatric trials to be conducted. Licensure in children is a problem across all medicines[35] in part because of the substantial additional time and costs involved. These acute population needs in antibiotics are increasingly gaining attention from not-for-profit business models such as GARDP[36] .

For Tx2 (pneumonia):

- Unlike BSI, HAP/VAP is an indication, however, similar to Tx1 (BSI), a sequential path to market and the intended population is expected. This would most likely be a first indication in cUTI >iAB > HAP/VAP. While theoretically possible to get a first indication in HAP/VAP, this is considered a very challenging proposition.

Off-Label Use:
For antibiotics and critical care settings in particular, prevalence of off-label prescribing (administering a medicine in a way that is not within the legal parameters of approval) is known to be common. One older study indicated a frequency of 20 – 45% of adult patients and up to 94% of pediatric patients receiving antibiotics in critical care[37]. There are many reasons for this, ranging from limited diagnostic possibilities to the time-critical nature of treatment. These constraints are likely compounded by the acknowledged disconnect between the patients for whom it is possible to enrol in clinical registration trials to those for whom the products will be most needed i.e., when the indicated use (product label) will likely align poorly with the intended use (in this case, as outlined in the need profiles). Other sources of data (i.e., in-vitro activity, pharmacodynamics and observational studies) can sometimes complement this evidentiary gap, especially when taken-up into clinical guidelines, and many efforts have been occurring to address this[38].

[34] The methodology adopted for the commercial modeling would capture this off-labels use, whereas the epidemiological modeling would not and therefore may underestimate the true 'need'.
[35] (European Medicines Agency, 2017)
[36] (GARDP, 2020)
[37] (Tansarli et al., 2012)
[38] Current efforts in this space are overviewed in 02. Enhancing Clinical Trial Conduct and 05. Streamlining Regulatory Requirements on the Global AMR R&D's Hub's Dynamic Dashboard (www.dashboard.globalamrhub.org)

DEVELOPER PERSPECTIVE ON DIAGNOSTIC 1: BACTERIAL vs OTHER

> *While a seemingly 'simple' problem, solutions here are considered to be medically 'complex'. Many diagnostic companies have been working on this important unmet medical need for over a decade, with existing solutions not currently thought to be sufficiently meeting this need. The primary barriers are broadly considered to be medical and pathophysiological over technical – requiring a need to differentiate not only the pathogen but the immune system's response to the causative pathogen. Due to the complexity of the immune system, technical solutions here are likely to require either analysis of 'genetic signatures' (i.e., circulating RNA) or 'multiple protein biomarkers' – either of these is medically complex. Newer technologies currently in development (>5 years from market) may be able to offer sufficiently high performance (high sensitivity, high NPV). However, the $5 test price point is unlikely to be attainable using today's technology and the $5000 instrument test a real stretch. These price points also do not allow for sufficient margin to pay for development costs and operating expenses. For such a test to have the desired impact on reducing inappropriate antibiotic use, its use would have to be worked into routine medical practice and supported with a variety of uptake incentives. There should also be appropriate reimbursement for such a high-medical-value test, taking into consideration the individual and societal value of decreasing inappropriate antibiotic use, since this would increase market adoption''.*
>
> ***Mark Miller, Executive VP, Chief Medical Officer, bioMérieux.***

OUTLINE 3: Diagnostic to determine whether an infection is bacterial or not – Dx1 (Bac. vs other)

Goal: To quickly provide actionable and evidence-based treatment guidance to the clinician on whether an infection is bacterial or not, in order to help reduce unnecessary use of antibiotics.

Specifications: Rapid, low cost, accessible to resource limited countries/settings, POC test. The product must use minimally invasive or easily obtained sterile site specimens (capillary blood or saliva) and may include a reader or small instrument. The product must have minimal storage requirements and be easy to use (completed in 1-2 steps) and requiring minimal training to perform the test and interpret the results.

- Aspirational cost: $5 per test and less than $5,000 per instrument (USD) (even lower cost of $1 - $3 desirable for LMICs)
- Intended use: Patients (aged over 2 months) presenting with acute febrile illness or acute respiratory illness
- Target user: Physicians, nurses, pharmacists, community health workers, and medical support staff.
- Timing: Pathogen determined as bacterial or not within 15 minutes
- Sensitivity and specificity: Most importantly the test must be accurate and reliable enough to support clinical decision making and gives users the confidence to act upon its result (to eliminate harmful treatment decisions and inform more targeted antibiotic use). The desired sensitivity and specificity are still being considered. Positive and negative predictive values that use sensitivity and specificity and importantly local prevalence of condition are the clinically relevant diagnostic metrics

DEVELOPER PERSPECTIVE ON DIAGNOSTIC 2: PATHOGEN ID & SUSCEPTIBILITY

> *With these two objectives rolled-into one device, the challenge for the development of this product is perceived by developers to be technical in nature. There currently exist two technical approaches to detecting susceptibility/resistance to antibiotics: growth-based (phenotypic) and genetic-based (genotypic). For the former, the main obstacle is getting the speed-to-result fast-enough when limited by bacterial growth rates, they are also unlikely to be POC-like. On the contrary, genotypic solutions only enable the certain identification of resistance, not of susceptibility (lack of resistance), hence the latter can only be inferred and only based on the minimum of >40 genes (for Gram negative pathogens), which keeps the cost high. One of these solutions would need combining with the need for rapid pathogen identification. While this is already possible at speed, simplicity of use and with high accuracy the capital costs are high''.*

OUTLINE 4: Diagnostic for rapid pathogen identification and resistance testing – Dx2 (ID/susceptibility)

The profile outlines what is needed from a diagnostic that rapidly identifies the pathogen and includes resistance testing for priority MDR Gram negative bacteria and is not limited to products that are existing or currently in clinical development. The assay must be applicable and usable in resource limited settings and may include antimicrobial susceptibility testing plus detection of resistant gene markers and other sophisticated technology.

Goal: Informed use of targeted treatment initiation at onset or swift transition from empirical to targeted treatment, based on the results of pathogen identification and susceptibility testing. The assay must be applicable and usable in resource limited settings.

Specifications: Rapid, low cost, accessible to resource limited countries, near-patient test with high sensitivity and specificity, with a wide panel of identification (prioritized pathogens), for direct detection of multiple target bacterial pathogens from lower respiratory sample (BAL or endotracheal aspirates), VOC or blood. The product must have minimal storage requirements and be easy to use, requiring minimal training to perform the test and interpret the results. Different panels maybe required for adult and pediatric populations. This diagnostic must be culture independent and should also be able to detect directly from a single sample, and in a single assay (ideally), determine antibiotic resistance to select antibiotics for identified pathogens.

- Aspirational cost: $5 per test and $5,000 per instrument (USD) (even lower cost of $1 - $3 desirable for LMICs)
- Intended use: Diagnosis of critical/life threatening bacterial infections, including BSI and pneumonia (HAP, VAP and CAP), on clinical suspicion. (Use in Community acquired pneumonia very aspirational at this point given required specimen/sample type at current state of technology)
- Target user: Trained laboratory personnel
- Noting that this diagnostic could be used for a range of other infections but timing, sensitivity specificity outlined in this profile are for critical infections
- Timing: Pathogen and resistance identified within four hours
- Sensitivity and specificity: The diagnostic should be accurate [high sensitivity (≥95%) and specificity (≥98%)] and be reproducible
- Relevant WHO Priority Pathogens: ALL

3.2 Global patient need: AMR patient burden

3.2.1 Therapeutics: Patient forecasts

Assessing the global need for the two therapeutic populations identified required estimating global patient cases (patients with MDR-severe [syndrome] caused by Gram negative bacteria[39]) in 2020 and 2040. This section presents those findings together with the results of some of the interim steps used in their bottom-up derivation, together with an analysis of rates to help in comparing countries.

Current and projected global patient needs: both syndromes

All-cause (hospitalized) pneumonia currently has a larger disease burden than BSI, with almost 1.5 times the latter's estimated cases worldwide. However, Gram negative bacteria are more prevalent in BSI (36%) than in pneumonia (13%) which together with the different pathogen proportions lead to BSI having the larger burden of MDR Gram negative cases than pneumonia by over twice as much.

According to a recent US analysis, pneumonia and BSI account for 40% and 14% of difficult-to-treat (DTR) episodes related to key site of infection by Gram negative pathogens in US hospitals[40]. Analysis from this study shows that while the almost two-fold higher global burden for BSI is forecast to remain until 2040, the rate of *growth* in MDR pneumonia infections is forecast to be slightly higher than for BSI.

The 'core pool' of analyzed countries represent 35% of the world's population. **Figure 12** shows the estimated global patient numbers for Gram negative MDR BSI and pneumonia in 2020 and 2040. In 2020, there were an estimated 3.7 million cases of MDR BSI and 1.7 million cases of MDR pneumonia attributable to Gram negative pathogens worldwide[41].

Projecting current data trends, without any intervention or change to the broader AMR policy context[42], patient numbers are forecast to rise to 5.5 million cases of MDR BSI and 2.8 million cases of MDR pneumonia by 2040. These estimates include the MDR cap that was built into the model. These data represent a growth trend – modeled conservatively – of +48% and +65% for MDR BSI and MDR pneumonia, respectively. If this therapeutic were the same agent whose label covers both syndromes, this would represent a hypothetical, current, global patient demand of 5.4 million.

[39] *E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, S. marcescens and E. cloacae*
[40] (Strich et al., 2020)
[41] In 80% of the world's population (considered a 'global' estimate for this study)
[42] It is noted that antibiotic use is not the only driver of AMR and particularly outside of HICs, WASH, socio-economic determinants and IPC are all substantial confounding factors

However, later sections will suggest that this interpretation of the data should be taken with caution due to the uncertainty of the population that will receive such a product in reality (see **Info Box** on 'Regulatory Pathways' pg. 63).

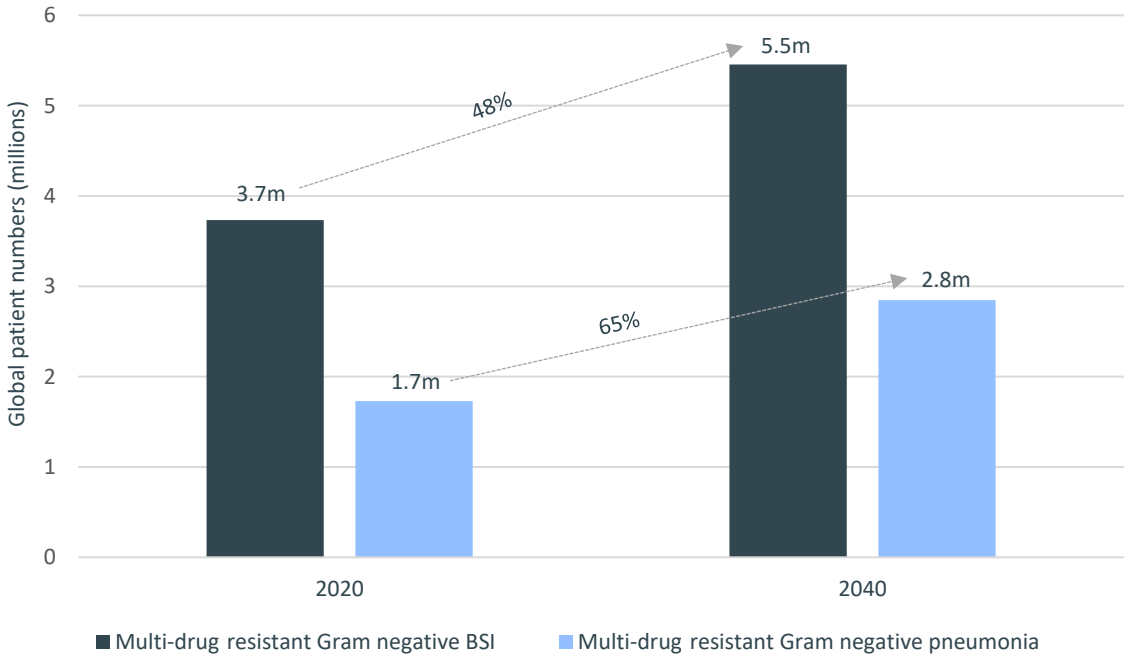


Figure 12: Estimated global Gram negative MDR BSI and pneumonia cases (2020 and 2040).

Of the six critical Gram negative pathogens prevalent in the two syndromes – five of them are common between the two, with four of them contributing the greatest MDR burden across both syndromes. *K. pneumoniae* (the second-most prevalent pathogen in both syndromes at around 30%), *E. coli* causing the greatest burden in BSI (43%) and *P. aeruginosa* causing the greatest burden in pneumonia (40%) (**Figure 13**). The latter pathogen together with *A. baumannii* are more commonly XDR. The relative ranks, by syndrome contributions, are forecast to remain the case for the next 20 years (see Section **3.2**). The figures for MDR Gram negative BSI and pneumonia represent [43]) showed that the average XDR/DTR as a percentage of MDR is slightly lower for BSI than for pneumonia, reflecting the different around 18% and 6% of their total estimated annual all-cause incidence, which is an indicator of the number of patients with more limited treatment options. These were calculated based on **Table 14**, which uses unpublished current industry best-practice assumptions to derive current antibiotic consumption.

While the proportion of MDR Gram negative pneumonia and BSI cases is expected to increase across all countries, in 8 of the 13 of our core pool countries this proportion is forecast to exceed 50% or more by 2040 (**Figure 16** BSI, **Figure 19** pneumonia). A supplementary analysis (not included here pathogen contributions (see also **Appendix 4e & 4f**).

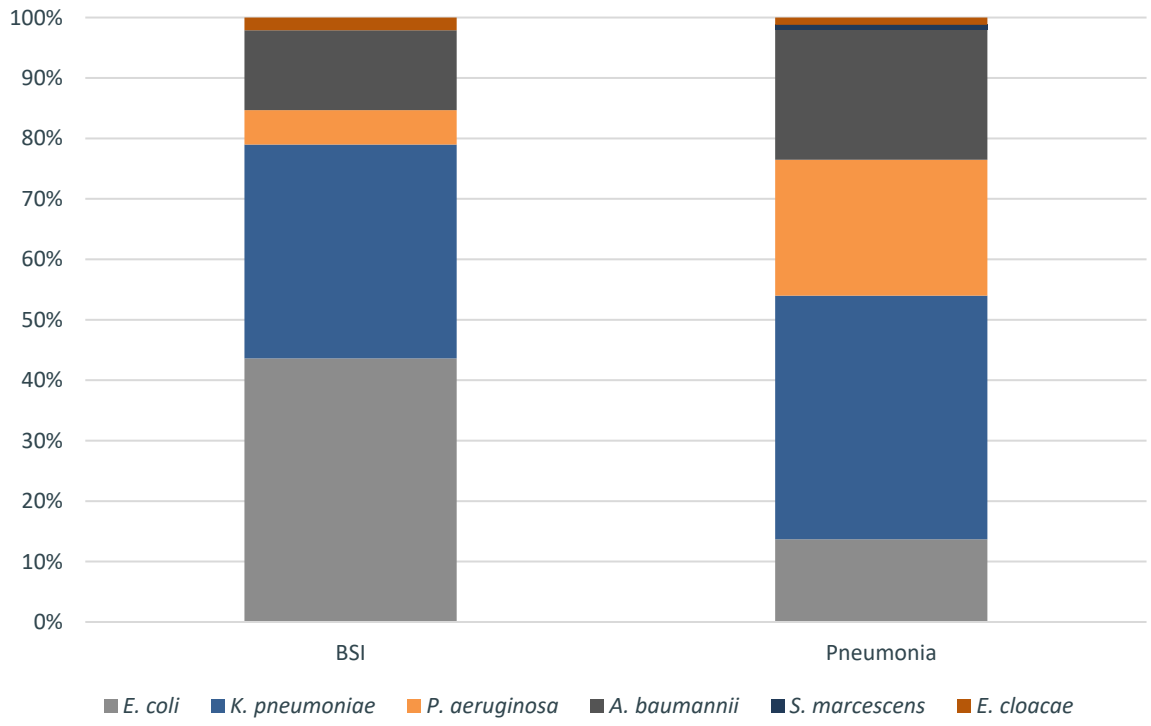


Figure 13: Relative proportions of the MDR pathogens of interest across the two therapeutic populations in 2020.

[43] Due to the previously noted challenge (Info Box on pg. 30) of appropriately distringuishing XDR/DTR from MDR

		Antibiotic Consumption Trend (2000 – 2015)				
		Reduced >5%	Slight reduction / no increase	Increased <10%	Increased 10-20%	Increased >20%
Current MDR %	<10%	20%	25% (UK)	30%	35%	40%
	10-20%	35% (US) (Japan)	35%	40%	50%	50%
	20-30%	40%	40%	50% (Italy)	60%	60%
	30-50%	60%	60% (Thailand)	60%	70% (Brazil) (Saudi Arabia)	70% (Turkey)
	50-60%	70%	70%	70% (South Africa)	80%	90% (Vietnam)
	>60%	70%	80%	90% (India) (Kenya)	90% (Egypt)	90%

Table 14: Matrix used to determine peak MDR rate assumptions per country. *Key: MDR Rates: Green - low, Blue - medium; Red – high.*

Current pathogen resistance proportions (by country)

Resistance proportions indicate the percentage of bacterial isolates taken from sick patients who are resistant to antibiotics. **Table 15** shows the resistance proportions for the individual Gram negative pathogens that can cause BSI and pneumonia by country / income region.

In general, MDR proportions, and thus need, are highest in LMICs/LICs and some UMICs. Regarding *A. baumannii,* it can be seen from **Table 15** that there is already a significant resistance problem with this pathogen across the majority of countries analyzed. MDR proportions are exceptionally high (at over 80%) for this pathogen and growth rates have thus plateaued in a number of countries. This demonstrates the existence of infections caused by this pathogen that have very limited treatment options.

K. pneumoniae also has relatively high resistance proportions, especially in LMICs/LICs and some UMICs. For *S. marcescens* and *E. cloacae* there is limited resistance data available, but cases of BSI and pneumonia due to these particular pathogens appear to be relatively low at the moment.

	Country	MDR *Escherichia coli*	MDR *Klebsiella pneumoniae*	MDR *Pseudomonas aeruginosa*	MDR *Acinetobacter baumannii*	MDR *Serratia marcescens*	MDR *Enterobacter cloacae*
HICs	UK	5%	7%	1%	7%	N/A	6%
	US	17%	17%	19%	44%	11%	10%
	Saudi Arabia	56%	46%	21%	93%	N/A	N/A
	Japan	26%	7%	11%	9%	7%	N/A
	Italy	22%	49%	22%	84%	N/A	N/A
UMICs	Brazil	23%	55%	13%	84%	N/A	29%
	Thailand	36%	37%	33%	N/A	N/A	N/A
	South Africa	21%	55%	18%	82%	15%	24%
	Turkey	32%	55%	34%	88%	17%	N/A
LMICs / LICs	India	88%	81%	35%	85%	35%	34%
	Kenya	47%	61%	27%	89%	22%	N/A
	Vietnam	46%	54%	46%	82%	N/A	N/A
	Egypt	61%	61%	39%	93%	N/A	N/A

Resistance Proportions Key:	<10%	10-29%	30-49%	50-69%	≥70%

Table 15: Resistance proportions for Gram negative bacteria by country (all indications). *Research and analysis using data from Pfizer's ATLAS[24] and SENTRY surveillance databases[25] and Public Health England Laboratory surveillance reports (See References for modeling). N/A: data not available.*

3.2.2 BSI: Patient burden

As a proxy for the most critical infections that have become systemic, BSI, can be caused by fungi as well as bacteria. Calculating 'all-cause' BSI was the starting point for our estimates. Current (2020) global all-cause BSI estimated through this study was **20,898,322 patients annually** – a lower incidence than for pneumonia. Of these 21 million patients, infections attributable to Gram negative bacteria were estimated to comprise a much higher proportion, with a global average of 37%, than in pneumonia. This trend was similar across income groups (HICs = 37%, MICs = 39%, LMICs = 34%). Looking at the focus of this study – the MDR proportions of the Gram negative BSI infections - we see, similar to pneumonia, that the proportions increase with decreasing income status (HICs = 6%, MICs = 16%, LMICs = 25%), with MDR incidence being 10% higher than in pneumonia, totaling 3.7 million cases annually.

BSI vs Sepsis

BSI and sepsis are both serious conditions that share similar clinical presentations. BSI (and many other infections) can progress to sepsis which is defined not only by the presence of an infection but also by organ dysfunction from a dysregulated host response to that infection[44].

[44] (Huerta LE & Rice TW, 2019)

Gram negative pathogen distribution in BSI

In 2020, *E. coli* (43%), *K. pneumoniae* (31%) and *P. aeruginosa* (12%) are the top 3 Gram negative pathogens contributing to MDR and XDR BSI cases and they are forecast to remain the top 3 pathogens until 2040.
Figure 14 shows the current, relative contribution to BSI by these pathogens. This compares similarly to the contributing Gram negative pathogens in pneumonia in terms of the top 3 pathogens, but very differently in terms of their relative proportions (**Figure 17**). The contributions from *E. cloacae* (BSI) and *S. marcescens* and *Enterobacter spp*. (pneumonia) appear comparatively minor.

Despite the dominance of *E. coli* in BSI and MDR BSI, the top two pathogens causing XDR/DTR Gram negative BSI are *A. baumannii* and *K. pneumoniae* (**Appendix 4e**), reflecting greater XDR resistance rates for these pathogens compared to *E. coli.*

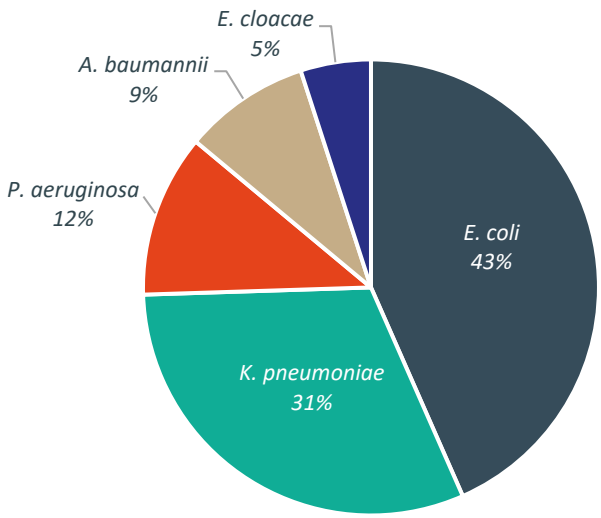


***Figure 14*: Gram negative pathogen distribution in BSI.** *Research and analysis based on Core Pool (13) country data for 2020.*

MDR-BSI: Current and forecasted global patient need

Figure 15 shows the estimated global patient numbers for Gram negative MDR BSI in 2020 and 2040, broken down by income group and by the origin of the calculations (i.e., the core pool of countries, or the 'uplift pool').

In 2020, there were an estimated 3.7 million cases of MDR BSI attributable to Gram negative pathogens worldwide. Projecting current data trends, without any intervention, patient numbers are forecast to rise to 5.5 million cases of MDR BSI by 2040. Similarly, **Figure 16** shows the estimated Gram negative MDR BSI patient numbers projected until 2040 across each of the 13 core pool countries. By far the largest projected need is forecast to be in India. This is due to high absolute numbers of BSI cases as a share of population (expected to reach 1.6 billion in 2040), and relatively high projected MDR proportions for most of the contributing Gram negative pathogens.

Another metric of need in terms of threat from MDR pathogens is the proportion of a country's total projected Gram negative BSI cases that are forecast to be MDR. With the exclusion of Saudi Arabia, in general the LMICs/LICs and some UMICs have a much higher overall proportion of MDR cases as compared to HICs. Individual countries with the highest estimated proportion of MDR cases as a percentage of total Gram negative BSI cases include India, Egypt, Saudi Arabia, Kenya, South Africa and Vietnam, all of which have over 45% of Gram negative BSI cases estimated to be MDR.

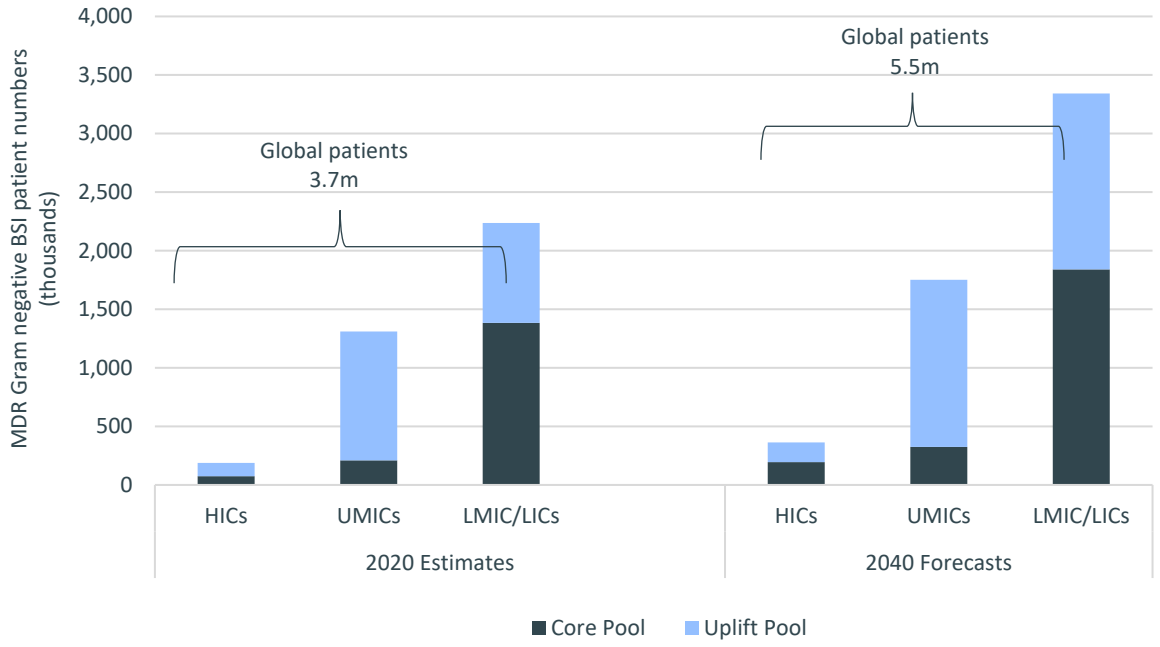


***Figure 15**: **Estimated Gram negative MDR BSI cases globally by income grouping (2020 & 2040). Dark blue**: Estimates based on 'core country pool (13)'. Light blue: Numbers derived from 'Uplift' countries (22).*

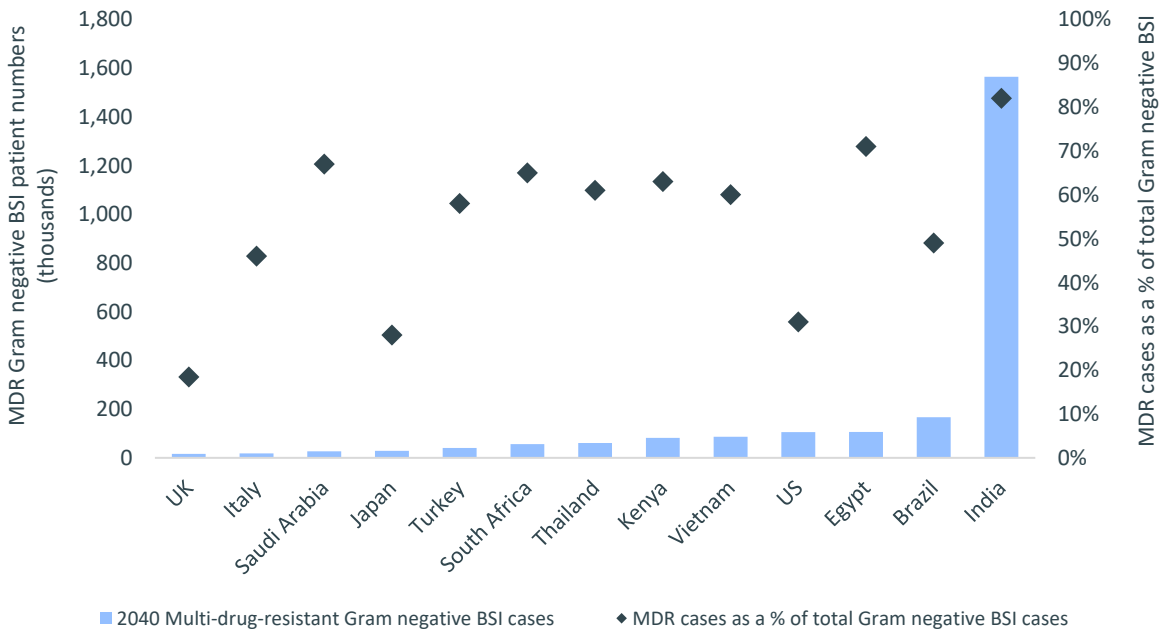


Figure 16: Estimated 2040 Gram negative MDR BSI patient numbers by country.

MDR-Gram negative BSI: Current and forecasted patient need by income group

Within the HIC pool, current (2020) resistance proportions vary between 5% and 53% (non-weighted average 23%) of Gram negative BSI cases, as shown in **Table 16**. However, these are set to increase across all countries over the next 20 years, reaching a new average of 38% (range 18% to 67%) by 2040. Similarly, MDR cases are currently estimated to range between 3,602 to 27,995 cases, annually, within the core pool of HIC countries. When lifted up to reach 80% of the global population, the current burden is estimated at 187,638. When projecting these cases into the future, it is estimated they will nearly double, at 396,980 cases by 2040 – even within HICs, with their correspondingly more robust health systems (in terms of stewardship and infection prevention and control [IPC] etc.).

Within the UMIC pool, both resistance proportions and MDR BSI cases are currently estimated to be higher than in HICs. Current (2020) resistance proportions are higher within a narrower range and vary between 36% and 69% (average 41%) of Gram negative BSI cases. While the proportion is set to increase across all countries in the next 20 years, the increase in the proportion is only marginally greater in the UMIC core country pool (at 17%) than the HIC core country pool (15%), with an average of 58% of cases by 2040. MDR cases are currently estimated to range between 19,591 (Turkey) to nearly 115,000 (Brazil) cases annually. However, when adding the 'uplift countries', such as China, Russia and Mexico, to the values, the estimated UMIC burden increases substantially (as is visible in **Table 17**), by over 1 million cases.

Projecting total UMIC cases into the future leads to a forecasted UMIC burden of 1.75 million cases annually attributable to MDR Gram negative BSI.

However, looking at the contribution to the estimated global burden from LMICs/LICs as seen in **Table 18**, it is notable how dominant this is estimated to be. MDR proportions found in BSI cases are already expected to be exceeding 50% in all but one of the 'core pool' of countries and the average proportion today of 59% is set to increase to 69% of Gram negative BSI cases by 2040. Both Egypt and India are set to exceed 70% of BSI cases being MDR by 2040. With an estimated current MDR case burden of over 2.2 million, the majority coming from our 'core country pool' (predominantly India), the relative contribution of the core pool of countries is estimated to lessen by 2040 with the 'uplift countries' forecast to almost catch up, contributing an almost equal contribution of the 3.3 million forecasted cases by 2040.

Incidence of Gram negative BSI	2020			2040		
	Incidence	GN BSI that is MDR (%)	MDR Cases	Incidence	GN BSI that is MDR (%)	MDR Cases
United Kingdom	68,785	5	3,602	87,036	18	16,047
United States of America	261,825	11	27,995	342,582	31	105,491
Saudi Arabia	27,225	53	14,565	40,297	67	27,143
Japan	100,159	19	19,200	103,391	28	28,545
Italy	31,578	28	8,937	39,631	46	18,367
Total of 'Core HIC Country Pool'	**489,572**	**23**	**74,299**	**612,936**	**38**	**195,591**
Uplift (France, Germany, S. Korea, Spain)		**23-45**	**113,339**			**167,389**
HIC Sub-Totals			**187,638**			**362,980**

Table 16: Estimated Gram negative MDR BSI cases in high-income countries/country pool (2020 & 2040). *Yellow: higher 2020-2040 growth to drive expected % MDR in 2040 relative to other countries; Blue: forecast population decline in S. Korea & Germany slowing 2020-2040 epidemiological growth; Orange: averaged (mean) of group percentages. Note: Countries lacking BSI breakdown for one or more of the five Gram negative pathogens of interest: US (1), Saudi Arabia (1). Countries lacking MDR data for one or more of the five Gram negative pathogens of interest: Saudi Arabia (1), Italy (1), Japan (1).*

Incidence of Gram negative BSI	2020			2040		
	Incidence	GN BSI that is MDR (%)	MDR Cases	Incidence	GN BSI that is MDR (%)	MDR Cases
Brazil	303,087	38	114,496	339,440	49	167,099
Thailand	95,603	41	39,314	100,340	61	60,920
South Africa	77,452	48	36,852	87,604	65	56,708
Turkey	51,569	38	19,591	70,439	58	40,755
Total of 'Core UMIC Country Pool'	**527,710**	**41**	**210,253**	**597,823**	**58**	**325,483**
Uplift (China, Russia, Mexico, Iran, Colombia, Argentina)		**36-69**	**1,099,468**			**1,426,162**
UMIC Sub-Totals			**1,309,721**			**1,751,645**

Table 17: Estimated Gram negative MDR BSI cases in upper-middle income countries/country pool (2020 & 2040). *Blue: forecast population decline in China & Russia slowing 2020-2040 epidemiological growth; Orange: averaged (mean) of group percentages. Note: Countries lacking BSI breakdown for one or more of the five Gram negative pathogens of interest: South Africa (1) and lacking MDR data for one or more of the five Gram negative pathogens of interest: Thailand (2), Turkey (1).*

Incidence of Gram negative BSI	2020			2040		
	Incidence	GN BSI that is MDR (%)	MDR Cases	Incidence	GN BSI that is MDR (%)	MDR Cases
India	1,587,250	76	1,214,077	1,916,085	82	1,564,932
Kenya	86,168	50	43,313	129,753	63	82,151
Vietnam	120,566	47	56,882	144,131	60	86,775
Egypt	107,217	64	69,085	149,499	71	106,252
Total of 'Core LMIC/LIC Country Pool'	**1,901,202**	**59**	**1,383,356**	**2,339,468**	**69**	**1,840,111**
Uplift (Indonesia, Pakistan, Nigeria, Bangladesh, Ethiopia, Philippines, Congo, Tanzania, Myanmar, Ukraine, Uganda, Algeria)		**29-72**	**853,105**			**1,501,412**
LMIC Sub-Totals			**2,236,461**			**3,341,523**

Table 18: Estimated Gram negative MDR BSI cases in lower-middle income & low-income countries/country pool (2020 & 2040). *Orange: averaged (mean) of group percentages. Note: Countries lacking BSI breakdown for one or more of the five Gram negative pathogens of interest: Egypt (5 – used data for a similar country). Countries lacking MDR data for one or more of the five Gram negative pathogens of interest: Kenya (1), Vietnam (1), Egypt (1).*

MDR Gram negative BSI: Current and forecasted patient need by demography

Demographic (age) data specifically for MDR Gram negative BSI is not available for the majority of countries analyzed. However, best available data for sepsis gives some insight into the age groups that may be most affected by these infections.

Hospital statistics and IHME GBD data for sepsis for the 13 analyzed countries suggests that in HICs, older adults i.e., 65 years and older, are disproportionately affected, whereas in UMICs and LMICs/LICs, infants less than one year old have the highest incidence rates compared to all other age groups. While, currently, children and neonates are disproportionately affected, the decline in population projections for this age group in many countries is likely leading to a lower increase in rates than observed for pneumonia.

Rates of Gram negative BSI by income group and country

Rates of current and projected cases of total Gram negative BSI and MDR Gram negative BSI follow a similar trend in that they are greatest in LMICs/LICs and UMICs, and lowest in HICs (**Table 19**). Currently, MDR Gram negative BSI is estimated to affect 17 per 100,000 people in HICs. This rate is estimated to be three times higher (at 50 per 100,000 population) in UMICs and four times higher (at 74 per 100,000 population) in LMICs/LICs.

These disparities continue in the projected rates for each income group until 2040 but with a higher growth rate in higher income regions. incidence rates increase to 33 per 100,000 in HICs, 73 per 100,000 in UMICs and to 89 per 100,000 in LMICs/LICs. Within the forecast period, for many of the LMICs/LICs analyzed, MDR proportions are forecast to plateau having reached high rates. This results in a slowing of the growth rate of projected MDR cases in LMIC/LICs as compared to higher income regions.

When looking at numbers of cases by income status in the 13 countries across 2020 to 2040, it can be seen that LMICs will account for about 37% of the total Gram negative bacterial BSI cases in these 13 countries and nearly 45% of MDR cases. The estimated and projected rates per 100,000 population of Gram negative bacterial BSI for the 13 countries is presented in **Table 20**. The estimated rates range from 51 cases per 100,000 in Italy to 161 cases per 100,000 in Kenya. There appears to be an inverse relationship between income status and MDR Gram negative BSI. The mean rate is lowest in HICs (mean = 78) compared to much higher but similar rates in the other income groups (UMICs = 121, LMICs/LICs =127). The number of Gram negative bacterial BSI cases increases across all 13 countries in 2040 with the rates per 100,000 ranging from 64 in Italy to 166 in Kenya. Interestingly, the overall projected Gram negative bacterial BSI rates per 100,000 in 2040 are only slightly higher than presently for HICs (mean = 92) and only slightly higher than presently for UMICs (mean = 126) and LMICs (mean = 130), in contrast to projected MDR BSI rates.

In 2020, at a more granular by country-level, dispararities become even more apparent. The estimated MDR rates range from 5.4 in the UK to 92 in India with correlation between higher rates of MDR and lower income status. Projected rates of MDR Gram negative bacteria BSI increase for all 13 countries in

2040, with projected rates ranging from 25 in Japan and 105 in Kenya. Once again, a correlation with higher projected MDR rates and lower income status, with an attenuated trend in 2040 compared to 2020 (HICs =33, UMICs = 73, LMICs/LICs = 89) is observed.

Income Group	Average Rates for Gram negative BSI per 100,000 population			
	Gram negative BSI (2020)	MDR Gram negative BSI (2020)	Gram negative BSI (2040)	MDR Gram negative BSI (2040)
HICs	78.2	17.2	91.7	33.3
UMICs	120.5	50.1	126.4	73.3
LMICs / LICs	126.5	74.1	130.2	89.0

Table 19: Current and projected estimated rates per 100,000 population for Gram negative BSI by income group.

Income Group	Country	2020		2025		2030		2035		2040	
		Total	MDR	Total	MDR	Total	MDR	Total	MDR	Total	MDR
HICs	United Kingdom	102.4	5.4	106.8	7.8	113.2	11.6	118.5	16.9	121.2	22.3
	United States of America	78.7	8.4	84.4	11.7	88.7	16.1	90.9	21.7	91.7	28.2
	Saudi Arabia	79.7	42.6	79.3	46.7	81.3	51.8	85.5	56.0	91.5	61.7
	Japan	79.8	15.3	82.0	19.9	84.2	21.9	86.8	23.2	90.3	24.9
	Italy	50.6	14.3	52.8	17.1	56.3	21.1	60.1	26.4	63.6	29.5
UMICs	Brazil	143.2	54.1	143.1	58.5	144.8	62.8	145.9	67.3	146.9	72.3
	Thailand	138.6	57.0	139.7	64.1	141.4	72.6	143.5	82.7	146.1	88.7
	South Africa	137.2	65.3	135.4	69.4	133.7	74.3	133.0	80.6	133.8	86.6
	Turkey	62.9	23.9	65.4	28.0	69.3	32.8	73.7	38.8	78.9	45.6
LMICs /LICs	India	120.0	91.6	118.9	92.2	119.0	93.8	120.1	96.3	121.9	99.6
	Kenya	161.0	80.9	159.5	87.8	160.5	94.7	162.5	90.3	166.0	105.1
	Vietnam	122.1	57.6	122.4	63.3	124.6	69.3	127.5	75.0	131.5	79.2
	Egypt	103.0	66.3	101.3	66.9	100.0	67.6	100.3	69.5	101.4	72.0

Table 20: Current and projected estimated rates per 100,000 population for Gram negative BSI for the 13 core countries.
Note: India data derived from GBD data.

3.2.3 Pneumonia: Patient burden

Pneumonia, as a syndrome, can be caused by many bacteria in addition to viruses and fungi. As for BSI, this calculation of 'all-cause' pneumonia was the starting point for the estimates. Current (2020) global all-cause pneumonia estimated through this study was **30,079,677 patients** annually. Of these 30 million patients, infections attributable to Gram negative bacteria were estimated to average 15% globally, with the proportion being higher the wealthier the income group (HICs = 19%, UMICs = 14%, LMICs/LICs = 11%). When looking at the MDR proportions of those Gram negative pneumonia infections we see the opposite trend, in that the proportions increase with decreasing income status (HICs = 3%, UMICs = 5.3%, LMICs/LICs = 6.7%) from a global average of 6% or 1.7 million cases **(Figure 18)**.

[45].

Gram negative pathogen distribution in pneumonia

Figure 17 shows the current (2020) relative contribution of the individual Gram negative pathogens in pneumonia, derived from analysis of the 13 selected countries. Looking to 2040, the top 3 pathogens are forecast to remain the same. Gram negative pneumonia has a greater contribution from *P. aeruginosa* (40%) *K. pneumoniae* (32%), and *A. baumannii* (12%) / *E. coli* (12%) in descending order. The contributions from *E. cloacae* and *S. marcescens* appear to be relatively minor. There is an increased proportion of *A. baumannii* and *P. aeruginosa* contributing to XDR Gram negative pneumonia cases (versus MDR), reflecting greater XDR resistance rates in most countries (along with *K. pneumoniae*) as compared to the other Gram negative pathogens of interest (**Appendix 4f**); in contrast XDR / DTR resistance proportions for *E. coli* are relatively low across most countries

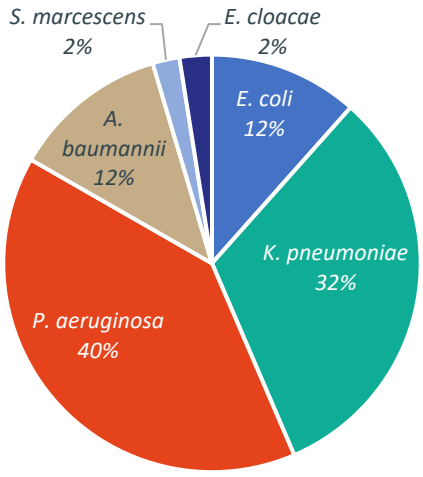


Figure 17: Gram negative pathogen distribution in pneumonia. *Based on Core Pool (13) country data for 2020.*

[45] These data are not shown due to the data limitations (Info Box on pg. 30) highlighted previously.

Current and forecasted global patient need (absolute)

In 2020, there were an estimated 1.7 million cases of MDR pneumonia attributable to Gram negative pathogens worldwide. Projecting forward current data trends, without any intervention, patient numbers are forecast to rise to 2.8 million cases of MDR pneumonia in 2040. **Figure 18** shows these estimates and forecasts as a global total and visualizes how the numbers were derived. The proportion of the cases estimated from the 'core country pool (13)' was analyzed as well as the contribution from the 'uplift country pool'. Additionally, the breakdown by income groups clearly demonstrates how, in 20 years' time, the burden of MDR Gram negative pneumonia will fall most heavily on UMICs and LMICs/LICs.

Similarly, **Figure 19** shows MDR pneumonia patient numbers projected to 2040 across each of the 13 selected countries that comprise the core country pool. In 20 years (2040), based on current data and trends and with no further intervention, MDR cases of Gram negative pneumonia are expected to increase across all countries. Eight countries representing all income groups – India, Egypt, Vietnam, Turkey, South Africa, Kenya, Thailand and Saudi Arabia – are forecast to have 50% or more of their Gram negative pneumonia cases being MDR by 2040.

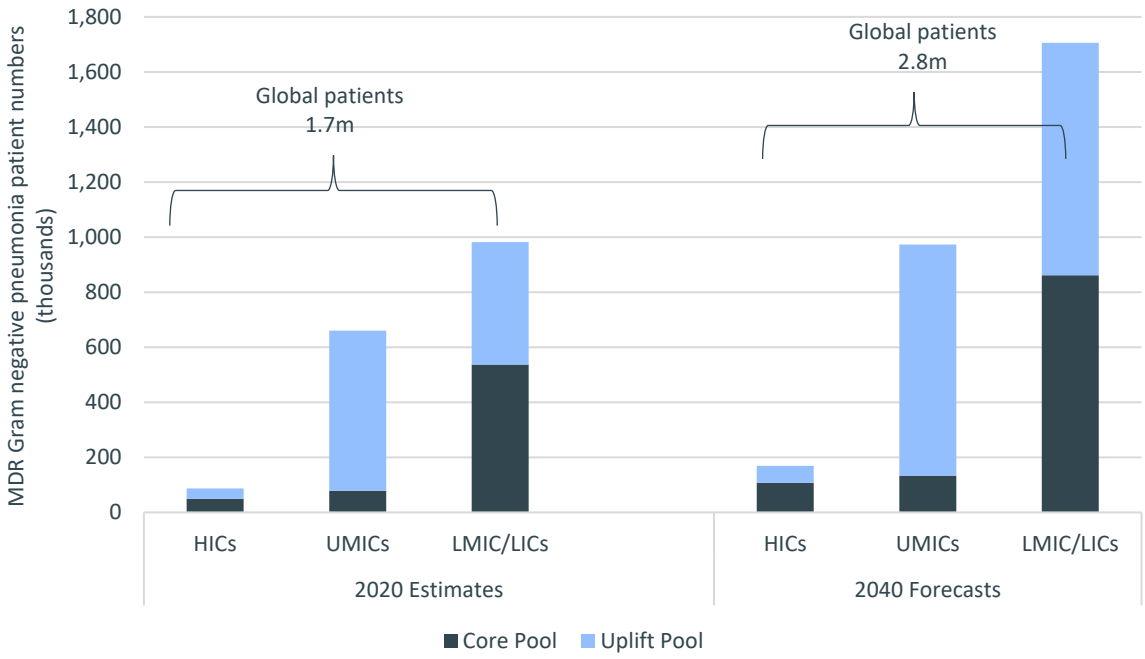


***Figure 18: Estimated Gram negative MDR pneumonia cases globally by income group (2020 & 2040). Light blue**: country pool used to 'uplift' the estimates; **Dark blue**: estimates based on 'core country pool (13)'.*

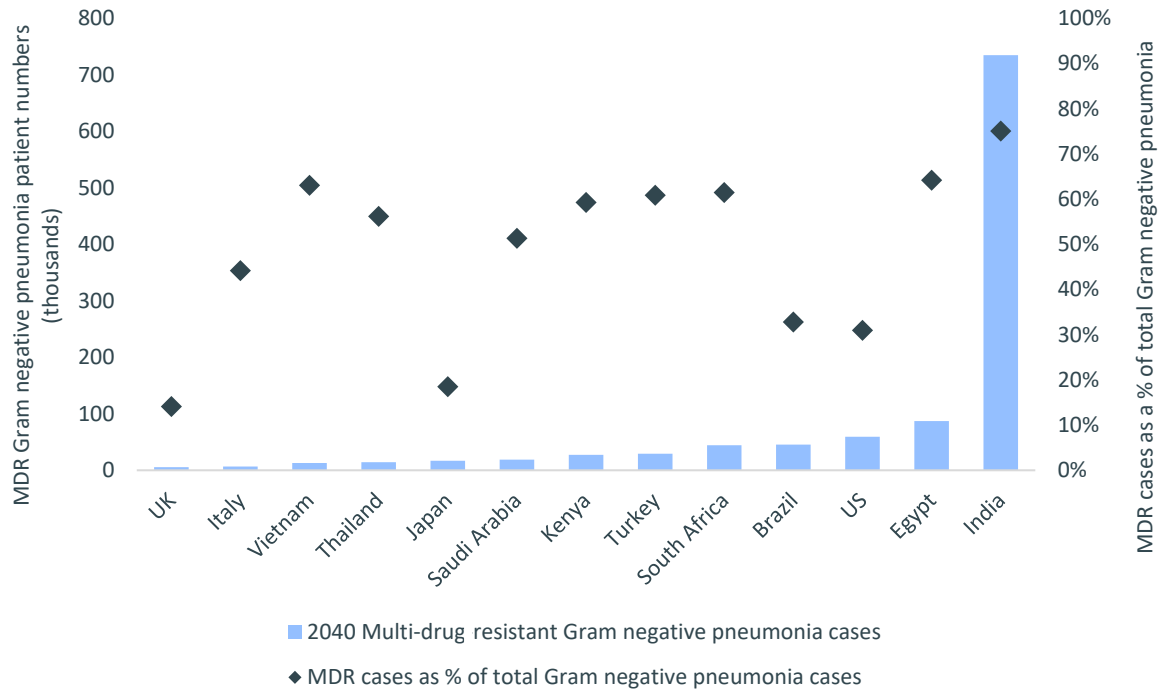


***Figure 19**: Estimated 2040 Gram negative MDR pneumonia patient numbers by country.*

MDR-Gram negative pneumonia; current and forecasted patient need by income group

Within the HIC pool (**Table 21**), current (2020) resistance proportions vary between 4% and 32% averaging 19% of Gram negative pneumonia cases. However, these are set to increase across all countries over the next 20 years, reaching a new average of 32% by 2040. Similarly, MDR cases are currently estimated to range between 1,096 to 25,509 cases annually within the core pool of HIC countries. When extrapolated to 80% of the global population, the current burden is estimated at 87,140 people. When projecting these cases into the future, they are estimated to nearly double, to 169,104 cases by 2040 – even within HICs with their more robust health systems (in terms of stewardship and IPC, etc.).

Within the UMIC pool (**Table 22**), both resistance proportions and MDR pneumonia cases are currently estimated to be higher than in HICs. At present, resistance proportions are higher within a narrower range and vary between 26% and 50% (on average 33%). In 20 years time, this is estimated to increase across all UMIC countries to between 33% and 61% (average 53%) of MDR Gram negative pneumonia cases.

For UMICs, the core country pool is estimated to comprise relatively fewer (14%) of the total cases in this income group. The group as a whole is forecast to have close to 1 million MDR Gram negative pneumonia cases by 2040.

Within the core country pool, Thailand is currently estimated to have the lowest number of cases (7,463) and is forecast to

remain that way until 2040. The highest number of cases is currently in South Africa (28,063), but is forecast to be overtaken by Brazil by 2040, with both countries exceeding 40,000 forecast cases. Compared to other LMICs/LICs, this could partly reflect the superior detection capacity enabled by their health systems as well as higher rates of HIV, TB and malaria.

In contrast, the current estimated burden in the LMIC/LIC country pool (**Table 23**) is thought to be close to 1 million cases with MDR proportions already close to, or exceeding, 50% of all cases.

With MDR proportions set to average 65% in this income group by 2040, total cases are set to reach 1.7 million. Including India, the LMIC group of four countries comprises the dominant share of cases, in particular, when adding the 12 uplift countries. With India's current high and growing proportion of MDR cases and large population, MDR proportions are set to exceed 60% throughout the region, leading to a very high fraction of patients not responding well to currently available therapies within 20 years.

Incidence of Gram negative pneumonia	2020			2040		
	Incidence	% of GN pneumonia cases MDR	MDR Cases	Incidence	% of GN pneumonia cases MDR	MDR Cases
United Kingdom	30,294	4	1,096	38,405	14	**5,418**
United States of America	149,908	17	25,509	191,887	31	59,371
Saudi Arabia	26,218	29	7,584	36,697	51	18,834
Japan	88,734	13	11,237	90,670	18	16,767
Italy	12,637	32	4,073	15,243	44	6,733
Total of 'Core HIC Country Pool'	**307,790**	**19**	**49,499**	**372,902**	**32**	**107,123**
Uplift (France, Germany, S. Korea, Spain)		**23-45**	**37,641**			**61,981**
HIC Sub-Totals			**87,140**			**169,104**

Table 21: Estimated Gram negative MDR pneumonia cases in high-income countries/country pool (2020 & 2040). *Yellow: higher 2020 - 2040 growth to enable expected % MDR in 2040 relative to other countries; Blue: forecast population decline in South Korea and Germany slowing 2020-2040 epidemiological growth; Orange: averaged (mean) of group percentages. Note: Countries lacking pneumonia breakdown for one or more of six Gram negative pathogens of interest: UK (3), Saudi Arabia (4), Japan (3), Italy (2). Countries lacking MDR data for one or more of the six Gram negative pathogens of interest: UK (1), Saudi Arabia (2), Italy (2), Japan (1).*

Incidence of Gram negative pneumonia	2020			2040		
	Incidence	% of GN pneumonia cases MDR	MDR Cases	Incidence	% of GN pneumonia cases MDR	MDR Cases
Brazil	101,045	26	26,658	138,335	33	45,350
Thailand	20,927	36	7,463	25,594	56	14,375
South Africa	55,941	50	28,063	72,077	61	44,285
Turkey	36,732	46	16,794	48,334	61	29,406
Total of 'Core UMIC Country Pool'	**214,644**	**33**	**78,979**	**284,341**	**53**	**133,415**
Uplift (China, Russia, Mexico, Iran, Colombia, Argentina)		**36-69**	**581,179**		**264**	**839,569**
UMIC Sub-Totals			**660,158**			**972,984**

Table 22: Estimated Gram negative MDR pneumonia cases in upper-middle income countries/country pool (2020 & 2040). *Blue: forecast population decline in China and Russia slowing 2020 - 2040 epidemiological growth; Orange: averaged (mean) of group percentages. Note: Countries lacking pneumonia breakdown for one or more of six Gram negative pathogens of interest: Thailand (3), South Africa (2), Turkey (1). Countries lacking MDR data for one or more of the six Gram negative pathogens of interest: Thailand (3), Brazil (1), Turkey (1).*

Incidence of Gram negative pneumonia	2020			2040		
	Incidence	% of GN pneumonia cases MDR	MDR Cases	Incidence	% of GN pneumonia cases MDR	MDR Cases
India - Derived from GBD data	727,714	64	467,515	979,112	75	734,584
Kenya	29,292	47	13,650	45,954	59	27,220
Vietnam	14,724	49	7,254	20,351	63	12,829
Egypt	91,677	53	48,663	135,725	64	87,087
Total of 'Core LMIC/LIC Country Pool'	**863,407**	**53**	**537,082**	**1,181,143**	**65**	**861,720**
Uplift (Indonesia, Pakistan, Nigeria, Bangladesh, Ethiopia, Philippines, Congo, Tanzania, Myanmar, Ukraine, Uganda, Algeria)		**29-72**	**444,932**			**844,317**
LMIC Sub-Totals			**982,014**			**1,706,037**

Table 23: Estimated Gram negative MDR pneumonia cases in lower-middle income & low-income countries/country pool (2020 & 2040). *Orange: averaged (mean) of group percentages. Note: Countries lacking pneumonia breakdown for one or more of six Gram negative pathogens of interest: Kenya (4), Vietnam (4), Egypt (3). Countries lacking MDR data for one or more of the six Gram negative pathogens of interest: Kenya (1), Vietnam (2), Egypt (2).*

MDR-Gram negative pneumonia; by age-group (demographic)

Demographic (age) data (in the groups 0 – 4 years, 5 – 69 years and 70+ years) specifically for MDR Gram negative pneumonia is unavailable for most of the countries analyzed. However, best available data for all-cause pneumonia or lower respiratory tract infections gives some insight into the age groups that may be most affected by these infections. Hospital statistics for all-cause pneumonia and IHME GBD data for lower respiratory tract infections suggest that regardless of income group, older adults (65 years and older) have the highest incidence rates of all age groups, followed by young children (0 – 4 years). With most analyzed countries forecast to have increasing growth of older adults continuing until 2040, this is likely an important driver of future MDR Gram negative pneumonia patient numbers.

Rates of Gram negative pneumonia by income group and country

Table 24 shows the estimated average rates per 100,000 population for total and MDR Gram negative pneumonia stratified by income group.

Data quality for Gram negative pneumonia epidemiology is not as robust as for BSI, however, the trends remain broadly similar. The highest rates of MDR Gram negative pneumonia, both current and projected, are estimated to be in LMICs/LICs and UMICs (**Table 24**).

Currently, MDR Gram negative pneumonia is estimated to affect nine per 100,000 population in HICs. This rate is estimated to be 23 per 100,000 in UMICs and 36 per 100,000 in LMICs/LICs. These trends are expected to continue in the projected rates for each income group, with incidence rates of 18 per 100,000 in HICs, 35 per 100,000 in UMICs and 47 per 100,000 in LMICs/LICs.

As with BSI, the projected MDR Gram negative pneumonia rates in LMICs/LICs and some UMICs slow to a degree due to the plateauing of high-resistance proportions reached for some pathogens during the forecast period.

Income Group	Average rates for Gram negative pneumonia per 100,000 population			
	Gram negative pneumonia (2020)	MDR Gram negative pneumonia (2020)	Gram negative pneumonia (2040)	MDR Gram negative pneumonia (2040)
HICs	51.6	9.4	58.4	18.3
UMICs	55.5	23.4	65.3	35.3
LMICs / LICs	65.9	35.8	71.0	46.9

Table 24: Current and projected estimated rates per 100,000 population for Gram negative pneumonia by income group. *Research & analysis based on 12 countries (Vietnam has been excluded from this analysis due to significant gaps in pneumonia epidemiology data).*

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Rates of Gram negative pneumonia by country

Turning to the numbers of cases by income status in the 13 countries across 2020 to 2040, LMICs will account for about 63% of the total Gram negative bacterial pneumonia cases and nearly 80% of MDR cases. **Table 25** shows the estimated and projected rates per 100,000 population of Gram negative bacterial pneumonia for the 13 core countries. In 2020, the estimated rates range from 15 cases per 100,000 population in Vietnam to 99 per 100,000 in South Africa.

The number of Gram negative bacterial pneumonia cases increases across all 13 countries in 2040, with the rates per 100,000 population ranging from 19 in Vietnam to 110 in South Africa.

In 2020, the estimated MDR rates range from 2 in the United Kingdom to 50 in South Africa. There appears to be a correlation between higher rates of MDR and lower income status, in 2020, with mean rates (by income status) being 9 for HICs, 23 for UMICs and 29 for LMICs/LICs. Projected rates of MDR Gram negative bacteria pneumonia increase for all 13 countries in 2040, ranging from 8 in the UK and 68 in South Africa.

Once again, 2040 projections suggest a correlation between higher projected MDR rates and lower income status (HICs = 18, UMICs = 35, LMICs/LICs = 38). Infection rates are conspicuously higher in LMICs with poor and immuno-compromised populations, by virtue of social-economic determinants of health and wellbeing. The rates of HIV/AIDS and TB are among the highest in the world and social inequality is especially marked. Both structural and infrastructural risk factors for infection are rife in LMICs/LICs. Hygiene, sanitation and housing are inadequate and there is limited access to clean water, energy and healthcare for many of these communities.

Income Group	Country	2020		2025		2030		2035		2040	
		Total	MDR	Total	MDR	Total	MDR	Total	MDR	Total	MDR
HICs	United Kingdom	45.1	1.6	46.6	2.5	48.6	4.0	51.3	6.2	53.5	7.5
	United States of America	45.1	7.7	47.8	9.9	50.0	12.7	51.0	14.5	51.4	15.9
	Saudi Arabia	76.7	22.2	77.6	26.6	79.1	31.9	81.1	36.8	83.4	42.8
	Japan	70.7	9.0	73.7	11.1	75.3	12.3	77.0	13.3	79.2	14.7
	Italy	20.3	6.5	20.8	7.3	21.6	8.3	23.0	9.7	24.5	10.8
UMICs	Brazil	47.7	12.6	50.0	14.1	53.1	15.7	56.6	17.6	59.9	19.6
	Thailand	30.3	10.8	31.4	12.8	33.1	15.4	35.1	18.7	37.3	20.9
	South Africa	99.1	49.7	101.5	54.2	104.4	58.9	107.2	63.3	110.1	67.6
	Turkey	44.8	20.5	46.1	23.2	48.2	25.9	51.1	29.4	54.1	32.9
LMICs/LICs	India	54.9	35.3	56.2	37.4	57.9	39.9	59.9	43.0	62.3	46.7
	Kenya	54.7	25.5	55.3	27.3	56.2	29.3	57.3	31.8	58.8	34.8
	Vietnam	14.9	7.3	15.4	8.4	16.4	9.5	17.6	10.8	18.6	11.7
	Egypt	88.0	46.7	88.3	49.1	89.1	51.9	90.4	55.2	92.0	59.1

***Table 25*: Current and projected estimated rates per 100,000 population for Gram negative pneumonia for the 13 core countries.** *Note: India data derived from GBD data. There are significant gaps in pneumonia epidemiology data available for Vietnam.*

3.2.4 Diagnostics: Patient forecasts

The 'total global patients eligible' for the two diagnostics identified was determined by combining patient estimates (need) with the clinical setting (use case) where the diagnostic is expected to be performed. This patient eligibility or 'realizable diagnostic demand' calculation was performed now and at five-year intervals to 2040. This section presents these findings together with results from some of the interim steps taken to derive the figures.

Current and projected patient needs: both diagnostics

The lack of a diagnostic that can differentiate an infectious disease caused by bacteria compared to non-bacterial pathogens, like Dx1 (Bac. vs other), has long been considered a bottleneck that affects our ability to move beyond empiric therapy (generally based on educated clinical guesswork). Newer devices to support the administration of antibiotics quickly, safely and effectively – but only when clinically necessary – would revolutionize the treatment of infected patients in primary care centers worldwide. It would avoid the unecessary (often over) use of antibiotics and enable widespread and early capture of patients before they become critically ill. At a later point in the patient journey – for the few whose infection worsens and where treatments do not work – the second modeled diagnostic allows a more specialized physician to be informed about the nature of the causative bacteria and what antibiotics those bacteria are susceptible to (Dx2 [ID/susceptibility]).

Figure 20 shows the estimated 20-times greater scale of the utility of Dx1 (Bac. vs other), contrasting quite sharply with that of Dx2 (ID/susceptibility), growing to an almost 30 times scale difference by 2040. This difference in scale reflects the different need and objective of these two diagnostics. For Dx1, its value is as a 'volume-based' utility through early and widespread capture of patients at their first point of presentation to the health system, generally in primary care facilities.

Dx2 (ID/susceptibility) will only be used for diagnosis of critically ill hospitalized patients. So not only is the 'patient pool' much smaller for this device, as it would be used primarily in critically ill hospitalized patients, but its more sophisticated nature comes at a higher cost and requires a more specialized context for its use, which affects overall penetration into hospitals. Health system constraints in non-HIC areas and the relatively more saturated HIC markets also play a role.

Figure 21 shows the same phenomenon plotted on the same scale. In 2020, five years prior to the modeled launch of such a device, Dx1 (Bac. vs other) is expected to have a global patient need/eligibility just short of 500 million patients, in contrast to Dx2 (ID/susceptibility), which is closer to 22 million patients annually. By 2040, when these hypothetical diagnostic devices will have been on the market for 15 years, the patient need is forecast to have risen to nearly 800 million and 30 million patients, for Dx1 and Dx2, respectively.

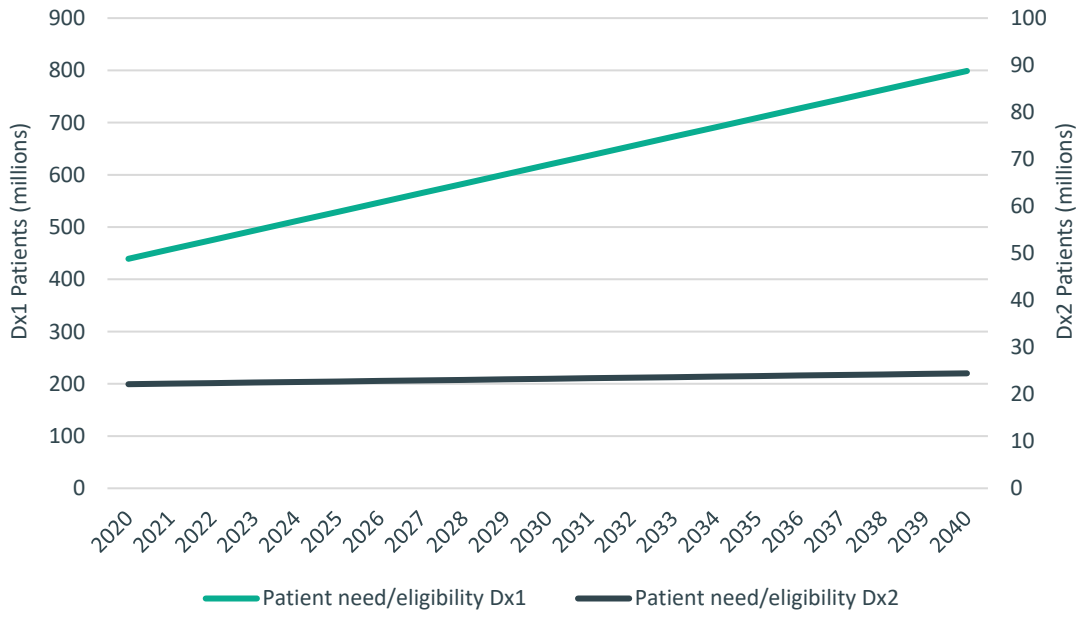

Figure 20: Estimated 2020 – 2040 global patient need for Dx1 (Bac. vs other) and Dx2 (ID/susceptibility).

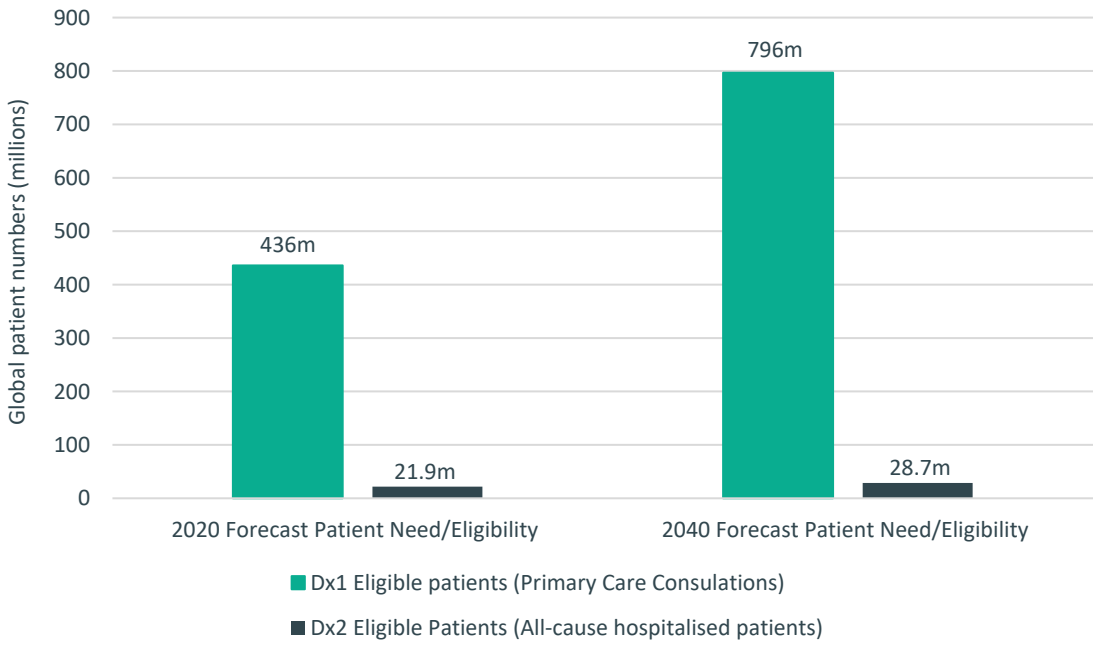

Figure 21: Comparative forecasted (2020 & 2040) global patient need for Dx1 (Bac. vs other) & Dx2 (ID/susceptibility).

Dx1 (Bac. vs other): Current and forecasted global patient need

Figure 22 shows the estimated patient numbers for Dx1 (Bac. vs other) globally, by income group and indicating the source of the estimates i.e., from the core pool of countries or from the global 'scale-up'. (In contrast to the therapeutics need assessment, the scale-up represents a lesser proportion of the estimate because groupH themselves selected countries in addition to the core country pool)[46]. These data indicate that – based on the use cases – primary care patients symptomatic for possible infection and eligible for Dx1 (Bac. vs other) comprise over 500 million patients globally at present.

Although substantially higher than the >1.5 million patients who could be expected to benefit from the therapeutic, these estimates still err on the conservative side[47]. Additionally, the figure quoted here is not simply an estimate of 'patient need', nor those presenting to a health system with possible infection, but additionally includes a consideration of eligibility, i.e., the share of those patients likely to be judged by a clinician to benefit from such a diagnostic.

When looking at the breakdown by income group, 27% of those 500 million patients are estimated to live in HICs, 23% in UMICs and – the dominant proportion – 50% in LMICs/LICs. Looking to 2040, the need for Dx1 (Bac. vs other), globally, is forecast to increase to nearly 800 million patients, an increase of over a half (54%) compared to 2020 estimates. This growing global need will be dominated by LMICs/LICs and UMICs. LMICs/LICs will see a close to doubling in patient need (108% increase) and UMICs an increase of 83%, whereas in HICs the need remains much lower (34% increase). The drivers of this are the relatively higher growth in >65-year-olds in UMICs and LMICs/LICs as compared to HICs, combined with the higher eligibility percentage of 8% in these income groups compared with 3% in HICs.

Dx2 (ID/susceptibility): Current and forecasted global patient need

The data indicate that – based on the use cases – hospitalized patients with all-cause pneumonia and BSI, and who are eligible for Dx2 (ID/susceptibility), are estimated at 21.9 million globally at present; 20 times lower in 'need magnitude' than for Dx1 (Bac. vs other). **Figure 23** shows the estimated 'need/eligibility' (expressed in patient numbers) for Dx2 (ID/susceptibility), globally, by income-group, and indicates the source of the estimates i.e., from the core pool of countries or from the global 'scale-up'.

[46] They were therefore able to select additional countries they considered to have the best data and to represent highest need among other criteria.

[47] As noted earlier; this diagnostic is likely to find patient needs in additional hospitalized primary and secondary infections as well as a potential sepsis screen for hospital and ambulatory care.

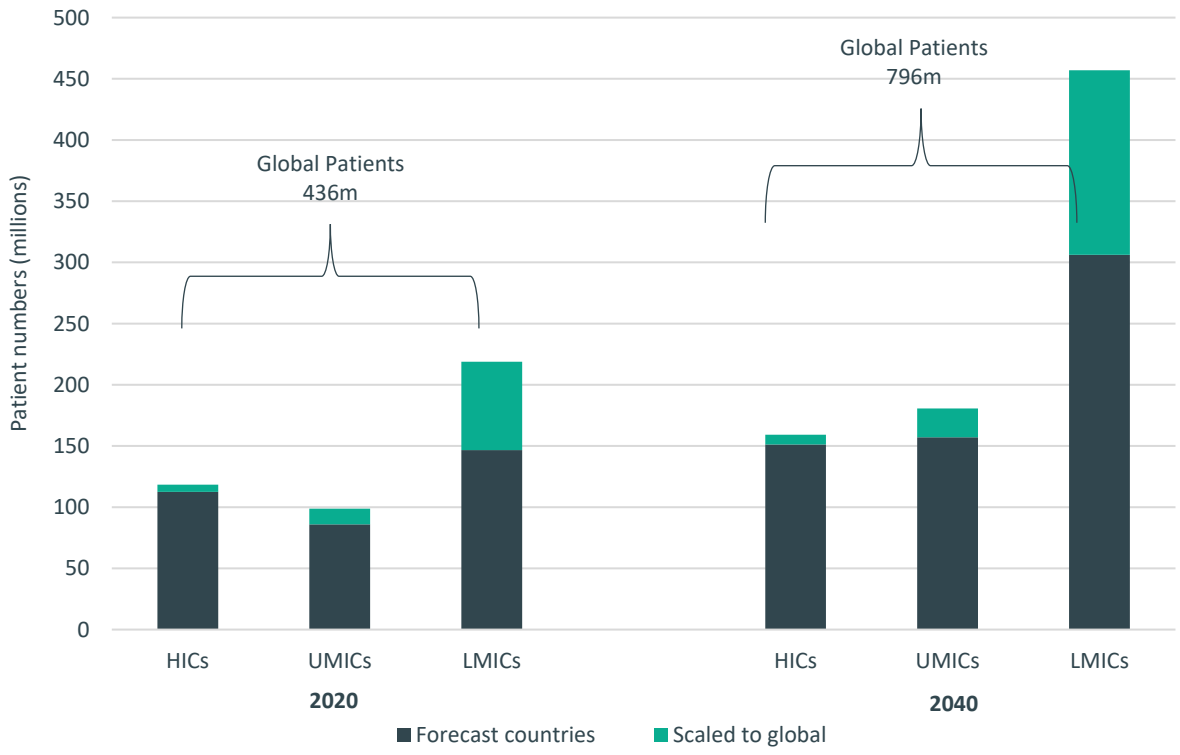

Figure 22: Forecasted patient need (eligibility) for Dx1 (Bac. vs other) globally by income grouping (2020 & 2040). *See pg. 28 for information on global scale up.*

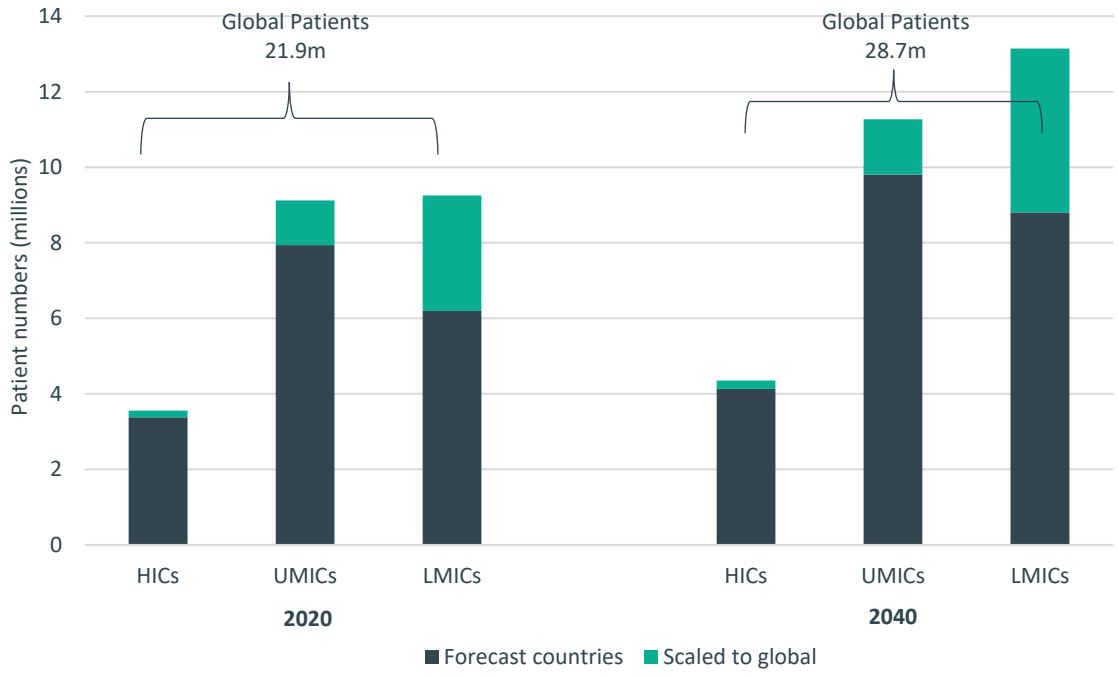

Figure 23: Forecasted patient need (eligibility) for Dx2 (ID/susceptibility) globally by income grouping (2020 & 2040). *See pg. 28 for information on global scale up.*

3.3 Current market model: Global access estimates

Figure 24 below shows the global penetration of all branded Gram negative IV antibiotics over the last decade (2010-2019) in terms of number of patients (by income-group), market share and growth. Overall, it shows that around 0.25 million people annually, around the world, received one of the newer antibiotics with activity against Gram negative pathogens. It also confirms the relative stability of this ~$500 million sub-market. Growth over the period has averaged 8% with an uptake in 2016 following five new product launches in the US and other regions, and early uptake of Zerbaxa (ceftolozane/tazobactam) and Zavicefta (ceftazidime/avibactam) (**Figure 25**). Notable is the declining proportion of the US and rising proportion of other HIC markets over this period. The overall low (UMICs) and negligible (LICs) patient volumes outside HICs, where the burden is highest, is also notable.

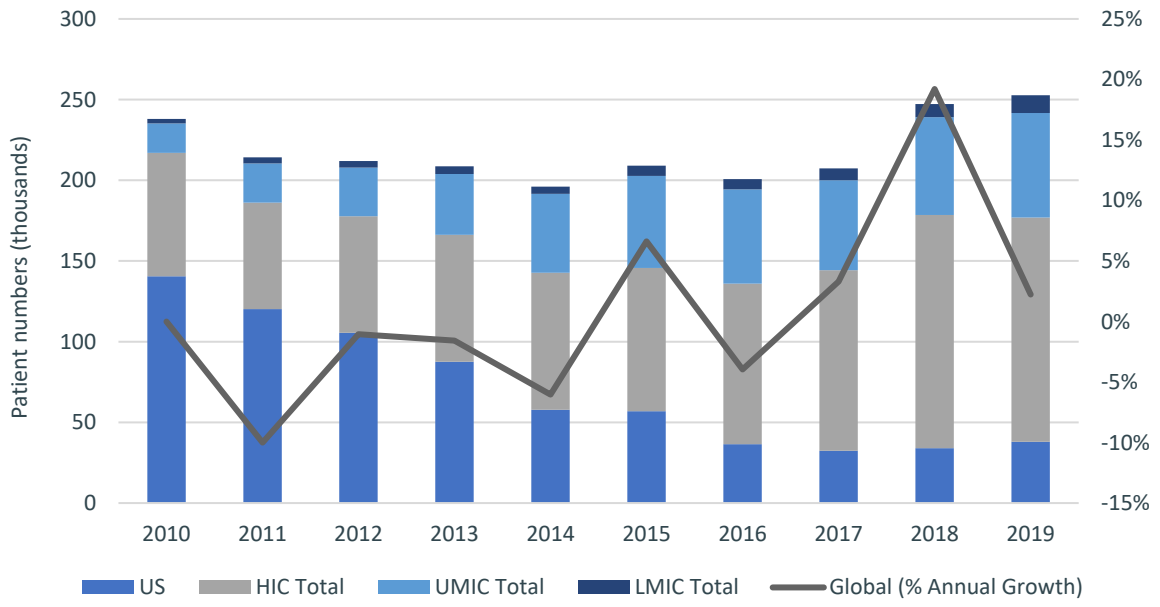

Figure 24: Total branded Gram negative IV global antibiotic market penetration (patient numbers and % annual growth) by income group over the last decade (2010-2019).

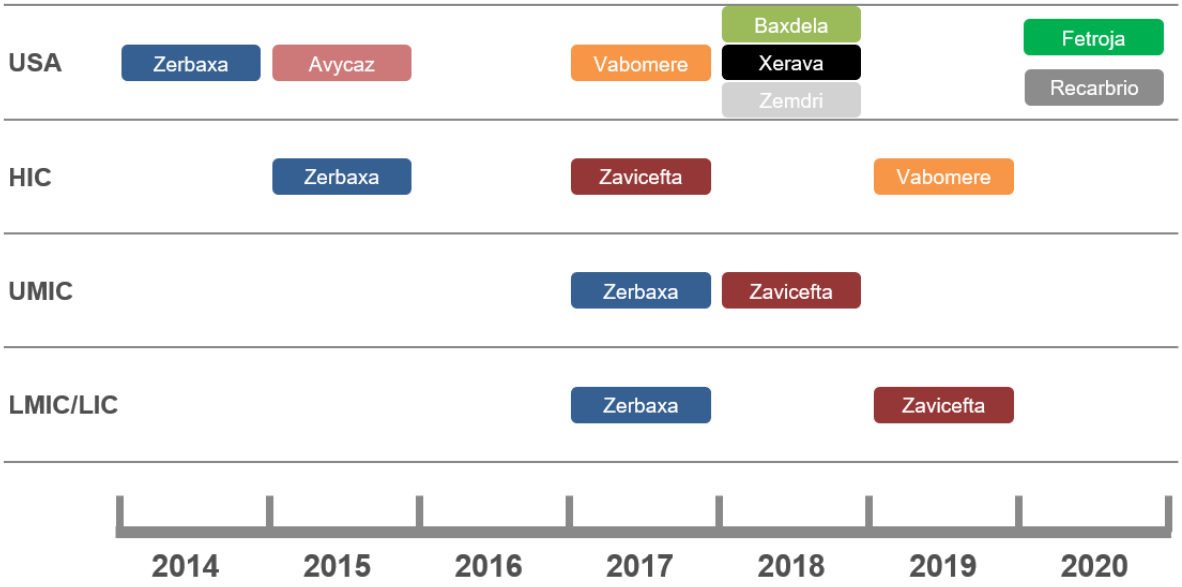

Figure 25: Regional uptake of newer branded Gram negative antibiotics 2014-2020.

3.3.1 Therapeutics

In this study, global uptake is modeled as a function of the roll-out by region, coupled with the patient shares. For our therapeutics, the key assumptions here – derived from analogue analysis – is that roll-outs occur in successive years based on a first launch in the US in 2025 (HICs: 2026, UMICs: 2027, LMIC/LICs: 2028).

Figure 25 indicates how poorly (or slowly) newer, branded Gram negative antibiotics, appear to be penetrating regions outside of the US. Following licensure, availability and access to patients can be simplified into two steps. The first is 'market access' a decision taken by a company to sell its product in a country or not[48] i.e., are the expected revenues from sales in that country expected to exceed the time and cost to register, agree reimbursement with payors, supply and distribute. The second, and the only component that this study can provide some insight into[49], is 'patient access' over which national governments have more influence and which *de facto* assumes the first step is successful. A study from a decade ago indicated that, even once licensed in a country, uptake of antibiotics – relative to other classes – was particularly slow[5]; likely driven by clinical stewardship caution. Before further exploring this second step, it should be noted that the first step (market access) is increasingly the concern with antibiotics – this is most acute in smaller (lower volumes) or lower value (priced) countries.

The analysis in **Figure 25** indicates this current poor penetration of newer agents outside of the USA. This is a finding corroborated by a

[48] Market access is more complicated - a simplified economic explaination is provided
[49] Due to the methodology employed, it was not possible to explore volume/value thresholds below which countries do not secure access and therefore how many fewer (than 72 countries) would attain access under the modelled scenarios

forthcoming more comprehensive study of uptake across all antibiotics[50].

This section of the report takes the epidemiologically-derived patient numbers from Section **3.2** and brings them together with the patient numbers derived from revenues from the commercial modeling; converted back to patient numbers (indicating 'actioned patient demand'). See Section **2. Methodology** for how the conversions from sales to doses to patient numbers was performed.

The analysis shows that 24,000 – 34,000 treatment courses for the two-defined antibiotics are forecast to be administered, in 2035, from assumed sales in around 70 countries globally. Looking at the two products separately, the results for Tx1 (BSI) broadly show (**Figure 26 & Table 26**) how five years after launch (in 2030) around 7% (7.39%) of the global need is forecasted to be met[51] with almost all of this in HICs (as would be expected). Five years later (2035) and only a year before peak sales – and therefore 'maximum' reach – the proportion of need being fulfilled is roughly similar at 7% (7.25%) despite an absolutely higher number of patients (by around 9,000 patients) forecast to receive Tx1 (BSI). The growth in absolute access, by that latter point, is driven by increased consumption outside non-HICs, where patient reach almost doubles. However, notable is that outside HICs the proportion of MDR cases expected to receive Tx1 does not reach 1% of the need, indicating a possible, pending access gap worth further urgent exploration (due to the role of the assumptions in these estimates).

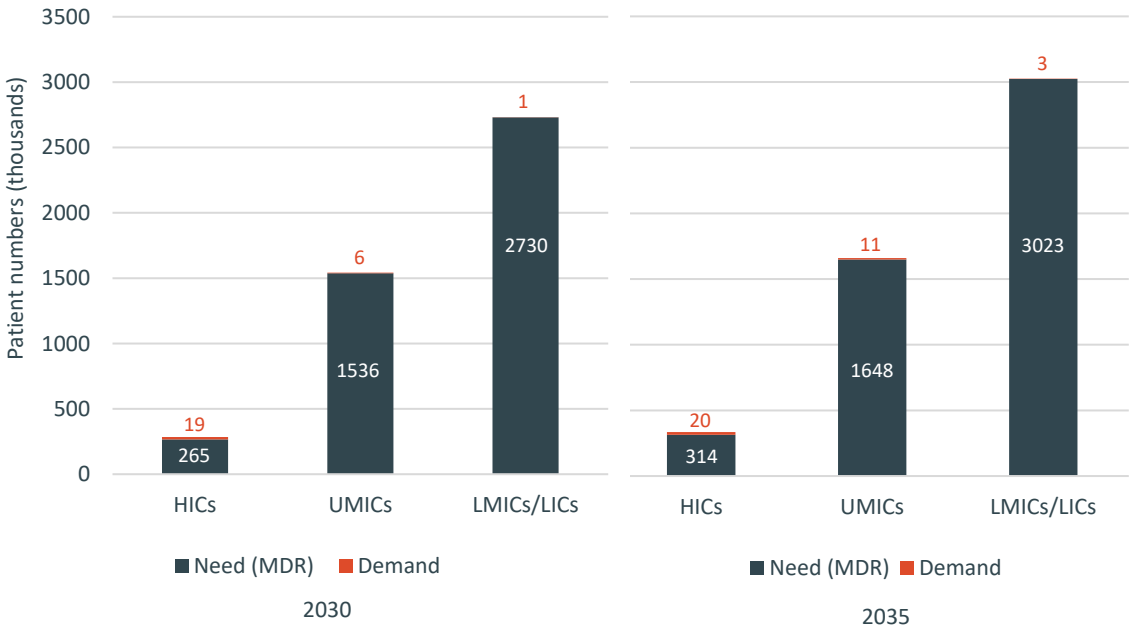

Figure 26: Estimated and projected patient numbers for Tx1 (BSI) in 2030 & 2035, broken down by income grouping and need vs. demand.

[50] (Outterson, Orubu, Rex, Årdal & Zaman, 2021)
[51] NB: It is possible that therapeutic equivalents could also be used to treat the defined population (need) modelled

Therapeutic 1 (BSI)						
World Bank Income Group	Patient Numbers (2030)			Patient Numbers (2035)		
	MDR cases	No. Treated (Tx1)	% of MDR cases expected to receive Tx1	MDR cases	No. Treated (Tx1)	% of MDR cases expected to receive Tx1
HICs	265,961	18,558	6.97	314,226	20,379	6.49
UMICS	1,536,803	5,862	0.38	1,648,459	11,216	0.68
LMICs/LICs	2,730,057	1,028	0.037	3,023,849	2,622	0.09

Table 26: Estimated patient numbers for Tx1 (BSI). *Expressed as MDR patients. Patients treated and the % between the two for all income groups.*

Table 27 details the same data for Tx2 (pneumonia) and **Figure 27** presents this data contextualized with how the forecasted patient reach for Tx2 (pneumonia) compares to the patient reach (number of patients estimated to be prescribed a branded Gram negative antibiotic) of the whole sub-class.

This analysis of access shows a similar picture to Tx1 (BSI) but more pronounced. Five years after launch it is forecast to have reached around 10.4% of MDR pneumonia patients globally (~95% of these in HICs). By 2035, a year before peak sales and reach (peak sales are assumed to coincide with peak reach, which may not be the case), while the total patients receiving Tx2 has increased marginally, in absolute terms, the proportion of total MDR pneumonia cases reached by Tx2 (pneumonia) falls by around 1%. While we cannot deduce that this means less patients accessing branded Gram negative antibiotics, due to the availability of competitors, it may indicate that penetration of these new agents maybe too low to ensure that patients with resistant infections are able to be effectively treated.

The forecasts for Tx2 (pneumonia) patient reach are slightly more favorable than for BSI. **Figure 27** presents these findings slightly differently than for **Figure 26** (for BSI) presenting the forecasted patients to be reached by Tx2 (pneumonia) against all patients. In LICs, penetration of less than 0.15% of the nearly 1.5 million patient burden is particularly concerning. It should also be noted that this modeling assumes that the therapeutics are developed by a multinational pharmaceutical company (MNC) which has global distribution capability; this is not necessarily an assumption that can be considered reliable into the future.

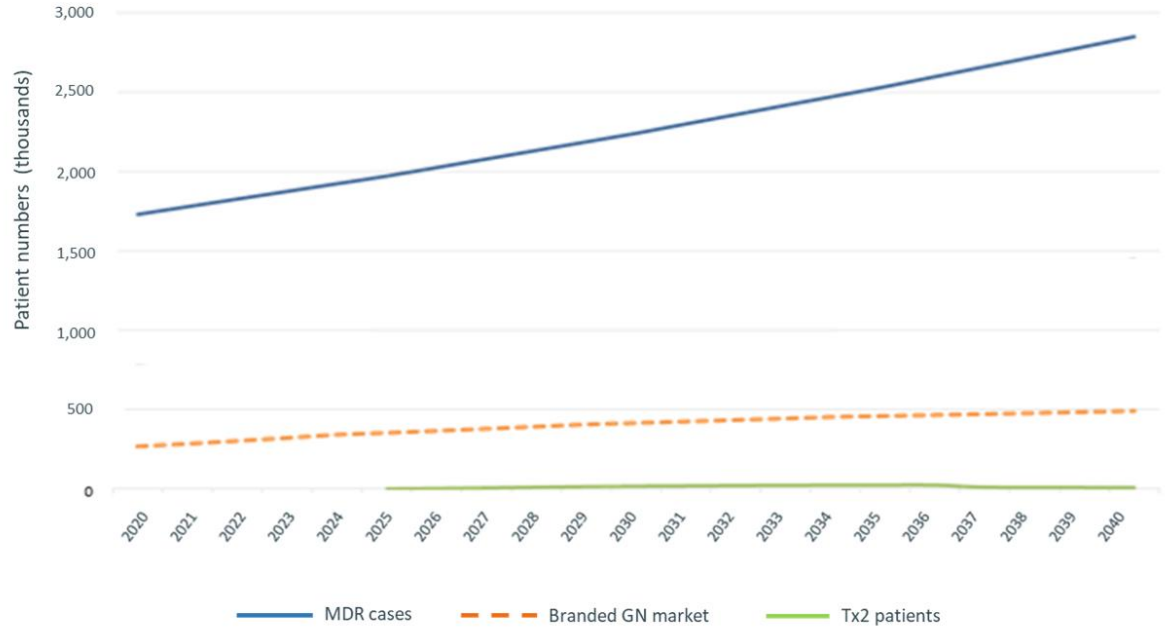

***Figure 27*: Estimated and projected patient numbers for Tx2 (pneumonia) from 2020 to 2040.**

Therapeutic 2 (pneumonia)						
World Bank Income Group	Patient Numbers (2030)			Patient Numbers (2035)		
	MDR cases	No. Treated (Tx2)	% of MDR cases expected to receive Tx2	MDR cases	No. Treated (Tx2)	% of MDR cases expected to receive Tx2
HICs	129,875	12,717	9.79	150,318	13,333	8.87
UMICs	814,081	4,397	0.54	894,346	8,412	0.94
LMICs/LICs	1,295,727	856	0.06	1,488,477	2,185	0.15

Table 27: Estimated patient numbers for Tx2 (pneumonia). *Expressed as MDR patients. Patients treated and the % between the two for all income groups.*

3.3.2 Diagnostics

The need for the diagnostics identified and prioritized by the EAG was detailed in Section **3.2.4**. This section aims to bring together the two workstreams of this study the 'patient need/eligibility' for these products together with the commercial assessment (expressed in patient numbers or 'cartridges'). This 'demand' represents an estimate of the number of patients that have been modeled to actually have access and be diagnosed. This analysis aims to explore whether insights can be drawn on the likely 'access' situation should these products – as defined – be successful in reaching the market in the timeframe modeled in this study, i.e., would patients, globally, be able to reach these under current market conditions.

Figure 28 shows the forecasted need/eligibility for Dx1 (Bac. vs other) plotted on the same chart as the two commercial scenarios that were modeled, expressed in patient terms (instead of revenue terms). The chart makes starkly clear that from an estimated need of around 700 million annual patients, globally, by 2035 only around 0.002% of this is expected to be realized at present under current market conditions. This low expected uptake and use of these diagnostic results from the unfavorable use case (see **Figure 11**), which shows the relative advantages of empiric prescribing over diagnosis under the current market situation (base case), with barely 15,000 patients estimated to benefit.

Table 28 shows how the revenue origin (patient location) for these products are modeled to be more equally spread across both HICs and non-HICs, with 60% of patient demand originating outside HICs. Under a more favorable scenario that included quite substantially improved reimbursement and donor support for uptake and use, the numbers of patients benefiting − despite a fraction of the estimate global patient need/eligibility − are substantially improved to over 200 million annual diagnoses, an almost 14-fold increase in global patient reach and therefore, potentially, less unnecessary antibiotic prescriptions.

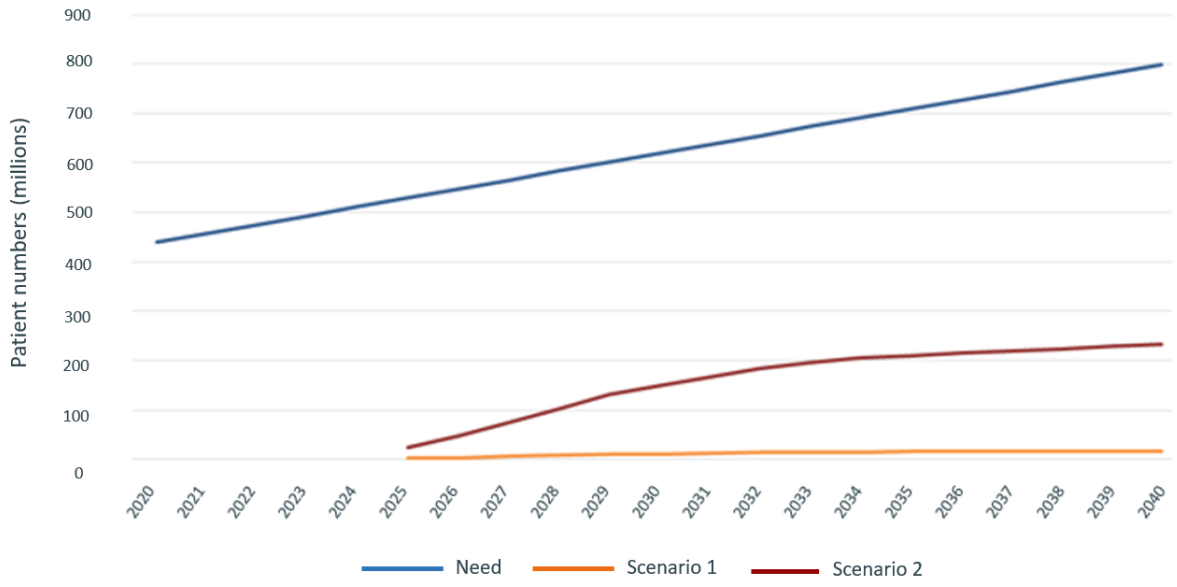

Figure 28: Patient need and demand (patients estimated to be reached) for Dx1 (Bac. vs other) under both scenarios 2020 to 2040.

	Dx1 (Bac. vs other) Patients Reached (cartridge demand)			
	Scenario 1 (Current Situation)		Scenario 2 (Favorable Situation)	
	2030	2035	2030	2035
HICs	5,701	6,260	69,830	76,694
UMICs	3,929	6,006	49,344	75,431
LMICs/LICs	1,622	3,180	29,400	57,635
Total	11,252	15,446	148,574	209,760

***Table 28*: Patient demand (cartridge numbers) in 2030 & 2035 for Dx1 (Bac. vs other) under both scenarios by income grouping.**

Similar to Dx1 (Bac. vs other), Dx2 (ID/susceptibility) shows a similar broad trend (**Figure 29** & **Table 29**), in that the forecasted need/eligibility for the diagnostic is far from being met, even under a more favorable scenario. Overall, the patient volumes being spoken about with a so much more sophisticated device are an order of magnitude lower than for Dx1. However, despite the lower uptake volumes of such a device as forecast, it would still represent around 3 million patients annually, globally, having the possibility to receive more appropriate and targeted treatment quicker, which would have substantial patient – and likely system cost – benefits by 2035. This, again, is a device whose utility and sales are likely to be split rather equally between HICs and non-HICs (56% of diagnosed patients located outside HICs in 2030). A more favorable reimbursement scenario here, while having the potential to increase patient reach by 2.5 times, makes substantially less impact for this device than for Dx1 because of its overall more positive local use case, which is expected to lead to more hospitals self-financing. However, the possibility of having ~30% of serious patient infections identified (across all regions) and susceptibility known with such a device (as in the favorable scenario), would have a very substantive impact on our global AMR response.

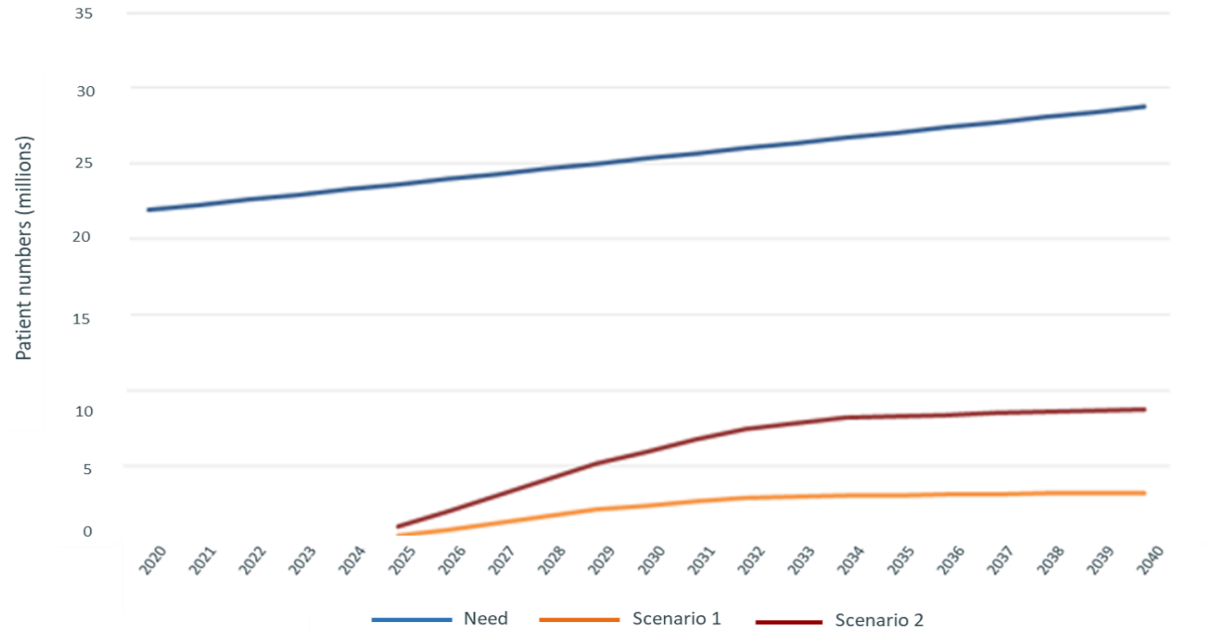

Figure 29: Patient need and demand (patients estimated to be reached) for Dx2 (ID/susceptibility) under both scenarios 2020 to 2040.

	Dx2 (ID/susceptibility) Patients Reached (cartridge demand)			
	Scenario 1 (current situation)		Scenario 2 (hypothetical, favorable situation)	
	2030	2035	2030	2035
HICs	1,237	1,343	2,149	2,332
UMICs	892	1,252	2,382	3,344
LMICs/LICs	268	486	1,446	2,620
Total	2,397	3,081	5,977	8,296

Table 29: Patient demand (cartridge number) in 2030 & 2035 for Dx2 (ID/susceptibility) under both scenarios by income grouping.

3.4 Current market: Global market potentials

3.4.1 Therapeutics: Market context

Communicable disease products currently comprise around $60 billion and 14% of the total global market for pharmaceuticals[52]. Further sub-divisions of this market (e.g. into antivirals, vaccines, antimicrobials etc.), emphasize that despite robust growth in this market segment overall (largely driven by new vaccines and anti-viral medication), growth in sales of systemic antibacterials is low and falling, from an annual revenue peak in 2010 of $15 billion to $8 billion in 2017[52], likely owing to competition from generics and limited innovation along product pipelines. The WHO's 2019 Model List of Essential Medicines[53] includes 37 antibiotics that are considered essential in treating 26 common and severe clinical infections, focusing on low-income and middle-income settings. Most of these are older off-patent antibiotics, the majority having been developed in the golden era of antibiotic development in the 1970s and 1980s. This range is responsible for treating the vast majority of infectious diseases caused by bacteria across the world. As the rate of development of new agents slows and resistance grows, the 'replenishment factor' continues to wane.

Existing antibiotics have recently been categorized for stewardship purposes through the WHO's AWaRe[54] categorization.

Expert opinion suggests that currently while branded antibiotics comprise only around 10% of global consumption, it represents around 75% of the commercial value of the antibiotics market. A segment of this overall branded antibiotic market (subsequently referred to as the sub-market or sub-segment), includes those branded antibiotics that target infections caused by Gram negative bacteria, identified by the EAG as the priority need (see Section **3.2**). The global sub-market value for branded Gram negative treatments is relatively small (**Figure 30**), at $507 million in 2019, with a relatively large share of 38% of the value coming from non-G7 countries.

Figure 31[7] shows some of the projected peak sales of newer antibiotics tend to be in the range of $150 – 350 million, and the most commercially successful of those shown is Teflaro/zinforo (ceftaroline fosamil), launched in 2010 for the treatment of a Gram positive (Methicillin-resistant *Staphylococcus aureus* - MRSA) bacterial infection.

Despite a reduction in the size of the anti-bacterial market (see reference[52] and **Table 34**) in the last 15 years, the presented analysis projects relatively strong growth in the market segment for Gram negative antibacterials from 2020 to 2024[55]. While this growth is expected to slow progressively in five-year increments to 2040 (**Table 34**), it is

[52] (Iervolino, 2018)
[53] (WHO Model List of Essential Medicines, 2019)
[54] (WHO AWaRe classification of antibiotics, 2019)
[55] Driven by 5 new product launches in the US and early uptake of Zerbaxa (ceftolozan/tazobactam) and Zavicefta (ceftazidime/avibactam) in other regions.

not expected to drop into negative growth figures as occurred over the last 20 years. Despite the forecasted slowing of market growth, **Figure 32** shows that this still results in a slow but steady growth in patients reached. These market trends are corroborated by other sources which show antibacterial market growth of 2 – 5% compared to 9 – 12% for the fields of oncology and immunology.

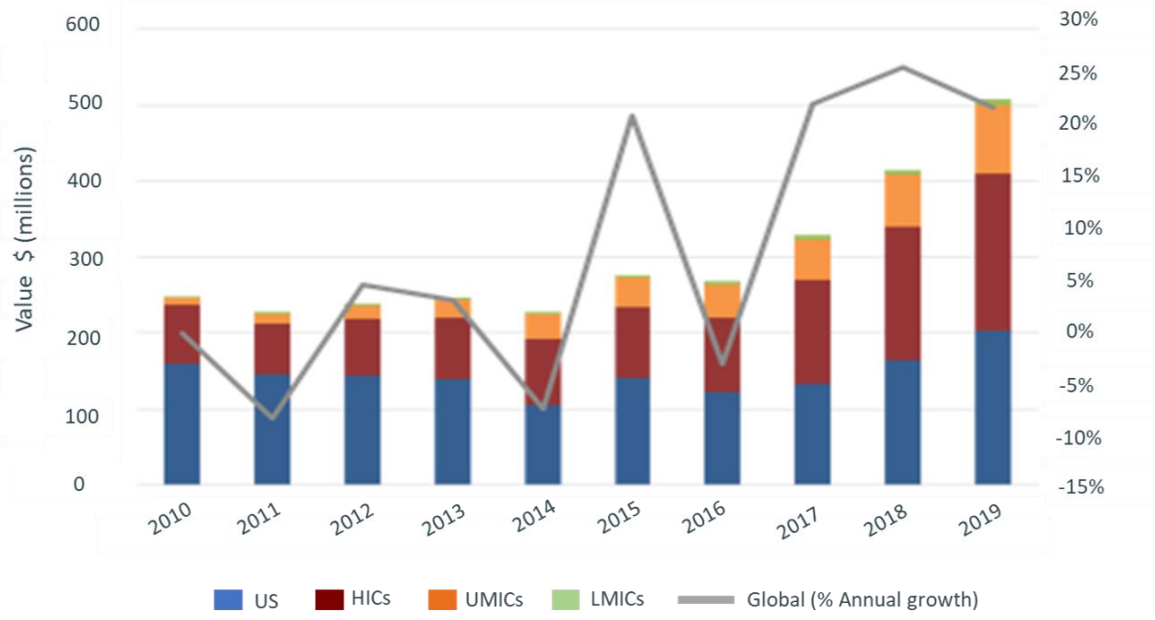

Figure 30: Historic value of branded Gram negative antibiotic market segment for last decade by income group and showing growth rate. Source: Based on IQVIA data.

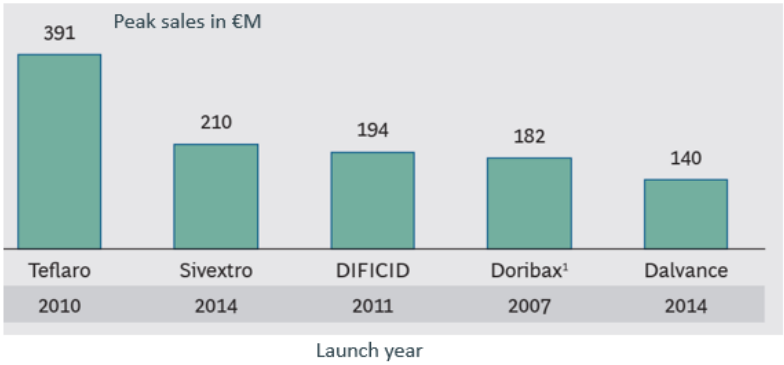

Figure 31: Selected antibiotic approvals from the last decade showing low peak sales forecasts. *Teflaro/zinforo (Ceftaroline fosamil), Sivextro (tedizolid), Dificid (fidaxomicin), Daribax (doripenem), Dalvance (dalbavancin). [1]Actual sales numbers from 2013. Notes: adjusted for inflation; Telavancin is not included because of lack of reliable revenue data (estimate: under 10 m EUR Peak Sales). Sources: EvaluatePharma, FDA, BCG Analyse . "Report to the president on combating antibiotic resistance." President's Council of Advisors on Science and Technology. 2014. "We need new policies to tackle antimicrobial resistance." London School of Economics and Political Science. "The fallacies of hope: will we discover new antibiotics to combat pathogenic bacteria in time?" Federation of European Microbiological Societies, Microbiology Review, 2006. (as cited in GUARD Report, 2015)[7].*

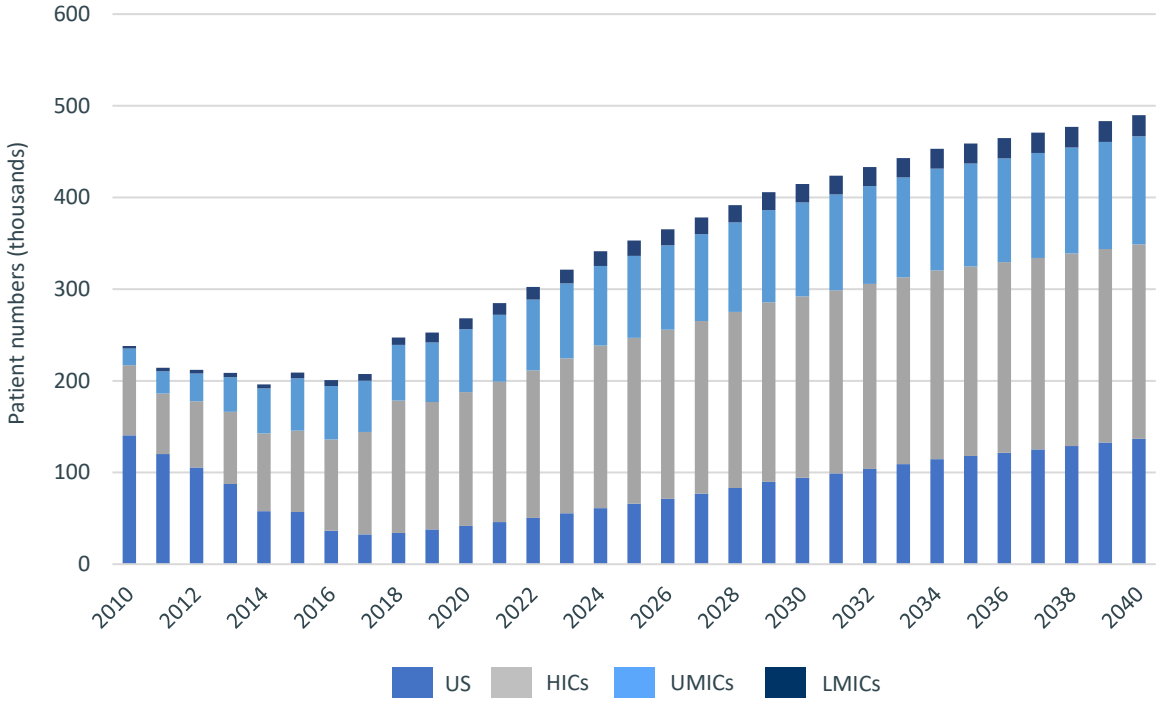

Figure 32: Recent past and projected future market size (as patient numbers) for the branded Gram negative antibiotic sub-market. *Research and analysis based on IQVIA MIDAS data. Note: this is a graphical representation of* ***Table 35****.*

3.4.2 Therapeutics: Revenue forecasts

Base case (current situation): both therapeutics

Despite both antibacterials having a good clinical profile and being 'needed' by clinicians for treating critically ill patients with Gram negative bacterial infections, such products – if they did become available in the US in 2025 as modeled – would be 'late entrants' jostling for position and sales within a small, existing, sub-market (currently comprising nine branded IV Gram negative competitors relatively stable in value at around $500 million). The model forecasts that at the time our products reach their peak sales, in 2036, this market will have grown from 270,000 to just under 500,000 patients in around 70 countries.

Figure 33 aims to contextualize the revenue forecasts of the two therapeutics by placing their first 5 years of sales at comparable relative years against the revenues generated for the most recent, best-selling competitor Avycaz (ceftazidime/ avibactam) and the sub-market from 2015 to 2019.

The modeling results show that neither product is expected to achieve $200 million in peak revenues nor to be able to capture more than 7% of eligible patients of this Gram negative sub-segment of the broader branded antibacterial market.

For comparison with our modeled products, the most recent commercially successful Gram negative-active product is Avycaz (ceftazidime/ avibactam), forecast to achieve peak year sales in the next five or so years. It is marketed globally through successive launches in multiple geographies and its clinical profile attributes

are the best analogue match with Tx1 and Tx2 from nine branded Gram negative products on the market today. However, this uptake curve has been included in **Figure 33** only for comparison. That product differs commercially from our need profiles because it was a 'first in class' product launching into a less competitive market place, at a time when few newer products were available to treat resistant Gram negative infections. Additionally, three years after launch it added a HAP/VAP label based on its REPROVE trial, showing non-inferiority to meropenem which acted as a differentiator for clinicians at the time.

The two modeled therapeutics are assumed to mutually exclusive (distinct 'non-cannibalizing' products). Combined peak annual sales in 2036 of **$311 million** are forecast. This equates to roughly **58,000 patients globally** – likely from around 70 countries[56] where launches could be expected 11 years after initial market entry. However, the assumption that these would be distinct and non-interacting markets is perhaps unrealistic given how close their profiles are. Indeed it is not inconceivable that the two need profiles could be met by a single – the same – product. In **Figure 33**, Tx1 & Tx2 product forecast revenues have been plotted against 2015-2019 revenues (i.e. first 5 years) of Avycaz (ceftazidime /avibactam), to show how much less of the market our products are expected to capture by launching later. In addition, the 2015-2019 revenues for the whole class (nine Gram negative-branded antibiotics) is also shown for scaling and context.

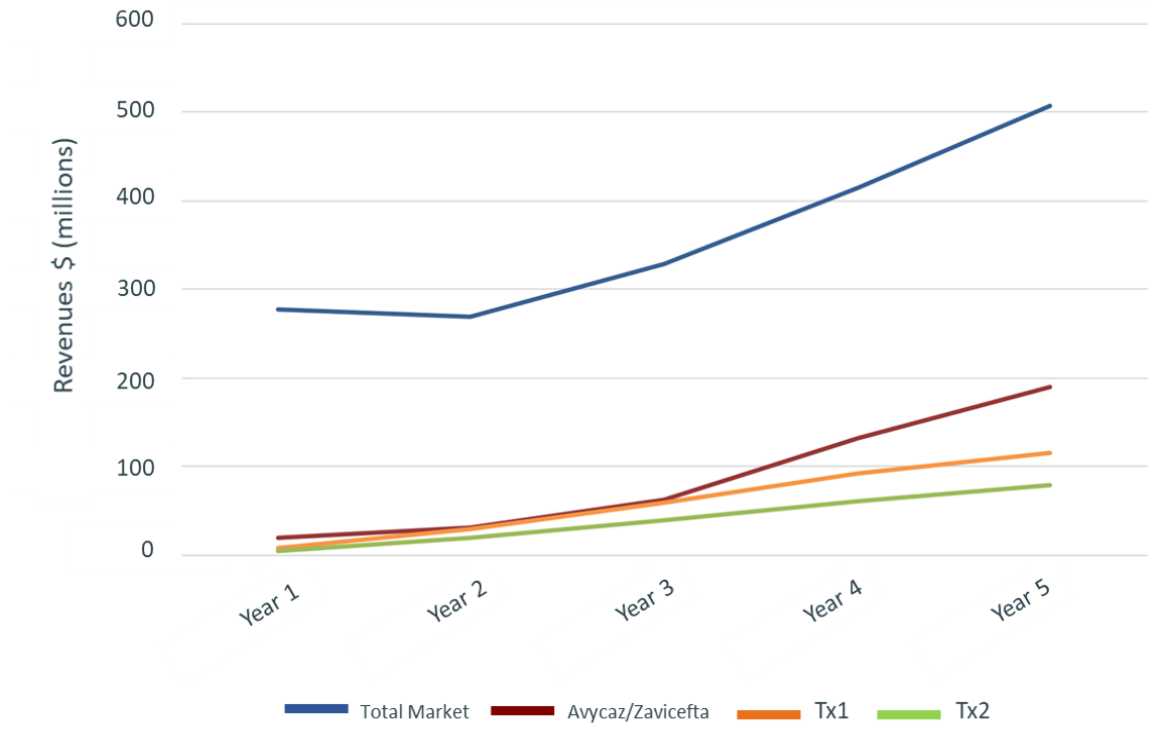

Figure 33: Projected revenues of Tx1 & Tx2, plotted at comparative[57] years post launch against the 2015-2019 revenues of the total branded Gram negative antibiotic market and the current best-selling competitor. *Based on IQVIA MIDAS data.*

[56] Given the lower forecast peak revenues it is not clearhow many fewer countries would gain access compared to the analogues

[57] Referenced to Avycaz/Zavicefta (ceftazidime/avibactam) years

Recap of Assumptions Underlying the Quantification of the Revenues

- ❖ The data, research and analysis to inform the development of the assumptions below is detailed in **Appendix 2**
- ❖ The more detailed and also product-specific assumptions can be found in the Section 2. **Methodology** and are recapped here for convenience
- ❖ The assumptions feature in the Section **4. Discussion** and are qualitatively evaluated – for their robustness – in Section 2. **Methodology**

Both therapeutics (Tx1 BSI and Tx2 pneumonia) are assumed:

- To follow an established Rx business model by a MNC with a global commercial apparatus
- That no drastic change to current policy environment in the next 20 years (forecast period) will occur
- To come to market with a non-inferiority label, initially not licensed in the indication of key interest (defined in the need profiles) and assumed to be restricted to later-line use
- To be mutually exclusive (they do not directly compete for the same patients)
- The therapeutics will both launch in 2025, into the existing market place, currently comprising 9x branded Gram negative antibiotics
- Market growth rates (in terms of total patients receiving branded Gram negative antibiotics) are projected to be stronger in the early part of the forecast period, flattening out closer to the forecast horizon of 2040, with the overall 2020-2040 CAGR projected at 3% per year.
- Have a premium branded price and uptake curve − based on current product analogues
- Undergo patent expiry (or LoE) globally in 2037 (12 years after US launch)

Taking a closer look at our modeled products side-by-side, **Figure 34** compares the estimated commercial uptake, revenues and peaks. Tx1 (BSI) has been estimated to generate slightly higher (+$57 million) peak year sales than would be expected for Tx2 (pneumonia). This is largely due to the higher incidence of MDR/XDR/DTR BSI and hence greater patient numbers (see **Section 3.2**) and less competition (as few products have a BSI label, and the former is expected to capture a slightly higher (2%) patient share than the latter for this reason.

However, the model is expected to be quite sensitive, with small changes in assumptions possibly shifting the relative balance fairly easily. This is due to the prevalence of off-label prescribing – which increases as patients become more critically ill and clinicians move from label-based prescribing to relying on the PK/PD profile. Additionally, product attributes currently not described in the profiles may be able to tilt the balance in prescribing between the two.

Despite the good profile and the unmet need for such products, the profiles are relatively close to what is currently available. This explains the relatively weak commercial assessment and brings into focus the challenge that such a product, if it became available, would face in differentiating itself in this group.

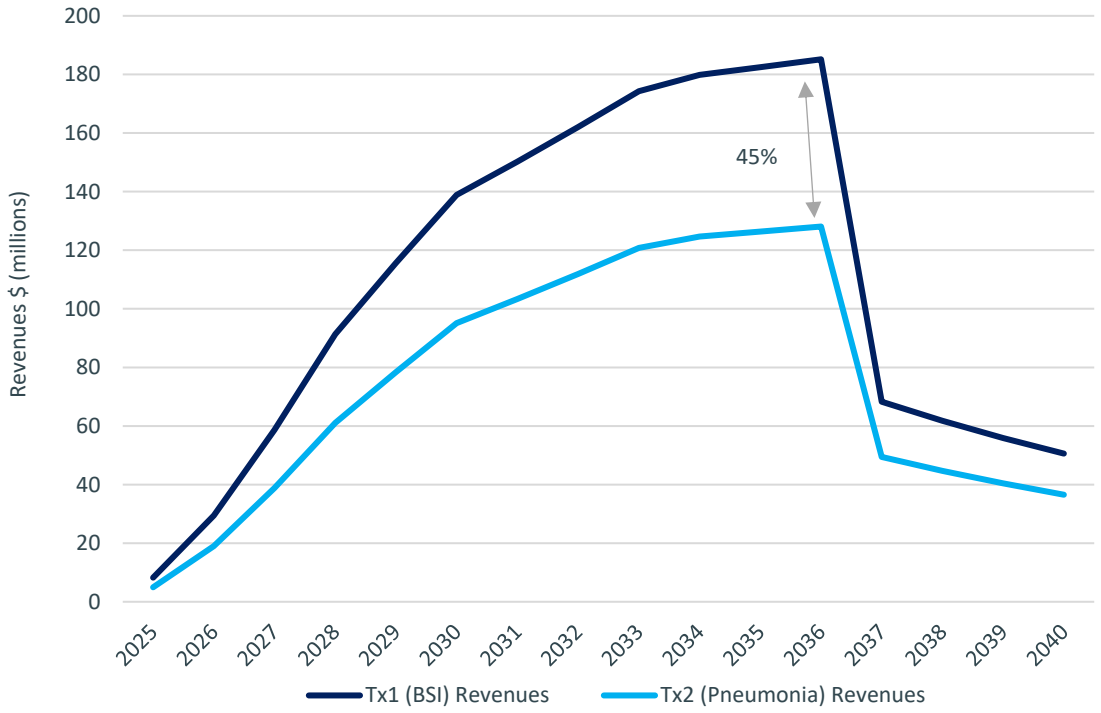

Figure 34: Both modeled therapeutics – projected global revenues 2025 (launch) – 2040.

Base case (current situation): Tx1 (BSI)

Tx1 (BSI) represents the larger (in terms of patient numbers) and most acute (higher mortality) patient need of the syndromes prioritized by the EAG. BSI is a syndrome with a disproportionate resistance burden (MDR and XDR) – it represents a proxy for when an infection begins to overwhelm the body, moving from a single tissue site to a critical systemic infection. The revenues that result from treating these patients, as forecast in this section, derive (see Section **2. Methodology**) from patient need and the market landscape into which this product is launched, where it becomes increasingly available to doctors. The position that it assumes in the clinical context and commercial market is determined by clinical and non-clinical attributes of the product itself together with many other factors that make up the current and future context. The key inputs of the model used to derive the forecasts can be found in **Table 7**.

Tx1 (BSI), launching in 2025, is estimated to generate **$184 million in revenue** (see **Figure 35**) from around 70 countries at its peak sales in 2036, before losing its exclusivity in 2037 when sales are expected to rapidly decline. At this peak, 12 years after achieving licensure in the US, it would be capturing 7.4% (35,000) of eligible patients being treated with a branded, Gram negative antibacterial globally. A discussion of the uncertainties surrounding this figure and the limitations in how it was calculated, is found in Section **3.5 Data Assessment.**

Despite the unmet need, the peak revenue projected here is low in absolute terms and when compared to other studies that have looked at thresholds for peak revenue attractiveness or sustainability for developers (see Section **4. Discussion**). The revenues are low due to the branded Gram negative antibiotic market being small and of relatively low value, compounded by the expectation that this product will capture a limited market and share of patients.

Today's pipelines (i.e., the current development landscape) and paths to approval will influence forecast revenues. While BSI is an easier development proposition than pneumonia as the compound is already in the body site of the infection (blood), this is not in itself a current regulatory indication nor path to market (see **Info Box** on 'Regulatory Pathways' pg. 63). One product (Vabomere [meropenem / vaborbactam]), to date, has achieved this label (EU only), but others have failed to do so. However, even if the product achieved a BSI label, it is considered unlikely to significantly affect uptake and use of the product over therapeutic alternatives.

From a commercial perspective, in the absence of superiority data, such a product would likely mimic that of a 'late entrant', due to physicians restricting its use to later lines based on considerations of stewardship (whereby it would be treated as a RESERVE antibiotic) and cost.

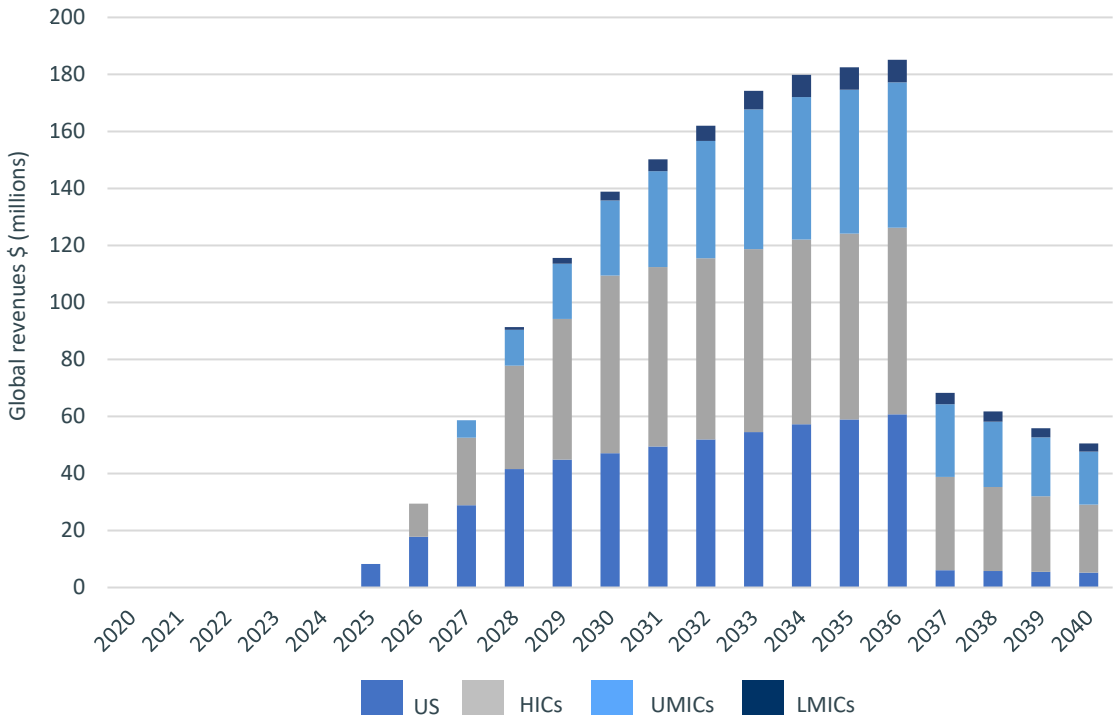

Figure 35: Tx1 (BSI) - Estimated global revenue curve with proportions by World Bank income grouping.

Forecasted revenue by income group: Tx1 (BSI)

Compared to Tx2 (pneumonia), the global uptake and roll-out of Tx1 (BSI), which aims to target patients with BSI caused by Gram negative pathogens, is forecast to be more heavily dominated by HICs throughout the product's branded life. The model forecasts the securing of a global patient share of 7.4% of the branded IV Gram negative market and revenues, at a peak in 2036 of $184 million. The global uptake of our therapeutics was modeled as a function of the roll-out by region, coupled with the patient shares. Five years following launch in the US in 2025, global revenues of Tx1 (BSI) are estimated at around $138 million.

Figure 36 shows how HICs are the dominant (79%) source of this revenue, at $109 million, with the rest of the world generating 21% or $29 million.

Looking at peak year sales in 2036, HIC revenues, while at +$17 million higher than six years earlier, have slightly diminished to 68% (-11%) of the total. Revenues from the rest of the world (at peak) total $59 million and are at a higher proportion of sales at 32% (+11%) of global revenues compared to six years earlier. UMICs are responsible for the bulk of that increase ($25 million) – as would be expected – over LMICs and LICs ($5 million). It is noteworthy that UMICs struggle to generate a third of global sales despite having five times the number of MDR cases. There is a low penetration of these new branded products in LMICs/LICs where, 11 years after the product's US launch, they still barely generate 5% of global revenue.

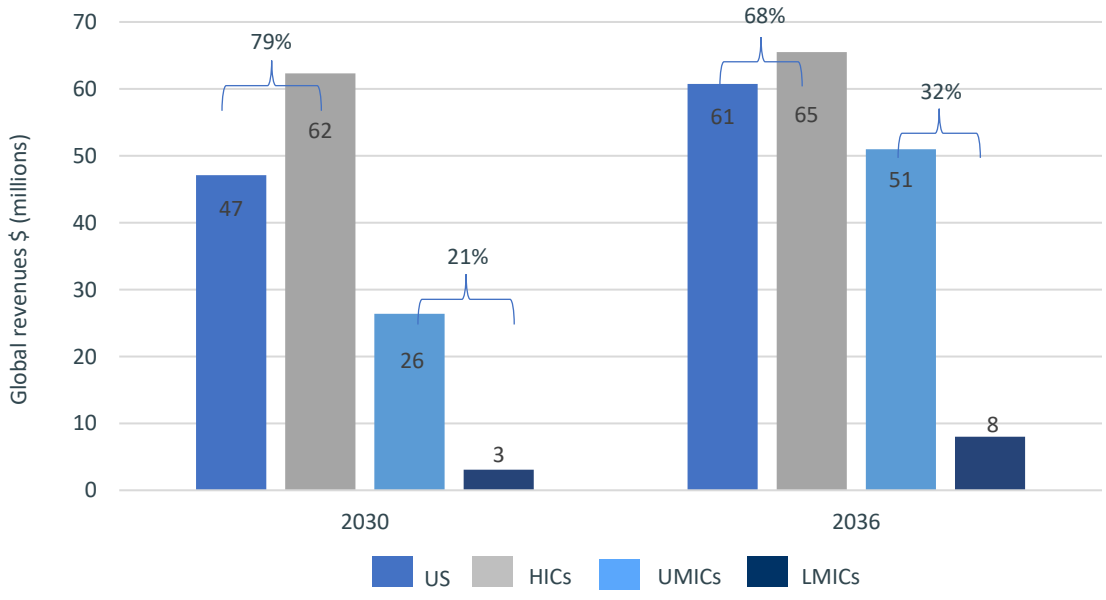

Figure 36: Tx1 (BSI) - Global revenue forecasts (2030 and 2036) broken down by World Bank income grouping.

Base case (current situation): Tx2 (pneumonia)

Tx2 (pneumonia) – also modeled to launch first in the US in 2025 – is estimated to generate lower revenues than Tx1 (BSI), with only $127 million in around 70 countries at its peak 12 years later (2036), before losing its exclusivity in 2037 when sales are expected to rapidly decline (**Figure 37**). It has been forecast to secure a lower global patient share at its peak than the BSI product, capturing 5.3% of the branded IV Gram negative antibacterial market, or 24,000 of the eligible patients expected to be treated globally. The absolute and, relative to BSI, lower penetration of this therapeutic is likely explained by a number of factors. While more patients, globally, suffer all-cause pneumonia, patient need for this product was estimated to be lower in terms of incidence of patients with an MDR Gram negative pneumonia infection. Developing such a product is a more challenging scientific task than for BSI, requiring a compound that can cross into the lung tissue from the blood. From a regulatory perspective instead – pneumonia is a site-specific infection and therefore has a formal product indication/label (HAP/VAP) and licensed use. Therefore, this product is likely to need to take gradual steps to reach that point, perhaps generating trial data first in UTI > iAB > HAP/VAP. The cumulative consequence of this path to market partly determines the competitive landscape that awaits it following launch, which is also estimated to be in 2025.

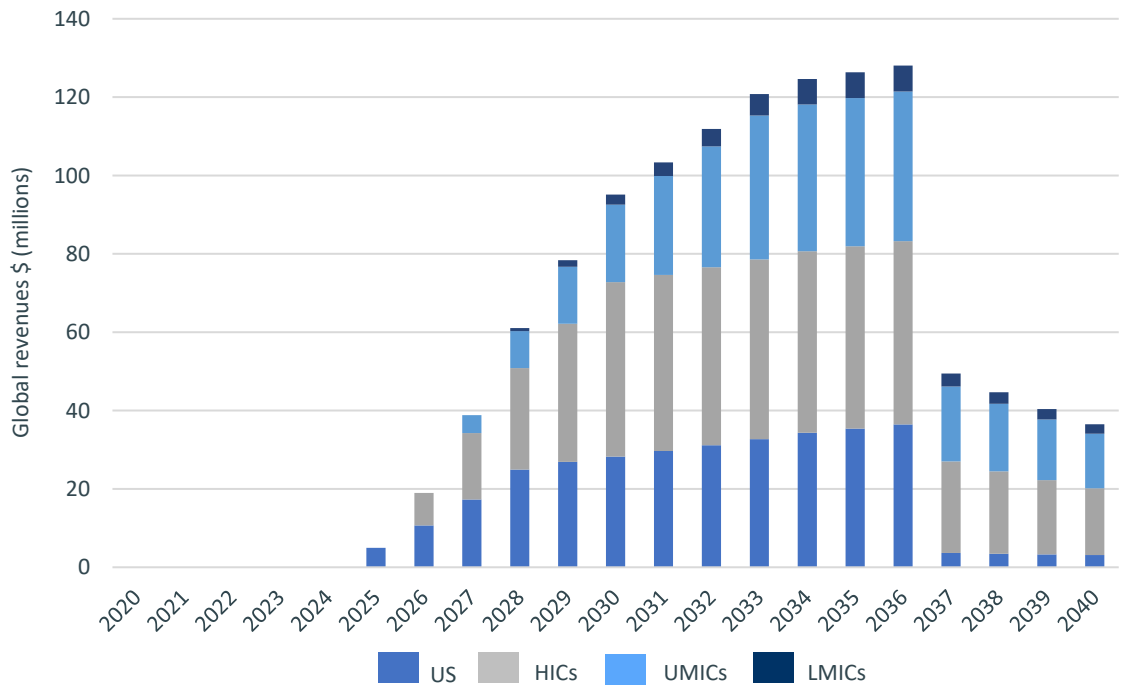

Figure 37: Tx2 (pneumonia) - Estimated global revenue curve with proportions by World Bank income grouping.

Forecast revenue by income group: Tx2 (pneumonia)

The therapeutic against severe pneumonia cases caused by MDR Gram negative pathogens – (Tx2 [pneumonia]) – was forecast by the model to secure a maximum global patient share of 5.3% of the branded IV Gram negative market and **$127 million in revenue** at the peak of its expected sales in 2036 (**Figure 38**). In 2030, five years after its first launch in the US, the revenue distribution by income region is, similar to Tx1 (BSI), again dominated (77%) by HICs. HICs are the source of $73 million of the total revenues in 2030, with the US comprising around a third ($28 million). This reflects that the global uptake of our therapeutics was modeled as a function of the roll-out by region, coupled with patient shares.

At peak year sales in 2036, while absolute revenue from HICs has increased to $83 million, this is a lower proportion from HICs than in 2030, at 65% (-12%). At this point, 12 years after launch in the US, the rest of the world is expected to account for $45 million in revenue (an increase of $22 million in six years) to a share of 35% by source of revenue and an increase (+12%) over 2030.

UMIC-group revenues exceed those of the US by this point, although – similar to Tx1 (BSI) – LMICs/LICs revenue will represent only 6% of the global share and $7 million in absolute terms by 2036. While this absolute value is similar to that for Tx1 (BSI), the proportion is slightly higher.

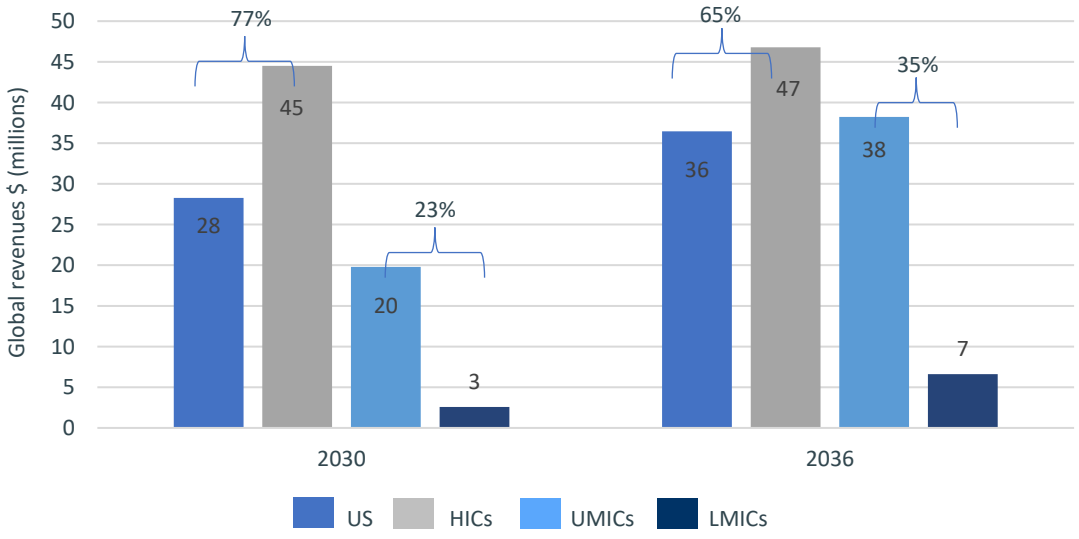

Figure 38: Tx2 (pneumonia) - Estimated global revenues broken down by World Bank income grouping.

3.4.3 Therapeutics: Revenue forecasts (alternative scenarios)

The previous section details the forecasting of the defined therapeutics and populations based on expert assumptions about how the market will likely look, and therefore receive, these products in the time-frame modeled. These forecasts are based on the overriding assumption that there will be 'no major changes' to the current market as it is today.

This section moves away from this baseline or 'most likely scenario' to postulate as to what might be the impacts on the model outputs (revenues or market potentials of our products) were there to be changes to the current market context.

In HICs, in the hospital setting of interest to this study, sales occur when a physician prescribes and administers a medicine to patients under their care. At that point a developer of the medicine generates a sale, i.e., a payor agrees to reimburse the developer at the price and within the terms agreed. Under current market conditions, revenue is simply a factor of [quantity of medicine – units] x [price per unit].

This section explores some basic and highly-simplified 'What If' scenarios concerning changes in the market context (such as those illustrated in **Table 31** & **Table 33**) that may cause variations in price and/or volumes. This would provide an indication of the possibilities or limitations to impact revenues from the levers we have under the existing market system, i.e., by increasing the pricing and/or peak share (volume) assumptions *ceteris paribus.*

What If Analysis

What If analysis is used to look at how changes in assumptions impact certain model outputs. The analysis in this section assumes no relationship between Price & Volume. In reality these parameters are very much linked but also very complex to model – the 'holy grail' of pharmaceutical forecasting. As such this highly-simplified exercise aims to provide only food-for-thought for policy makers and indicate areas for possible future work.

Extensive literature elsewhere[6,8,12] has highlighted the importance of 'delinkage' in this field. Instead of the link – due to the current patent-based system of development - between rewards to the developer and volumes used, a delinked approach would make rewards independent from these volumes with beneficial impact on stewardship. While not possible for us to model here, efforts to achieve this are currently being designed and/or trialed at national-level in the United Kingdom, the United States and Sweden[58] and have precedent in other niche market areas as various forms of 'subscription models' [59, 60]. The extent these could be trialed/implemented more broadly is worthy of further exploration.

[58] (Global AMR R&D Hub Dashboard on Incentives)
[59] (Moon & Erickson, 2019)
[60] (Louisiana Department of Health, 2019)

Scenarios A and B: Price / Valuation Changes

The analysis below (**Table 30**) uses the base case (current situation) for both of our therapeutics to explore two alternative pricing scenarios. Both scenarios take the pool of 72 countries that are currently purchasing branded IV antibiotics for Gram negative infections. Scenario A fixes the ratio of prices between the four income groups (at: 1: 0.45: 0.45: 0.3) and then increases the prices – for the whole group – to see the impact on global revenues. Scenario B takes only ten high-income G20 countries from within the pool of current purchasers and explores how high prices need to rise in those countries in order to have global revenues increase to certain thresholds.

For **scenario A**, it can be seen that prices in all currently purchasing countries, in each income group, globally, must increase nearly 5 times (380%) for Tx1 (BSI) – and over 6 times (550%) for Tx2 (pneumonia) – to reach the higher peak revenue per-product threshold of $700 million, which can be considered as financially attractive for a developer. For the lower threshold of developer attractiveness (peak revenues of $400 million), prices still need to triple (220%) for Tx 1 (BSI) and quadruple (320%) – in every currently purchasing country – for Tx 2 (pneumonia).

Whereas for **scenario B**, it can be seen that when only ten, currently purchasing, high-income, G20 countries improve their pricing (or valuation), a much higher price level is necessary to reach the per-product revenue thresholds, as expected. For the higher threshold of $700 million in total global peak revenues, prices for Tx1 (BSI) must increase over 7 times (620%) and for Tx2 (pneumonia) by a multiplier of ten. For the lower revenue threshold of $400 million, the price multiplier would need to be 3.2 and 5.3 for Tx1 (BSI) and Tx2 (pneumonia), respectively.

The two scenarios concerning the pricing/valuation lever show that while this can be an effective tool to improve overall revenues, policy makers may be faced with the need to either increase valuations greatly over the current situation or ensure a majority of countries do this globally to impact the development part as well as the access part of the challenge. **Table 31** provides some indication of both how this could be achieved and the challenges with price/valuation as a lever in this specific field. This is explored a little further in Section **4. Discussion.**

.

Hypothetical Pricing Scenario	EAG Need Profile	Modeled Peak Year (2036) Global Revenues ($)	
		Target Peak Revenues	Price Multiplier
Base Case (current market situation)	Tx1 (BSI)	185 million	-
	Tx2 (pneumonia)	128 million	-
A: All 72 currently purchasing^ countries increase their prices* by a factor of…	Tx1 (BSI)	~400 million	~2.2x
		~700 million	~3.8x
	Tx2 (pneumonia)	~400 million	~3.2x
		~700 million	~5.5x
B: Only the (10) high-income G20 countries currently purchasing^ increase their prices* by a factor of…	Tx1 (BSI)	~400 million	~3.2x
		~700 million	~6.2x
	Tx2 (pneumonia)	~400 million	~5.3x
		~700 million	~10.0x

Table 30: Impact of pricing / valuation scenarios on total global revenues forecasts of the modeled antibiotics. *^Branded IV Gram negative antibiotics (as per IQVIA MIDAS database); *Maintaining the current income-bracket determined pricing ratios between regions.*

Pricing/Reimbursement as a Lever for Improving Market Attractiveness	
Benefits of this Market Lever	Challenges with this Market Lever

• Can send a signal to developers that these products are valued highly by health systems and society
• Can support intra-country access
• A tool within the control & remit of sovereign countries
• Toolkit of health system tools & options already exists, that can be selected/adjusted/combined as per the policy goals of each health system
• It's per-product nature enables countries to define which, and the extent, of the products it values (and any terms/conditions)
 	
For further discussion of this topic readers are referred to a recent Hub-commissioned study[61]
	• The ability for healthcare payors to increase prices/valuation of these products is challenging due to a number of reasons:
	  ○ Health Technology Assessment (valuation) frameworks are not currently capturing values of antibiotics beyond the single patient
	  ○ Data deficiencies, and data not necessarily being about patients with pressing public health need. hinders clinical differentiation (over alternatives) and 'value demonstration' to payors.
	• Prescriber/physician 'price sensitivity' (may be enhanced when the differential between new products and existing generic products increases further than at present).
	• Possibility that 'critical mass' of countries will not be reached, so signal to market insufficient
	• Challenges of payors being able/willing to justify high prices for today's weak innovation, in order to support tomorrow's products

Table 31: Summary of some of the benefits and challenges with using 'price' as the market support lever for new antibiotics.

[61] (Vogler, Habimana, Fischer & Haasis, 2021)

Scenarios C and D: Volume / Patient Share Changes

Table 32 highlights two scenarios that may influence, both positively and negatively, the volumes of branded new antibiotics that our societies purchase. Some of these factors work at the level of individual product volumes (market shares) and others at the level of the class or market segment (only on Gram negative active antibiotics). The analyses below use a positive and a negative scenario to explore both the uncertainties of the market context and the influence and sensitivity to volume as a market lever in the context of new antibiotics.

Scenario C takes the base case (current situation) for both of our therapeutics and assumes they are able to capture a 30% share of the sub-market at their peak in 2036, up from less than 10% under the current situation. For comparison, Avycaz (ceftazidime/avibactam) is expected to peak at 25% after 5 years following its US launch.

Table 33 explores reasons that such a scenario could be realized. With a peak patient share secured of 30% of the market, this represents a 342% (or a 4.4-fold factor) increase in volumes for Tx1 (BSI) and a 539% (or 6.4-fold factor) increase for Tx2 (pneumonia). However, such increases would see the revenues exceed the higher, $700 million global revenue threshold, reaching $818 million at peak. This same scenario C is represented graphically in **Figure 39** for Tx1 (BSI) where the colored bars demonstrated the base case forecasts (and their income group derivation, in color) with the dotted line representing this new Scenario C in terms of the revenue impact. While these scenarios are predominantly exploring the economic impacts of different scenarios; there are also human consequences. As such, **Figure 40** plots the same Scenario C but representing patient-reach/access impact for the second therapeutic (Tx2 pneumonia). The increased number of patients accessing or being prescribed this new antibiotic under this scenario is visible.

Hypothetical Scenario	**Therapeutic**	**Modeled Peak Year (2036) Global Revenues**	
		Peak Share Volume / Value	Volume Change Multiplier
Base Case (current market situation)	Tx1 (BSI)	7.4%/ $185 million	0
	Tx2 (pneumonia)	5.3% / $128 million	0
C: Individual product capturing higher peak share	Tx1 (BSI)	**30%** / $818 million	4.4x (individual product)
	Tx2 (pneumonia)	**30%** / $818 million	6.4x (individual product)
D: Individual product impact from a contraction of whole market sub-class^	Tx1 (BSI)	7.9%* / $44 million	**-30% **** (market sub-class contraction; see **Table 35** for income-grouping specifics)
	Tx2 (pneumonia)	5.8%* / $61 million	

Table 32: Impact of volume scenarios on total global revenue forecasts of the modeled antibiotics. Bold *indicates the variable that was changed for each scenario. ^9x products currently comprising the Branded IV Gram negative antibiotics (as per IQVIA MIDAS database); *These slight changes to the peak patient share occurred due to the income-group proportions varying between scenarios. **Aggregate market contraction based on forecasted market growth by income-group region.*

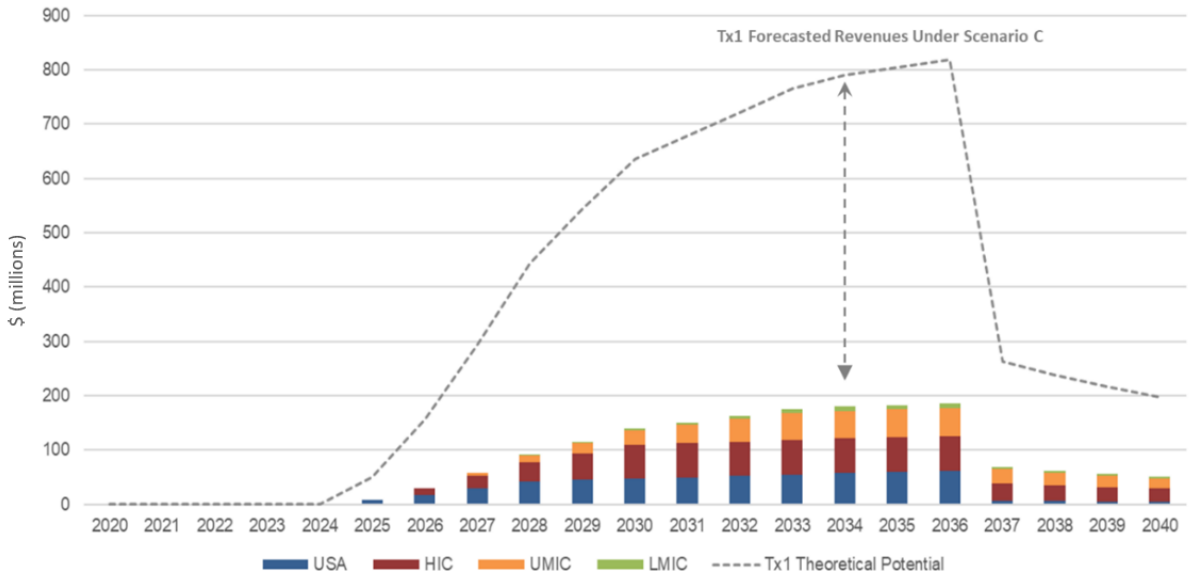

Figure 39: Scenario C for Tx1 (BSI) showing the impact on revenues reached were such a product able to secure 30% of the market at peak.

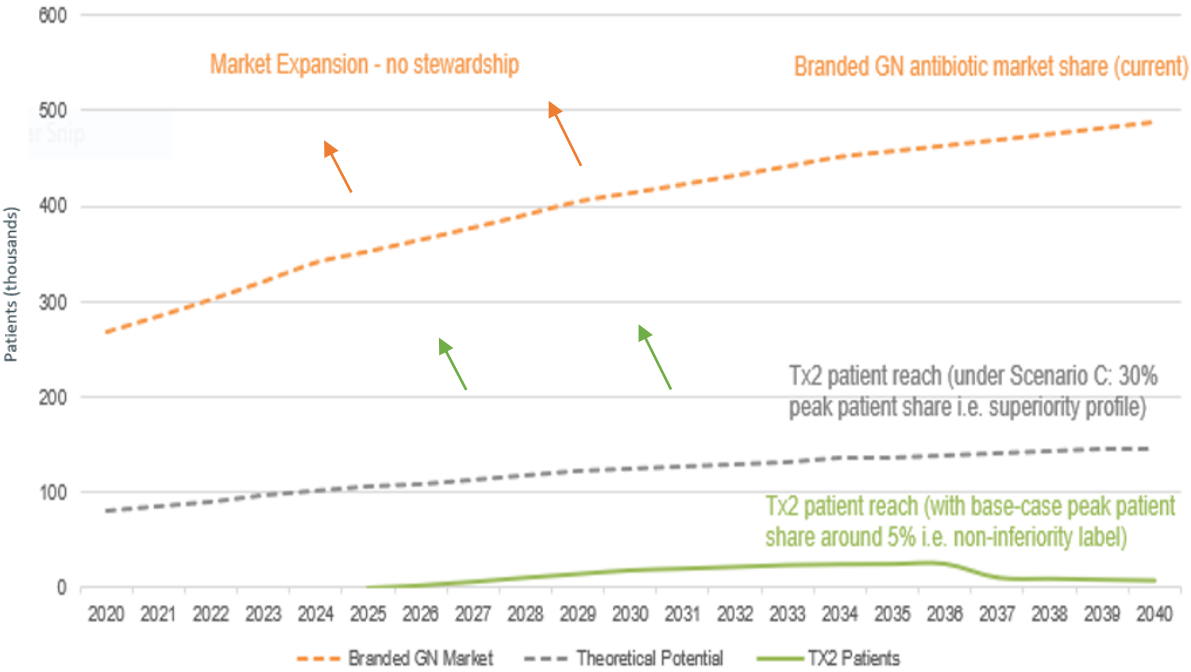

Figure 40: Scenario C for Tx2 (pneumonia) showing the impact on patients reached were such a product able to secure 30% of the market.

Under volume **Scenario D**, we attempt to show the impact on forecasted peak revenues and patient share (in 2036) of our two individual antibiotics were there to be a contraction in the volumes of the whole sub-market of which they are part. Some situations that could cause such a contraction are illustrated in **Table 33** and include a reduction in class growth due to more stringent stewardship across Gram negative / RESERVE category products, lower MDR Gram negative infection prevalence or further market withdrawal of big (MNC) pharmaceutical companies with their global commercial apparatus. A contraction in the overall market by a factor of 0.3-fold (or 30%) from 2019 patient numbers (and then the following cumulated impact year-by-year due to the CAGRs as shown in **Table 35**), saw a contraction of the peak revenues for our therapeutics of around 66% to $61 million (Tx1 BSI) or $44 million (Tx2 pneumonia) at peak year in 2036.

Scenario C: Possible volume-increasing scenarios	Scenario D: Possible volume-lowering scenarios
• An increase in incidence of bacterial infections &/or MDR rates • Product was a first entrant or able to demonstrate clinical differentiation i.e., 'clinical superiority' over standard of care • Clinical trial networks or other mechanisms made a substantial impact on the speed and quality of data generation for new antibiotics. ***NB**: We assume that a genuinely 'breakthrough new MoA' or the launch of a highly efficacious 'alternative [non-small molecule]' antibiotic, could potentially create a 'new market'. As this would likely still compete for patients within the existing small-molecule antibiotic market (modeled here) the complexity of this scenario is beyond the scope of this work.*	Of all products in the sub-market: • A general lowering of incidence of bacterial infections &/or MDR through public health interventions such as improved IPC, socio-economic development, water, sanittaion and hygiene (WASH), generic antibiotic controls etc. • Stewardship measures gain in support, becoming more stringent either globally (or in innovation-financing countries specifically) • Company unable to or choosing not to pursue a broad global/multi-country commercial and distribution strategy Of individual products in a sub-market: • A rapid and aggressive emergence of resistance to a new agent • Regulatory delay/warning or narrowing/conditionality of approval

Table 33: Examples of factors that may impact sold volumes of branded new antibiotics.

	Historical CAGRs		Future Projected CAGRs			
	2010-2014	2015-2019	2020-2024	2025-2029	2030-2034	2035-2040
USA	-19.9%	-9.7%	10.0%	8.0%	5.0%	3.0%
HICs	2.7%	11.9%	5.0%	2.0%	1.0%	0.5%
UMICs	27.9%	3.2%	6.0%	3.0%	2.0%	1.0%
LMICs/LICs	12.2%	14.8%	8.0%	4.0%	2.0%	1.0%

Table 34. Actual, expected (and historic) market segment growth rates, by income group, used for base-case modeling for both therapeutics. *Note: These data underlie the results section **3.4.2** and are represented graphically, as patient numbers, in Figure 33.*

	Historical CAGRs		Future Projected CAGRs			
	2010-2014	2015-2019	2020-2024	2025-2029	2030-2034	2035-2040
USA	-19.9%	-9.7%	-5.0%	-4.0%	-3.0%	-2.0%
HICs	2.7%	11.9%	-4.0%	-3.0%	-2.0%	-1.0%
UMICs	27.9%	3.2%	-3.0%	-2.0%	-1.0%	-0.5%
LMICs/LICs	12.2%	14.8%	-2.0%	-1.5%	-1.0%	-0.5%

Table 35. Adapted market segment growth rates, used to derive Scenario D (market contraction) assumptions.

3.4.4 Diagnostics: Market context

The diagnostics sector shares many similar traits with the pharmaceutical sector. It is characterized by a number of larger diagnostics companies with a broad global presence combined with smaller private companies. Innovation is driven by these companies and fed and supported by academia and the wider research environment. It is also characterized by high R&D costs and, for health systems to adopt new diagnostics, clinical efficacy and cost effectiveness must both be evidenced by way of large-scale and valid studies[62]. But there are also differences. The regulatory environment is more fragmented and uptake is one of the main bottlenecks, as their use often requires a capital outlay, a specialized facility and staff. Additionally, their price – relative to generic empiric antibiotics – remains prohibitive. Finally, this market is dwarfed by the much larger and more mature market for antibiotics.

In-vitro diagnostic (IVD) tests that analyze specimens outside the body[63] comprise around 14% in value-terms (2017) of the much broader medical device market. Molecular testing is currently regarded as the gold standard for diagnosing infectious disease, and is also one of the IVD market's fastest growing segments. Molecular testing includes technologies and techniques such as DNA microarray analysis, mass spectrometry and nucleic acid amplification, with dominant applications in diabetes, oncology, genetic testing and infectious diseases[64].

The IVD market is more geographically spread out than that of pharmaceuticals, with growth rates in middle income countries (MICs) exceeding those in HICs (with 2020 total market value of around $85 billion globally) [65].

Estimates put the size of the molecular diagnostics market in 2021 at $18 billion in annual global sales[52], approximately 25% of the overall IVD market, thought to have a current value (in terms of global sales) of around $70 billion[66]. With high growth rates in 2010, just over 50% of the molecular

[62] (Review on AMR, 2015)
[63] (Morel et al., 2016)
[64] (GlobeNewswire, 2021)
[65] (MarketsandMarkets Analysis, 2020)
[66] (Awasthi & Stanick, IQVIA 2018)

diagnostics market is focused on infectious disease testing[63] (more recent estimates were not available at the time of publication). This compares to aggregate industry global antibiotic sales estimated at $40.85 billion, with the industry being dwarfed by the size of the prescription pharmaceuticals market.

The diagnostics prioritized for quantification in this report can be seen in **Figure 41**[67] set in the broader IVD landscape. It shows that Dx1 (Bac. vs other), is the simpler and swifter test, competing with existing POC tests on the market. The 'industry perspective' in Section **3.1.2**, however, revealed why this apparently simple test remains a largely elusive goal for industry. Likewise, in the bottom right-hand corner, we see the more complex diagnostics profile (Dx2 [ID/susceptibility]) modeled in this report. Any product fitting this profile would be launching into a competitive landscape of products, variably meeting the goals defined in the profiles and, while less rapid and convenient, representing a key tool for improving diagnosis of AMR and appropriate prescription of novel antibiotics. The rapid increase, globally, in molecular diagnostic testing capacities witnessed during the Covid-19 pandemic may prompt a step change for other molecular diagnostics[68]. A second factor that has had a very big impact on the diagnostics market, at least in LMICs, was donor market support. For example, GeneXpert – MTB/Rif (*M. tuberculosis* /rifampicin) cartridge sales volumes have tripled since 2012 when the donor community first supported their uptake and roll-out in LMICs[68].

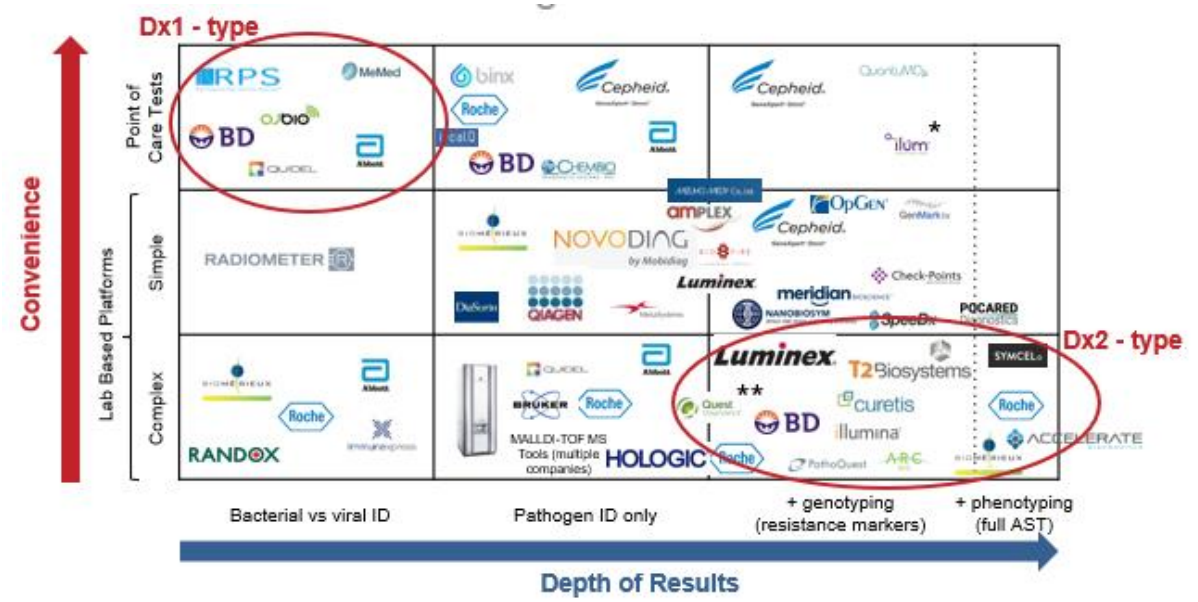

Figure 41: The prioritized diagnostic products depicted within their competitive commercial landscape. *Developed from a wide variety of sources such as company websites, all in the public domain & (WHO, 2019)[67]. *Decision Support Company, Laboratory Services Company. Note: two logos indicated multiple products from the same manufacturer.*

[67] (WHO Landscape of diagnostics , 2019)
[68] (Treatment Action Group, 2020)

Does the unprecedented uptake of Covid-19 diagnostics present an opportunity for AMR diagnostics?

As the Covid-19 pandemic spread, demand grew not only for faster testing but also testing in much higher volumes. This has driven four main developments In the IVD Industry, namely: (1) Broader adoption of diagnostics based on reverse-transcription PCR; (2) More POC molecular testing; (3) Accelerated development and adoption of new technologies and (4) Manufacturing-capacity expansion in Asia and shift of supply[69]. These developments could prompt structural shifts that will have long-term implications for diagnostic-test manufacturers.

In India, it is reported, that only one laboratory was performing molecular assays for COVID-19 in January 2020. Five months later by May 2020, 600 Indian RT-PCR laboratories had been set up in an effort to help manage the pandemic, increasing testing capacity 1,000-fold[70].

3.4.5 Diagnostics: Revenue forecasts (base-case & hypothetical)

Revenue forecasts: both diagnostics

Unlike the patient need and demand (see **Figure 20** & **Figure 21**), which are a scale-different for the two devices' commercial modeling, shows that under current conditions (see **Info Box Scenario 1** on pg. 120), and in terms of value, the two diagnostics are much more similar, with global annual revenues forecast in the range of **$275 – $400 million**. It would make sense that the more sophisticated and expensive device – Dx2 (ID/susceptibility) – while not generating the volume sales, is priced higher and therefore able to bring reasonable developer returns on a value basis (**Figure 42**).

When changing the model inputs to assume that a more favorable market context arises in the next decade, in terms of reimbursement and donor support for LMICs (see **Info Box Scenario 2** on pg. 121), the impact on revenues is substantial. This holds true particularly for Dx1 (Bac. vs other), which will be primarily used in primary care settings and bring value more similarly across income groups.

Under this more favorable scenario, revenues in 2030 are expected to be nearly 8 times higher than under the base-case scenario, in 2030 reaching **$2.14 billion**. The comparable figure for Dx2 (ID/susceptibility) is substantially less affected by the more favorable context, contributing an additional $104 million in revenues to reach just short of **$500 million** – around 1.6 times higher than under the base case; as will be explored further in this section.

[69] (McKinsey & Company, 2020)
[70] (WHO News,16 Aug 2020)

Recap of Assumptions Underlying the Quantification of the Dx Revenues

- ❖ The data research and analysis to inform the development of the assumptions below is detailed in **Appendix 3**
- ❖ The more detailed and also product specific assumptions can also be found in **Appendix 3** and Section **2. Methodology**
- ❖ The assumptions feature in the Section **4. Discussion** and are qualitatively evaluated – for their robustness – in Section **2. Methodology**

Both diagnostics (Dx1 Bac vs other and Dx2 ID/susceptibility) are assumed to:

- Both launch in 2025, into their respective market places
- Instruments are assumed to be purchased only once for each setting
- Are mutually exclusive (they do not compete for the same patients)
- Sales have plateaued but not peaked in the modeling period. No patent expiry or LoE assumed
- Instrument and test pricing for LMICs/LICs is guided by sponsored price assumptions as per need profile. For other income groups, pricing in line with existing product analogues or groupH estimates
- Uptake & adoption assumptions the same for both diagnostics. Linear uptake curve 5 – 10 years post-launch
- Prices fixed for the forecasting period to those of 2020 variable assumptions per provider sector
- Market projections based on population growth trends 2020-2040 in >65 years for each region

Assuming the current market context remains unchanged from now (the base case / Scenario 1) and that the peak sales year will be in 2030 – 5 years after launch – Dx1 (Bac. vs other) is estimated to generate **$275 million** (**Figure 42**). For Dx2 (ID/ susceptibility), the figures are slightly higher, at **$315 million**. Ten years later (2040), when uptake is expected to be much greater, global revenues for Dx1 (Bac. vs other) are expected to grow 47% to reach **$403 million** – a much higher level of growth than for Dx2 (ID/susceptibility) whose revenues would grow 25% to reach **$394 million**. However, estimated revenues and therefore market attractiveness can also be seen to improve when the model assumes more favorable changes to the current market context.

These could include improved acceptance and appreciation of societal benefits of described diagnostics and health systems, leading to better uptake and reimbursement in all regions. These improvements are most marked for Dx1 (Bac. vs other). See **Figure 43**.

Scenario 1: Base-case (current situation)

See Table 10 on pg. 54 for full details.

A less positive scenario representing the current market situation: broadly assumes no substantive developments in Dx reimbursement and use within clinical practice, system uptake and adoption/use (globally) over and above the current status quo.

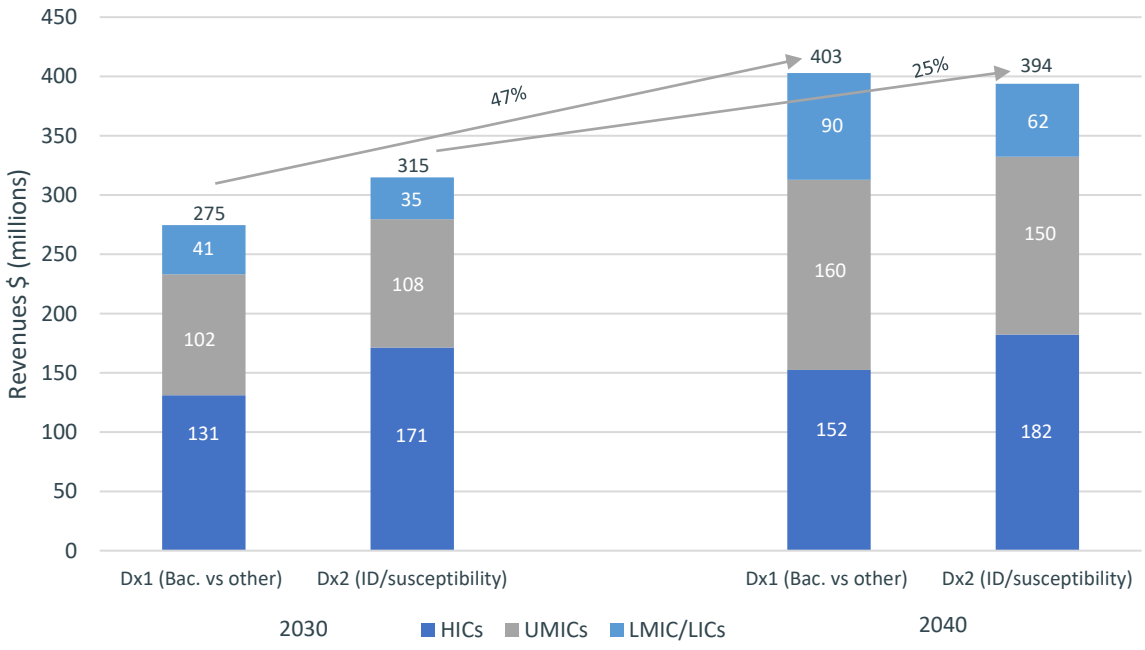

***Figure 42**: Dx1 (Bac. vs other) & Dx2 (ID/susceptibility): Projected global revenues 2030 & 2040 by income group. Scenario 1: Base-case scenario (current situation).*

The more favorable outlook under this scenario also improves revenues for Dx2 (ID/susceptibility) from $315 million to **$495 million** (**Figure 43**) in 2030 and increasing to **$600 million (+21%) in 2040.** Under the more favorable context, global revenues for Dx1 (Bac. vs other) in 2030 are expected to be **$2.1 billion** compared to **$275 million** under the status quo scenario. Ten years later (2040), Dx1 revenues would grow further by 32% to **$2.8 billion**. The developer of Dx2 (ID/susceptibility) is forecast to benefit less from a more favorable change in the market context mainly due to a better local use case helping even in current conditions. Dx1 in contrast, does require more favorable reimbursement for broader uptake based on its more challenging local use case.

Scenario 2: Hypothetical (favorable)

*See **Table 10** on pg. 54 for full details.*

A more positive scenario: Assumes changes to the policy and reimbursement context whereby AMR becomes more prioritized and supported topic, that improves current system uptake, reimbursement clinician adoption and use. Specifically, normative support from WHO, third-party donor-support for uptake/roll-out in LMICs/LICs and broad reimbursement in both HICs and UMICs.

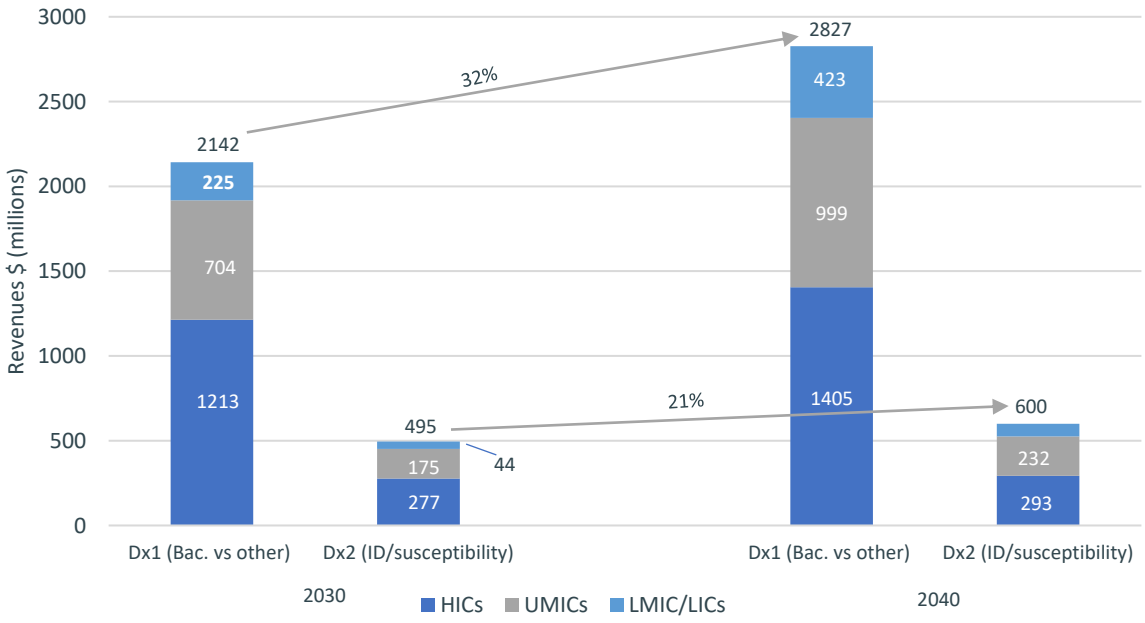

Figure 43: Dx1 (Bac. vs other) & Dx2 (ID/susceptibility): Projected global revenues 2030 & 2040 by income group. Scenario 2: Favorable situation (improved reimbursement/donor context).

Base-case (current situation): Dx1 (Bac. vs other)

This explores the current estimated revenues for this high-priority diagnostic that determines whether an infection is bacterial or not. For such a high utility in terms of the number of patients (an estimated 0.5 billion globally) who could benefit from such a device being available in primary care settings, revenues plateauing at around **$403 million** within 15 years since launch are not attractive for developers (**Figure 44 & Table 36)**.

In terms of POC testing, the potential benefits of prescribing an antimicrobial for healthcare personnel and patients are likely to outweigh the benefits of using Dx1 (Bac. vs other) in most clinical settings and geographic regions (see Illustrative Use Case **Figure 11** & **Appendix 3**). This is because, unless reimbursed, Dx1 (Bac. vs other) adds cost and time to both the patient and the health care professional (HCP), while the potential clinical benefits of not using an antimicrobial accrue only in the long term and at a societal level, not at the individual level in the short term. This cost/benefit imbalance becomes even larger in LMICs/LICs compared with HICs. This clinical/commercial context was further explored in the multiple interviews conducted for this work, the findings of which are provided in **Appendix 3a**.

The derivation of these revenues and how they break down by income groups globally can be seen in **Figure 44**.

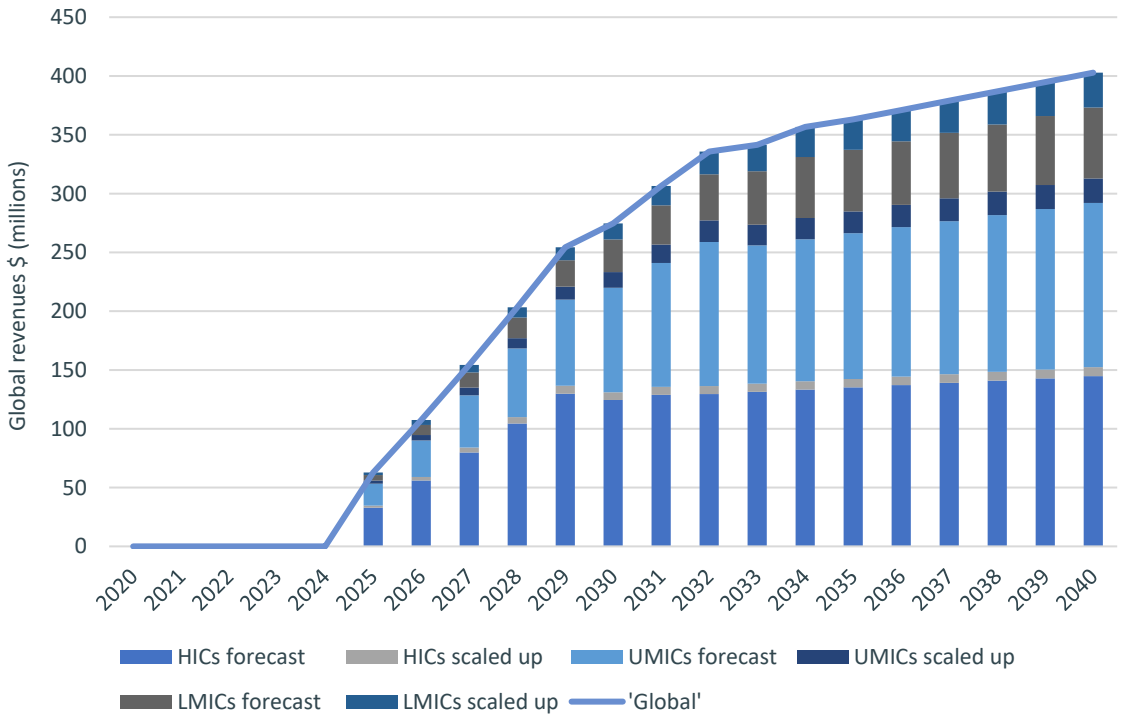

Figure 44: Dx1 (Bac. vs other) projected global revenues (2025-2040), including their derivation for the modeling and income-group source. Scenario 1: Base-case (current situation).

This shows that early in the product's life (2030), 48% of the $275 million revenues (**Table 36**) are expected to originate in HICs, compared to 37% in UMICs and 15% in LMICs/LICs. By 2040 this is expected to be more evenly balanced, with the HIC proportion dropping (-10%) to 38%, shifting slightly towards other income groups (+3%), 40% in UMICs and (+7%) 22% in LMICs/LICs. The instrument uptake assumptions driving this global roll-out can be seen in **Figure 45**. For Dx1 (Bac. vs other) to be used more broadly will require additional incentives such as: 1. Reimbursement of tests, 2. Instrument investment support, and 3. Inclusion of Dx1 (Bac. vs other) in good-practice guidelines at national, regional and global level. A successful roll-out and a measurable impact on AMR can only be expected if this happens across all regions, but in particular in LMIC/LICs, and as long as it is accompanied by educational efforts to foster acceptance of the idea of antimicrobial stewardship for HCPs and patients at the individual and societal level.

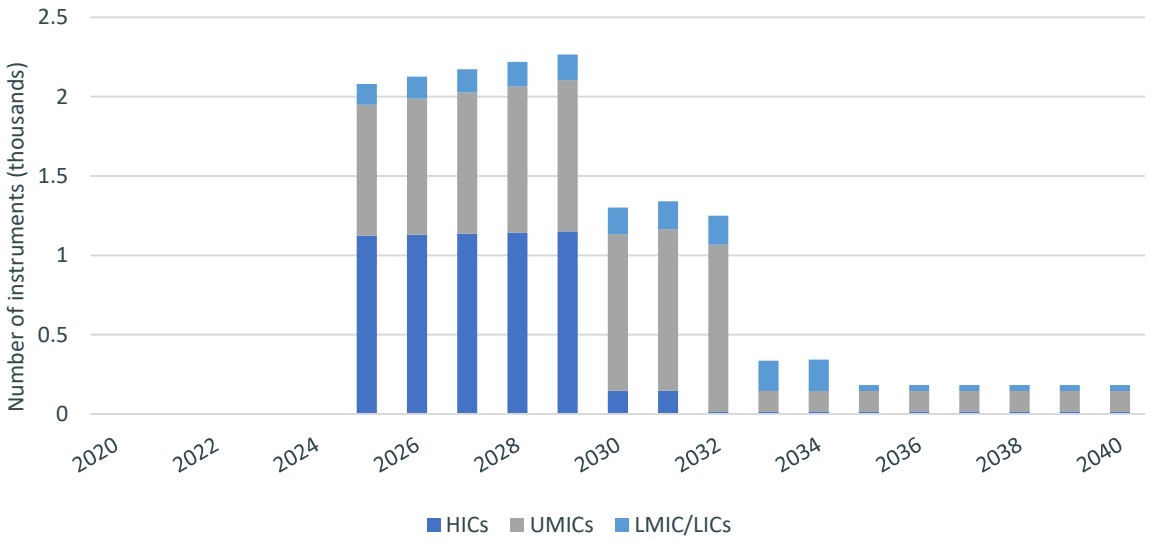

Figure 45: Dx1 (Bac. vs other): New instruments per year – uptake assumptions.

Hypothetical scenario (broader reimbursement): Dx1 (Bac. vs other)

Estimating the likely revenues that would be generated from Dx1 (Bac. vs other), points to just $403 million in peak sales by 2040 under current market conditions (**Table 36**). This compares to $20 − 150 million in ballpark development costs for such a POC IVD device[71,72].A hypothetical scenario which assumes a shift in the policy and market context towards further support for greater uptake and use of such a device has a substantial impact on patient access to it, but also on revenues accruing to its developer.

Figure 46 below shows how the expected revenue impact from a favorable change in the policy context would have a substantial impact particularly on this device, with revenues increasing 7-fold to $2,827 million by 2040 (**Table 36**) − as access and uptake would expand globally.

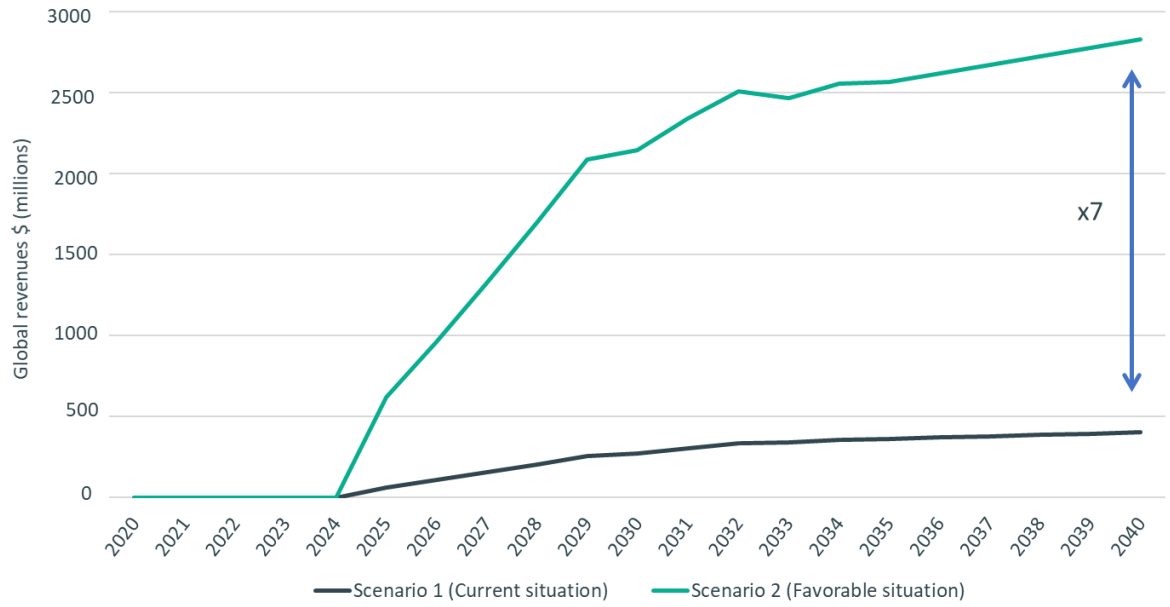

Figure 46: Dx1 (Bac. vs other): Projected global revenues under the two different scenarios.

[71] The higher range includes platform development costs, note that post-launch costs (for commercialisation) are estimated to be around double the pre-launch costs

[72] (Dolginow, D, Tynan K, Doheny N & Keeling P, Diaceutics PLC 2021)

		Dx1 (Bac. vs other)							
		Scenario 1 (current situation) No substantive changes to reimbursement and uptake above current status quo				**Scenario 2 (favorable situation)** Hypothetical scenario: Broad reimbursement in HICs and donor funding for LMICs			
		Global	**HICs**	**UMICs**	**LMICs/ LICs**	**Global**	**HICs**	**UMICs**	**LMICs/ LICs**
# Instruments & Tests/Patients	**2030**	Inst: 12k Pts: 11m	Inst: 6k Pts: 6m	Inst: 5k Pts: 4m	Inst: 1k Pts: 2m	Inst: 175k Pts: 149m	Inst: 78k Pts: 70m	Inst: 74k Pts: 49m	Inst 22k Pts: 29m
	2040	Inst: 17k Pts: 17m	Inst: 6k Pts: 7m	Inst: 9k Pts: 7m	Inst: 2k Pts: 4m	Inst: 245k Pts: 233m	Inst: 82k Pts: 82m	Inst: 117k Pts: 85m	Inst: 46k Pts: 66m
Revenues (Launch 2025)	**2030**	$: 275m	$: 131m	$: 102m	$: 41m	$: 2,143m	$: 1,213m	$: 704m	$: 225m
	2040	$: 403m	$: 152m	$: 160m	$: 90m	$: 2,827m	$: 1,405m	$: 999m	$: 423m

Table 36: Dx1 (Bac. vs other) Summary outputs.

Figure 47 shows the derivation of this amount in revenues and how they break down by income groups globally. Early in the product's life (2030), 57% of the $2,143 million revenue is expected to originate in HICs, compared to 33% in UMICs and 10% in LMICs/LICs. By 2040, the more favorable scenario is estimated to positively impact HICs and UMICs to a greater extent than LMICs.

In 2030, HICs are the source of 50% of the revenues. UMICs slightly increase their share of revenues over the 20 years, but only marginally to 35% – an increase of 2%. Despite their huge need, LMICs/LICs are forecast to be the source of 15% of revenues by 2040.

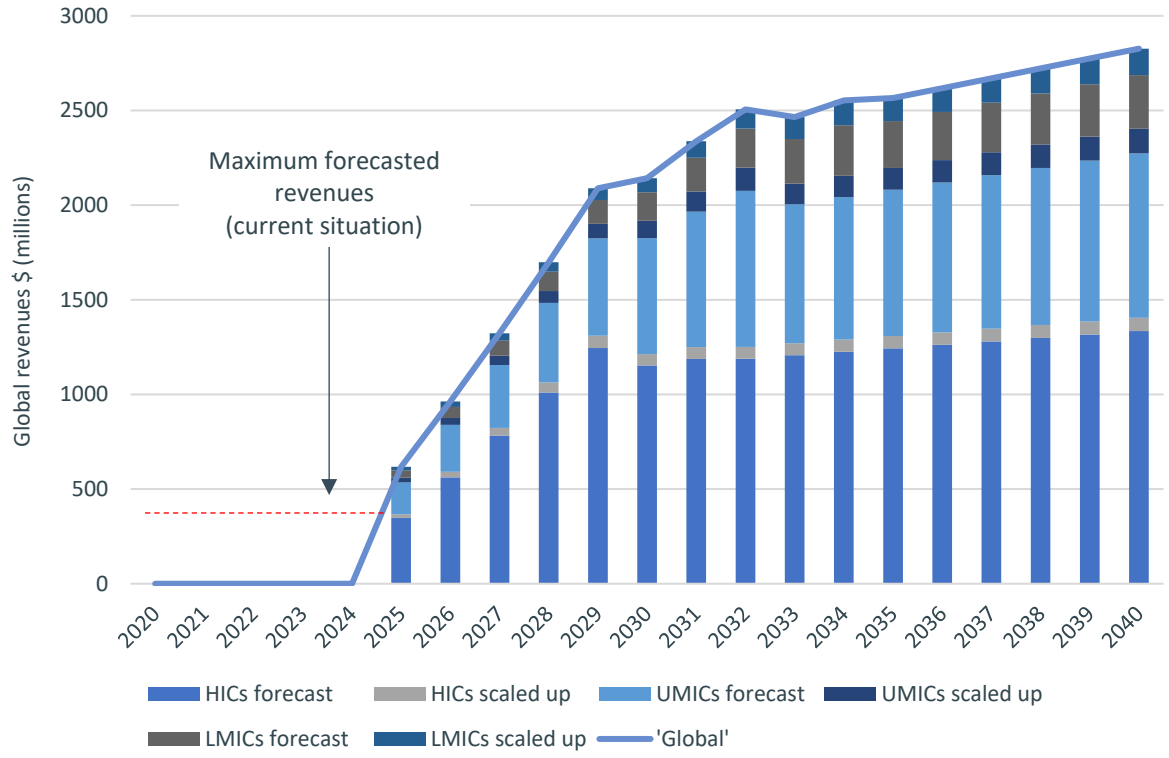

Figure 47: Dx1 (Bac. vs other) Projected global revenues (2024-2040), including their derivation for the modeling and income-group source. Scenario 2: Favorable situation (improved reimbursement and donor context).

Dx2 (ID/susceptibility): Base case

This high-priority diagnostic Dx2 (ID/susceptibility), is designed to determine whether an infection is bacterial or not and to understand its potential resistance to particular antibiotics reliably within four hours. Revenue forecasts plateauing just short of **$400 million in the 15 years** since launch are also relatively low (see **Figure 48**) for such an aspirational and technically sophisticated device.

Given the attributes of Dx2, the estimated percentage of patients eligible for this diagnostic is very high, at 90%. This is based on the significant short- and long-term clinical and economic benefits of using Dx2 (ID/susceptibility) at patient, hospital and society level. The local use case for HICs and UMICs predicts a reduction in mortality, a lower risk of nosocomial infections and decreased direct hospital costs. Cost reductions include reduced usage of expensive antimicrobials and length of stay in Intensive Care Units (ICUs), while other benefits include increased hospital capacity (short term) and preserving the long-term effectiveness of 'reserve antibiotics'. See **Appendix 3b** for further information on this topic gathered through multiple interviews.

Dx2 income-group shares of global demand remain more or less the same over time and are more weighted towards UMICs and HICs compared to Dx1 (Bac. vs other), reflecting the more developed hospital infrastructure in these countries. Estimates regarding 2030 under the current market situation show 90% of revenues originating in the more developed markets (HICs = 54%; UMICs = 34%) with the less developed income groups (LMICs/LICs) comprising only 11%, 5 years after launch. By 2040, while revenue slightly increases across all income groups, the relative shares do not change much and continue to be dominated by the wealthier, more developed countries (HICs = 46%; UMICs = 38%; LMICs/LICs = 16%).

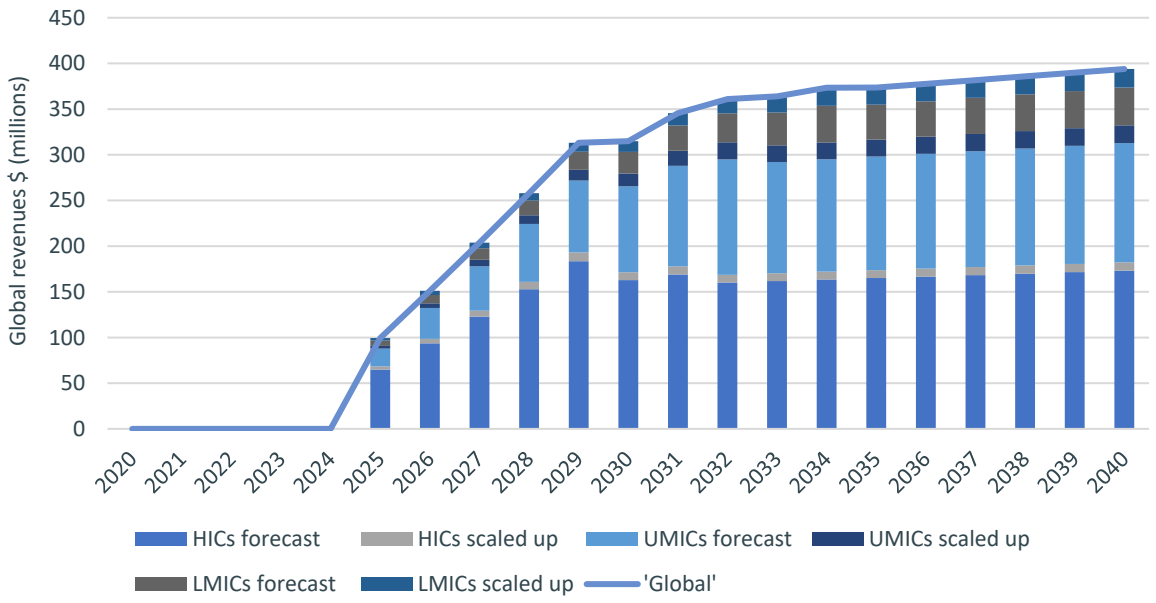

Figure 48: Dx2 (ID/susceptibility): Projected global revenues, including their derivation for the modeling and income group. Scenario 1: Base-case (current situation).

Hypothetical scenario (Broader reimbursement): Dx2 (ID/susceptibility)

The hypothetical scenario which assumes a shift in the policy and market context towards further support for greater uptake and use of such a device impacts patient access to it but also revenues accruing to the developer (**Table 37**)**,** though less substantially than for Dx1 (Bac. vs other). Revenues are forecast to increase just 1.5 times (from $394 million) by 2040 (15 years since launch) to **$600 million** (**Figure 49**). The relatively slight impact of a favorable context on this diagnostic is likely due to the already high uptake that was assumed in the base-case scenario, suggesting that 'available tertiary care sites' for further uptake were limited.

The estimates in 2030 under the more favorable scenario (market context) show that in the early years after launch this leads to a slight strengthening of the dominance of more developed countries as a source of the revenues, comprising 91% (HICs = 56%; UMICs = 35%) of all revenues (see also **Figure 50**)**.**

While the HICs with the more developed hospital infrastructures are still dominant 20 years later, LMIC/LICs are the source of only 9% of the expected income, a lower proportion than under the base-case scenario, but still representing a growth of $134 million in revenues in absolute terms. The instrument uptake assumptions driving this can be seen in **Figure 51.**

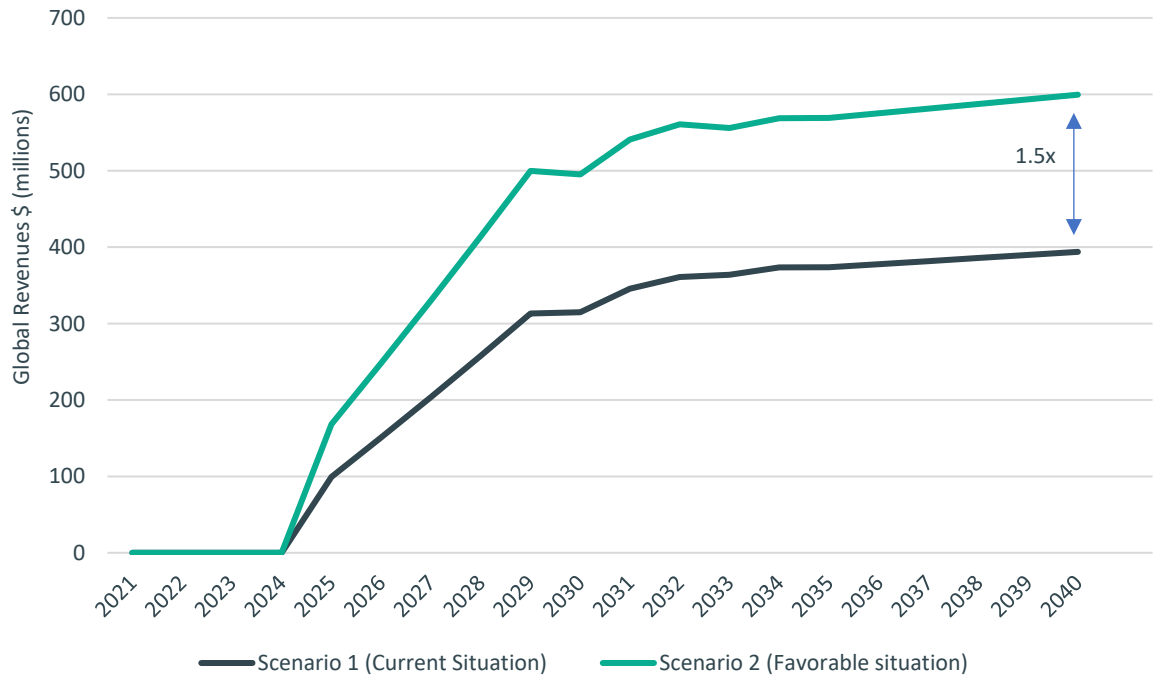

Figure 49: Dx2 (ID/susceptibility): Projected global revenues under the two different scenarios.

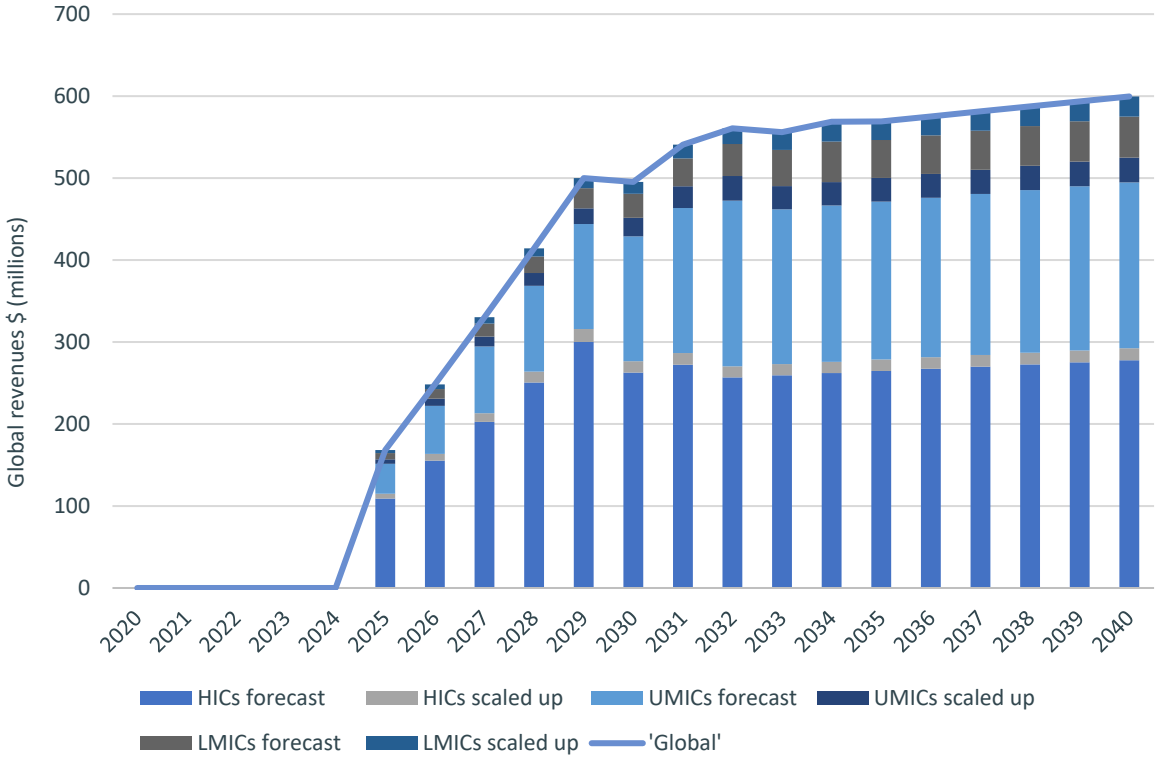

Figure 50: Dx2 (ID/susceptibility) Projected global revenues, including their derivation for the modeling and income-group. Scenario 2: Favorable situation (improved reimbursement and donor context).

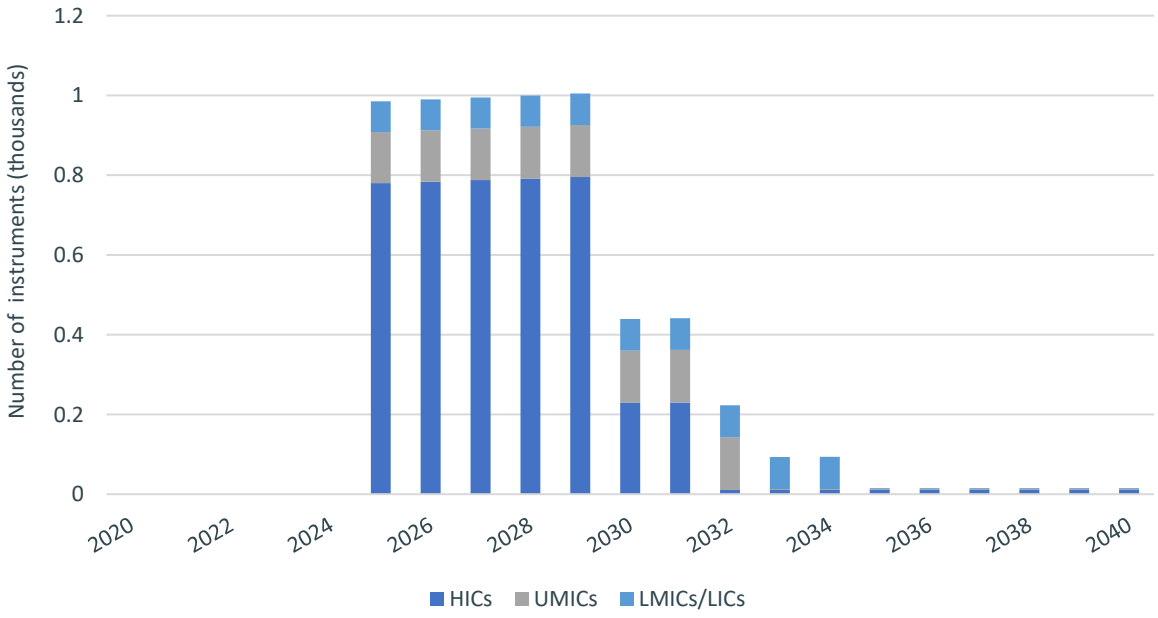

Figure 51: Dx2 New instruments per year – uptake assumptions.

		Dx2 (ID/susceptibility)							
		Scenario 1 (current situation) No substantive changes to reimbursement and uptake above current status quo				**Scenario 2 (favorable situation)** Hypothetical scenario: Broad reimbursement in HICs and donor funding for LMICs			
		Global	**HICs**	**UMICs**	**LMICs /LICs**	**Global**	**HICs**	**UMICs**	**LMICs /LICs**
# Instruments & Tests/Patients	**2030**	Inst: 5.4k Pts: 2.4m	Inst: 4.2k Pts: 1.2m	Inst: 0.8k Pts: 0.9m	Inst: 0.5k Pts: 0.3m	Inst: 11.8k Pts: 6.0m	Inst: 7.2k Pts: 2.1m	Inst: 2.1k Pts: 2.4m	Inst 2.5k Pts: 1.4m
	2040	Inst: 6.4k Pts: 3.2m	Inst: 4.5k Pts: 1.4m	Inst: 1.1k Pts: 1.3m	Inst: 0.8k Pts:0.5m	Inst: 15.0k Pts: 8.8m	Inst: 7.8k Pts: 2.4m	Inst: 2.8k Pts: 3.5m	Inst: 4.3k Pts: 2.8m
Revenues (Launch 2025)	**2030**	$: 315m	$: 171m	$: 108m	$: 35m	$: 496m	$: 277m	$: 175m	$: 44m
	2040	$: 394m	$: 182m	$: 150m	$: 62m	$: 600m	$: 293m	$: 232m	$: 75m

Table 37: Dx2 (ID/susceptibility) Summary outputs.

3.5 Data assessment and wish-list for further work

At the outset of this task to quantify the patient needs and market potential for the four need profiles defined by the EAG. The BoM of the Global AMR R&D Hub were keen to better understand where the data gaps are that are inhibiting global action to curb AMR. We hope this overall assessment (in **Table 38** and **Table 39**) not only helps to interpret the results presented in the study but also provides a path, or direction, for this and future work in the area.

The estimates and forecasts presented in this study result from the creation of a number of epidemiological and economic models. Those models and their outputs, similar to other studies in the field, are based on a number of assumptions and limited data exist to inform these assumptions and the model. As much as possible, analyses are carried out by using multi-country sources to allow cross-comparability, complemented by national data and expert opinion in other cases (see **Appendix 4**).

The analyses do not include a sensitivity analysis on the findings, which would be a typical approach in informing how the uncertainty of inputs translates to uncertainty of outputs. This was due to the complexity and scope of the work[73]. Instead, different scenarios were tested and presented.

One of the pivotal assumptions employed for this study is that the quantifications – across all need profiles – represent only 80% of the world. Data deficiencies in the remaining 20% were considered too substantial to feasibly estimate. In general, the EAG assessed the quantification across this whole study as being on the 'conservative' side and as such the results should be interpreted in this light.

[73] Combined with operational and resource limitations

Qualitative Therapeutic Assessment

Derivation of Global Patient Numbers/Need (epidemiology)	**Data Availability and Quality**	The qualitative assessment of this can be found in **Table 3** in Section **2.4**. Detailed data gaps are highlighted in **Appendix 4**. Overall data quality for this stream of the work has been qualitatively assessed as being 'medium' in terms of availability and quality, globally, and relative to the other streams within this study. Particular weak points were identified as: ○ MDR vs XDR (see **Info Box** on pg. 30), variability in its definition and its stringency or consistency in its application. The latter measure was subsequently removed from this work due to an 'unknown level of overlap' with the former. ○ Breakdown of incidence by demography (age-group analysis) especially, to reach neonatal sepsis was not possible due to data insufficiencies. The age calculations included are based purely on incidence of lower respiratory tract infections / pneumonia or BSI – no actual age-related data was found for Gram negative pneumonia / Gram negative BSI or MDR / XDR cases. ○ Absence of nationally available data on BSI (as this is not considered standardized), the proxy of 'sepsis from the GBD' enabled the gaps to be filled but these are not identical clinical concepts (see **Info Box** on pg. 70). ○ Pneumonia incidence data lacking (across all income regions but especially in LMICs/LICs) particularly for HAP, VAP and CAP.
	Assumption Strength and Robustness	The detailed assessment of this can be found in **Table 3** in Section **2.4**. Assumptions were used in places, to fill data gaps. However, the assumptions impacted the patient number forecasting substantially more. Acknowledged weak points were identified as: ○ Population growth figures – that the forecasted patient numbers are largely driven by assumptions on population growth figures at an income-group level was noted. Particularly, under accounting for some large countries such as China (UMIC) and Nigeria (LMIC) within each group was noted as a limitation. ○ Projected MDR proportions for individual Gram negative pathogens – No secondary research was available on this topic and hence current and historical proportions were used to inform YoY growth rates. That these were *de facto* held constant likely leads to more conservative estimates. Extensive country-specific primary research would be needed to reach this insight. ○ MDR proportion plateau and then capping – this assumption is widely used in industry modeling but prompted some concern among expert epidemiologists and no public data was available to support this. That MDR proportions are assumed to peak is something requiring further primary research. Gram positive MDR i.e., MRSA, in contrast, is thought to decline over time.

Derivation of Global Market Potential (revenue forecasting) 	**Market data to derive revenue and access assessment** 	The detailed assessment of this can be found in **Table 7** in Section **2.6**. Overall data quality here was qualitatively assessed as being relatively more plentiful and robust than on the epidemiological side. IQVIA MIDAS market audit data was purchased as part of this work due to its proprietary nature. Two global MNC pharmaceutical companies confirmed that the data were accurate within a +/-5% range. One notable weakness is that IQVIA data are known to be weaker for LMICs and LICs. Alternative data providers in these regions such as sanisphere[74], were contacted but were unable to supply data in a comparable format to IQVIA (to support supplementation) and did not have the global reach of the former. Bringing the 'patient need' estimates together with the 'commercial' estimates was an exploratory approach to looking at global access and while conceptually useful has noted limitations. These largely arise due to bringing two different methodological approaches together and the non-linearity, with regards the populations identified and how those needs can feasibly be reached by developers (BSI not being an indication, and the prevalence of off-label use in the critically ill). Furthermore, it was not possible from the methods employed to understand how 'country-level' market access would likely be impacted by the lower revenues than see with the analogues. This is one of the more concerning aspects of these markets, at present, and would be worthy of specific, further, exploration.
	Market assumptions to support derivation of revenue and access assessment 	The detailed assessment of this can be found in **Table 7** in Section **2.6**. A number of the assumptions used to adapt the 'existing market data' into analogues and forecasts specifically for our defined need profiles are worthy of note based on the qualitative assessment conducted: ○ Developer - use of Avycaz (ceftazidime/avibactam) as one of the main analogues assumes that a large MNC with the requisite global commercial apparatus/reach is behind the products. The 'Recommendations' explore how this assumption maybe increasingly vulnerable. ○ Product analogues - some concerns were raised that too narrow an approach was used to define the 'analogues'. Older [now off-patent] products such as Cubicin (daptomycin) and Gepotidacin hypothetically could be closer matches, but the non-inferiority label was anyway considered to preclude further 'value' being attributed. ○ Uptake assumptions - other studies indicate that uptake of newer, branded, antibiotics may be slower than other therapeutic areas, this may also be slowing further as stewardship measures are being strengthened globally. These assumptions may therefore be on the optimistic side, particularly for future projections. ○ Pipeline analysis - reveals that the assumptions that such a product would be launched in the US market in 2025 is currently considered unfeasible as the only viable candidates for this are statistically unlikely to be approved due to standard product attrition rates. ○ Consumption trends - that these were based on [relatively] old data was noted and perhaps a source of underestimation. ○ Market growth projections - which underlie the forecasting are somewhat robust as they can be deduced from the current pipeline (which is an indicator of future products on the market)[5]. ○ The approach throughout the study was to focus on the future potential of the gobal markets rather than forecasting the actual market itself.

Table 38: Overall assessment of therapeutics data & assumptions used in this report. *Key: Red – Low; Orange – Medium to low; Yellow –Medium to high; Green – High.*

[74] (Sanisphere LTD)

Qualitative Diagnostic Assessment

Derivation of Global Patient Numbers/Need (epidemiology)	**Data Availability and Quality** 	The qualitative assessment of this can be found in **Table 11** & **Table 12** in Section **2.6** and list of data sources is found in **References for modeling**. Overall data quality for this stream of the work has been qualitatively assessed as being 'medium' in terms of availability and quality, globally, and relative to the other streams within this study. Particular weak points were identified as: ○ The narrow epidemiology derivation of patient numbers for Dx2 likely leads to an underestimation of its potential utility, which will be broader than (BSI and pneumonia) and probably broader than the tertiary care setting determined for Dx2. ○ For Dx1, while febrile illness data was extensively researched (**Appendix 4**), it was considered of too low quality for supplementary inclusion. ○ The notable paucity of granular healtcare system data for LMICs/LICs for the diagnostic patient need should be noted as a particular weakness.
	Assumptions Strength and Robustness 	The qualitative assessment of this can be found in **Table 11** & **Table 12** in Section **2.6** and list of data sources is found in **References for modeling**. The use of 'clinical consultation sites/use cases' to determine patient numbers – particularly for Dx 1 the question of how closely a primary care setting relates to 'community care' (where the value of this product is considered highest) was debated. Although if this is considered 'community' or not depends on the country.
Derivation of Global Market Potential (revenue forecasting) 	**Market data to derive revenue and access assessment** 	The qualitative assessment of this can be found in **Table 11** & **Table 12** Section **2.6** and list of data sources is found in **References for modeling.** The almost complete absence of market data (in the same way as we have for therapeutics through IQVIA) for diagnostics required the adoption of a bottom-up approach (the conversion of projected patients into revenues based on commercial assumptions and analogues). Extensive consultation and analysis informed these assumptions (**Appendix 3**) but their collective weakness is noted in terms of their impact on the estimated revenues.
	Market assumptions to support derivation of revenue and access assessment 	The qualitative assessment of this can be found in **Table 11** & **Table 12** in Section **2.6** and list of data sources is found in **Appendix 4**. ○ The pricing assumptions (as defined in the 'need profiles') prompted some concern as to their feasibility – even during the time period modeled. The assumptions, however, were only applied to the sponsored LMIC/LIC markets. In all other markets in UMICs and HICs, more realistic pricing has been used, in line with currently available tests based on analogues. ○ Uptake assumptions are also considered conservative, as no instrument replacement was assumed and the slowing of uptake after the initial period could be overly conservative. ○ Competitive environment is more difficult to deduce with diagnostics as no single 'pipeline' data source provides an indication of the devices approaching market. ○ Donor support assumptions are very speculative and a more thorough dialogue with this community would be welcomed to strengthen these.

Table 39: Overall assessment of diagnostics data & assumptions used in this report. *Key: Red – Low; Orange – Medium to low; Yellow – Medium to high; Green – High.*

Recommendations for future work

Three formal areas proposed by the EAG to explore in more depth, as below, and as included in the core recommendations section:

- Options to stabilize the priority antibiotic market segment (Priority pathogen-targeting or Gram negative) beyond individual products should be investigated, thereby sending an urgent signal to private investors/companies/capital markets and secure a whole market segment of high public health importance
- Considering if and how voluntary cooperation on demand-aggregation mechanisms (pooling volumes through procurement or similar) can help ameliorate the challenges of low and geographically thinly-spread demand across many individually unattractive markets
- Mobilization of donor-support and exploration of supra-national coordination of procurement and widespread distribution options particularly for diagnostics and especially for LICs and LMICs

However, additionally, the EAG highlighted a number of supplementary areas – perhaps for other actors – that could be usefully explored:

- **Using Current Modeling Approach:**
  - Model other 'populations/product needs (animal vaccines, TB Tx)'
  - Modeling pricing/volume/patent possibilities
  - Modeling alternative distribution/access mechanisms (esp. Dx)
  - Explore further 'linked' pull-incentive options (demand pooling, reimbursement)
- **Expanding Beyond Current Modeling Approach:**
  - Modeling 'other' technology markets i.e., companion diagnostics, non-small-molecule therapeutics
  - Modeling delinked pull-mechanisms
  - Expanding cost/benefit framework to incorporate social values to motivate size of pull-mechanisms

4. DISCUSSION

PATIENT NEED

Despite the acknowledged limitations of current data in the area, the estimates and forecasts of the global AMR burden (or 'patient need' for the purposes of this report) for the specific patient populations, are an invaluable contribution to this field. Overall estimates of the human burden of AMR have often drawn on the 'Review of Antimicrobial Resistance' in 2014 chaired by Jim O'Neill[75], who estimated that ~700,000 people die as a result of drug-resistant infections each year, with a projected rise to 10 million by 2050, in the absence of a global response. The publication of the current study coincides with the forthcoming release[76] of the most recent estimates of the total global burden of AMR, based on 17 pathogen-antibacterial combinations by the GRAM Project[77] of the GBD Group/IHME, providing a crucial addition to our knowledge base.

Patient treatment needs in AMR do not lie in a single product or maintaining effective treatment of a single syndrome. Multiple pathogens can cause a range of infectious syndromes, occurring at different body sites and be resistant to a variety of antibacterial agents. For the acute priority syndromes prioritized by the EAG for exploration within this study – severely ill hospitalized patients with MDR Gram negative BSI, and those with pneumonia, caused by >2 'critical' priority pathogens − BSI is estimated to harbor both the larger current (2020) and future (2040) burden (3.7 to 5.5 million cases) of MDR than pneumonia (1.7 to 2.8 million cases) by almost two-fold, despite the latter syndrome being associated with the larger overall disease burden. While these figures are important to understand the size of the resistance problem in some of the most critical, hospitalized, infections – it is also acknowledged that the most severely ill patients are those for whom off-label prescribing can be more common[37]. Additionally, BSI itself is not a product indication[78]. The pathway from these identified patient populations to a prescription with the defined products is therefore often imperfect.

Recent data emerging from India during the Covid-19 pandemic indicate that Gram negative bacteria were isolated from 78% of hospitalized inpatients, with carbapenem-resistance proportions in *A. baumannii* and *K. pneumoniae* of 92.6% and 72.8%, respectively[79]. These numbers are in line with our current Gram negative proportion estimates (83% –76%) and MDR resistance proportions (76% – 64%) as sourced from GBD data. However, our study builds on these current estimates and shows that by 2040, India will no longer be an outlier and, despite rates and the absolute burden remaining high, India's proportion of MDR will actually fall. That the disproportionate burden of AMR will remain outside high-income – or traditional innovation-financing – countries is a notable message from this study. Yet the growing burden (increasing MDR proportions and syndrome incidence) is set to see MDR negatively impacting even the ability of health

[75] (O'Neill AMR Review, 2014)
[76] (Murray et al., 2021 Forthcoming)
[77] (GRAM Project, The Oxford GBD Group)
[78] An indication being a syndrome listed on the products label and therefore licensed for patient use by medicine regulators.
[79] (Vijay et al., 2021)

systems in HICs to effectively treat 1 in 3 patients by 2040, with some countries faring even worse. The plethora of ways in which modern medicine is being undermined through this – quantified here – increasing global resistance burden has recently been powerfully illustrated in more human, less quantitative terms[80].

Despite the narrow focus of our study, it should nevertheless be interpreted in a broader context. Whilst acknowledging the significant resistance burden exerted across all infectious pathogens, particularly malaria, HIV/AIDS, Gram positive bacteria and fungi, the consultative process used here concurred with the views of many other stakeholders and studies[21,11] in identifying Gram negative bacterial infections as one of the most acute problem areas in bacterial drug-resistance. The WHO's PPL remains the authoritative global source for public health priority signaling in AMR, complemented by its regular reviews of antibacterials in clinical and pre-clinical development[81], and repository of TPPs[82] to guide developers towards priority global public health needs.

If BSI represents the more critical of the two therapeutic needs identified, then neonatal sepsis is the neglected demographic apex of this. Our study had hoped to shed further light on this, but was constrained by available data. While demographically granular data on MDR were not available, sepsis data[83] confirms that infants <1 year old have the highest burden in all age-groups within LMICs/LICs. The antibiotic modeled for the BSI population could conceivably result in the fulfilment of this need, although substantial barriers remain between the initial licensure of the product and getting it to the relevant patient group (even through the current, off-label route). In this regard, our study adds weight to the important work being done by the Global Antibiotic Research and Development Partnership (GARDP), through its neonatal sepsis program[84]. Without such public and philanthropically-funded support, patient needs such as this have little chance of being met through the current market mechanism alone.

DATA

Improving the understanding of all aspects of AMR has long been acknowledged as a necessary precondition for strengthening the collective, global response to AMR. This spans a broad spectrum from laboratory-based surveillance, antibiotic prescribing and consumption, to syndromic surveillance, environmental monitoring and use of antimicrobials in agriculture, horticulture and animal health. With respect to the AMR burden specifically, this data component was recently reiterated by the Global Leaders Group on AMR, who deem this an immediate priority for informing future deliverable actions[85].

Explicit from the outset of this study – tasked directly from national policy-makers – was the wish for the data gaps encountered to be documented and made transparent, in order to foster a better understanding of where

[80] (Wellcome Trust, 2021)
[81] (WHO Antibacterials in pipeline, 2020)
[82] (Health Product Profile Directory, WHO)
[83] The clinical expressions of BSI and sepsis are quite similar; but these are distinct terms (see Section **3.2**).
[84] (GARDP Neonatal Sepsis Factsheet, 2019)
[85] (Global Leaders Group on Antimicrobial Resistance, 2021)

data gaps and deficiencies remain. To achieve this goal, our approach has been to build upon the growing AMR knowledge base, leveraging the best available data from a wide variety of sources, and complement this with expert know-how (and assumptions) to compensate for inevitable gaps.

Our study confirms that data are still limited in some areas and that compiling estimates remains a challenge[86], particularly so in UMICs and LMICs/LICs, whose data infrastructures and capabilities will take time and resources to be enhanced.

Section 3.5 'Data Assessment' is complemented by **Appendix 4** detailing the deep-data dive that was performed in the area of febrile illness. Specific epidemiological areas highlighted for strengthening include: febrile illness data, resistance burden within demographic populations, XDR/DTR as separate from MDR, and pneumonia incidence data (including HAP, VAP and CAP). Where data were insufficiently robust, or missing, assumptions were used in their place. The reliance of our estimates on assumptions was inevitable given the broad and global reach of the task. While the estimates and forecasts are likely over-reliant on population growth as the driver of the forecasts, in general the assumptions erred on the conservative side (in terms of population growth and using historic, and capped, MDR proportions). On the commercial side, diagnostic data is substantially less available across the whole scope of this work and while data is broadly available on the therapeutics side, it is notably weaker in LMICs/LICs.

TX - COMMERCIAL

Peak year sales of $127 million – $184 million indicate that products to meet these critical public health needs currently show muted market potential that is unlikely to be attractive to developers.

Comparisons are difficult as peak sales are used less commonly than NPV assessments in the academic literature and private sector data tends to be proprietary[5]. A previous study supported by the German government forecasted peak sales in a similar range[7]. Furthermore, investor analysis shows that across all antibiotics in the last 10 years, only Avycaz (ceftazidime/avibactam) and Dificid (fidaxomicin) have ''reasonable sales''; all other antibiotics have peaked below $150 million and/or have slow growth rates[87]. These findings validate the forecasts modeled here.

What constitutes an 'attractive' market is the source of some debate, with figures ranging from $250 million[88] to >$1 billion[89], depending on sources and assumptions[5, 11, 89, 90]. A narrower range of estimates was used to inform our therapeutics scenario analysis. The higher figure of $700 million could be viewed as reasonable when factoring in the tendency for large companies to make investment decisions across different (and often more attractive) therapeutic portfolios. The lower threshold acknowledges that for smaller or more specialized companies, lower amounts (in the region of $300 million – $400 million)

[86] (Dunachie, Day & Dolecek, 2020)
[87] (Carr & Stringer, 2019)
[88] (Årdal et al., 2018)
[89] (Årdal et al., DriveAB Report 2018)
[90] (Baraldi, Ciabuschi, Callegari & Lindahl, 2019)

could also be attractive[88]. For larger companies, in particular, 'relative attractiveness' is an important consideration and antibiotics have likely always fared badly as compared to medicines for chronic diseases[4]. Moreover, a workshop hosted by the Global AMR R&D Hub, as part of this study, collated estimates and generated expert insights that broadly concurred with the ranges set out here[91].

A broader interpretation of these single-product estimates could be more useful for policy-makers and indicate next steps for further work. While acknowledging that not all bacteria on the WHO's PPL are Gram negative, the majority (and all of those deemed 'critical') currently are. Our study used the current, global market segment for branded IV Gram negative antibiotics as a market-based proxy for these 'higher priority needs' and showed that, at present, the value of this 'segment' – of the overall antibiotic market – is fairly stable and valued at around $500 million a year. A value that matches the hoped-for figure in terms of single products. In addition, it is quite likely that all future Gram negative antibiotics coming to market will be classified with RESERVE status for stewardship purposes (under WHO's AWaRe categorization system), meaning that they should be used only as a last resort to treat MDR or XDR bacteria[92].

This market-segment value not only provides a useful default for where priority therapeutic needs lie but it can also correlate with how investors look at the attractiveness of an investment opportunity – in terms of the total available market (TAM) or if a product were to secure 100% peak share, what would that value be. If this is how investors (and by extension private capital owners) assess potential, perhaps an entire sub-class /market segment approach to policy intervention could have merit and be worthy of further exploration. Collaterally, this could have the public policy advantage of moving towards stabilizing the broader ecosystem for the longer term given that priority needs will likely evolve, as does AMR itself.

The second framework expansion, previously explored by others[5], that could help address the disconnect between the current private and societal values of these type of products, is the incorporation of broader healthcare and societal benefits into how much we pay for them. This could prove critical in translating their clear societal value into policy decision-making. Such approaches[93] have been given a recent boost through the UK's reimbursement pilot scheme, based on the STEDI[94] value-framework[95]. Most recently, progress announced at the European level to cooperate on Health Technology Assessment across Europe could prove a valuable vehicle for such developments to be more broadly adopted[96]. A related project in the diagnostics field, VALUE-Dx[97], has similar objectives for supporting policy-makers in further capturing and incorporating a broader set of values

[91] (Global AMR R&D Hub, News/Events)
[92] (AWaRe, WHO 2020)
[93] (Morton et al.,2019)
[94] STEDI: Spectrum, Transmission, Enablement, Diversity and Insurance are the proposed set of public health values of antibiotics not currently captured by value assessors
[95] (Neri, Hampson, Henshall & Towse 2019)
[96] (Council of the EU Press Release, 2021 Jun 22)
[97] (VALUE-Dx)

these critical health technologies present to health systems.

The broader valuation framework mentioned above, helps payors justify higher pricing and reimbursement for new antibiotics used within their health systems. However, usage of broader value frameworks is relatively new and not necessarily a viable tool for all health systems[61]. Opportunities for using more common pricing/reimbursement tools for improving valuation has recently been explored[61]. The present study builds upon these findings to examine how these traditional levers could, collectively, impact the overall market potential of a product, as viewed by a developer.

The pricing scenarios investigated as part of this study indicate that to reach the $700 million revenue threshold, all currently branded Gram negative antibiotic purchasing countries would have to increase their prices by around 380% – 550%. If only a handful of countries[98] were able or willing to do so, then prices would more likely have to rise 520% – 900% over current levels to achieve this level of investment return. Such high increases may prove challenging for many health systems, due to a number of reasons, from competing policy priorities[99], physician sensitivity to price differentials over [generic] SoC and (in part) the previously-noted challenges of being able to generate the evidence to justify 'added value'.

While pricing/reimbursement reform for antibiotics – backed by broader value assessment – is likely a critical policy response, the findings from this study when taken together, point to the limitation of pricing/reimbursement reform alone to address the economic challenges facing the development of such needed new antibiotics.

It should be noted that, in reality, the two therapeutic profiles could be satisfied by a single product, although for the purposes of this work they were considered both separate and non-competing. The chance of the described product/s being brought to market within the timeframe modeled i.e., by 2025 is seen as fairly low. In the most recently published clinical pipeline review[81] of 37 antibacterial agents, a product would already have to be in Phase II-III development (currently only two compounds could be candidates and only one of these is considered 'innovative') and standard attrition rates of 30%[100] make successful launch unlikely under the models' assumptions. A second assumption (arising from the modeling) worth additional reflection is that an MNC will put resources into a global roll-out[87]. Currently, only two large players with such global reach remain in the market − Merck and Pfizer. Fluctuating interest on the part of companies, as well as struggles faced by smaller companies striving to enter the market, are well documented[87]. Despite this optimistic scenario (i.e. assuming MNC involvement), global access and availability is still relatively weak when compared to both the absolute need and its geographic or income-group distribution. The efficiency of the current model to meet the need is set to worsen over time.

As a minimum, these findings strengthen the call that access planning – in a truly global sense – should be embedded early and

[98] (Aagaard, Malpani & Zorzet, ReAct 2021)
[99] (Vogler, Zimmermann & Habimana, 2016)
[100] (Thomas et al., 2016)

strongly into all development plans for these products[101,102], perhaps even as a condition for further public support for development. The data also suggest the exploration of a number of additional measures may be beneficial, such as supplementary distribution mechanisms (or alternative mechanisms in certain situations or scenarios), building on and leveraging existing models and initiatives, particularly in LMICs and LICs.

The pivotal role of supply chain resilience and efficiency is a factor garnering increasing attention. A recent study explores this in more depth, emphasizing the imperative of financing to ensure this can be realised[89]. Such proposals have also been made for HICs less familiar with these types of interventions[103]. Given that less than 1% of patients outside HICs have been forecast to be able to access such a product by 2040, the donor community, development bodies and foreign ministries could be usefully and further engaged in the dialogue.

The economic modeling conducted here was performed in the context of our current reality, in which antibiotic development and distribution remains predominantly in the hands of commercial markets. Attractiveness is therefore still determined by the amount and price the buyers in the market are able, or willing, to pay. Extensive research and literature over the last 15 years has outlined how market intervention can be best achieved. While 'delinkage' (removing the link between volume and revenues) is broadly accepted as the optimum solution to the particularities of this market, the practical ways to achieve this on a global scale remain elusive with the policy debate having made limited progress. The extent that newer models could be implemented certainly warrants further investigation. With this broader debate in mind – but with this model anchored in the current patent-based system – we have also explored possible favorable and unfavorable impacts of these on the market potentials, through the existing market levers of price and/or volume.

On the volume side, the study provides a compelling argument for improving data generation for any new antibiotics coming to market. If a product was able to better differentiate itself over SoC (i.e., securing a 30% peak market share[104]), it seems that the market could reward such a product more appropriately. However, such policy or regulatory developments to make this scenario a reality are not considered feasible in the short-to-medium term, despite laudable developments in this area[105], i.e., adaptive data requirements and clinical trial networks. A second volume-scenario provides a moment for policy-maker reflection; were there to be a volume contraction of the whole sub-market – perhaps due to greater stewardship stringency – revenues for all new individual products would shrink to levels that would eliminate the chance that such high priority antibiotics would be developed.

In our base-case scenario, absolute volumes of both antibiotics forecasted to be sold in the year prior to peak share is reached in 2036, indicating relatively limited patient reach of <60,000 patients annually spread over 70+

[101] (Stewardship & Access Plan (SAP), CARB-X)
[102] (Access to Medicine Foundation Report, 2020)
[103] (Årdal, Lacotte, Edwards & Ploy, 2021)
[104] As could be the case if a product were to succeed in demonstrating 'superiority' over standard of care
[105] (Global Response, Wellcome Trust 2020)

countries. This presents a number of challenges for both companies and countries. For countries, we may see a worsening of current country-level licensing/access challenges demonstrated both in this study for more recent Gram negative launches and supported further by a recent study comprising a broader pool of antibiotics[50]; a likely symptom of the developer challenges justifying rapid licensure in a broad number of countries to secure relatively few sales (particularly in the case of smaller countries).

This relatively slow global uptake of new antibiotics, the low and fragmented volumes and likely limitations to price as a lever (noted earlier), potentially point to the limitations of 'patent' levers (e.g. patent extensions, priority review vouchers etc.) as the solution to the challenges in this space, despite a recent resurgence of interest[106].

Formal statistical analysis was not used within the current study to indicate how the uncertainty of the inputs and assumptions impacted the models' outputs. However, the inputs and assumptions used have been made fully transparent and are accompanied by a qualitative assessment of their robustness. Due to the scope and scale of the task and the data gaps, the model erred on the conservative side. Therefore, throughout the report the estimates and forecasts are considered modest. Nevertheless, the modeling and, in particular, the scenarios should be interpreted with due caution. Areas for further in-depth exploration have been indicated.

DIAGNOSTICS

The previously noted higher and growing burden of high priority resistant organisms outside HICs is a rallying cry for improving the more targeted and prudent use of all antibiotics, but particularly newer ones in these settings. This is one of the main positive impacts of both the diagnostics examined here.

Under the current market context, the need for a POC, primary care diagnostic for rapid identification of a bacterial infection (vs other etiology), was conservatively forecast to reach more than 800 million patients globally over the next 20 years. The use case for such a diagnostic in primary care – or the uptake of such a device – was considered generally more challenging.

Looking at the more sophisticated device, for more informed early prescribing (pathogen ID and susceptibility) in patient admission, the need – estimated conservatively – is 20 times lower, with eligible annual patients reaching <30 million globally in the next 20 years. Despite this, the use case for such a device was considered more positive even at baseline (potentially reaching 10% of the projected hospital need). For both these devices, around 80% (Dx1) and 85% (Dx2) of the realizable need is forecast to lie outside HICs.

The relatively low realizable patient needs for the specific diagnostics covered by this study potentially reflect the slight bias in the modeling towards HIC assumptions and the system constraints in stopping these devices from reaching eligible patients. There are likely to be many unquantified, collateral

[106] (Batista, Byrski, Lamping & Romandini, 2019)

patient diagnoses beyond those quantified here. Additionally, work in the area that aims to capture broader cost savings to health systems and even social benefits from improved diagnosis would be an invaluable addition to this study. Despite the very different patient reach and nature of these diagnostics, they were both forecast to generate only around $275 million – $400 million in yearly revenues in the 15 years following their launch – although this represents a much greater uptake for Dx1 (Bac. vs other) compared to Dx2 (ID/susceptibility).

Estimates in the field of diagnostics are acknowledged to be substantially more challenging than for therapeutics markets. The scenarios modeled here have provided insight into the uncertainty of the estimates together with an indication of what policy intervention could achieve. Under a more favorable scenario, with enhanced reimbursement and donor support, revenues increase from ~$400 million to >$2.8 billion for the primary care diagnostic (Dx1) by 2040. The revenue increase for Dx2 (in the hospital setting) still only just reaches $600 million.

This relatively low increase could indicate the relatively more positive use case under the base-case but perhaps also suggesting that uptake in this context cannot be easily overcome through reimbursement/pricing and that structural barriers and incentives (i.e., health system development), may be a key constraint.

Perhaps the more significant observation from this analysis arises when converting the revenues back to patients to find that the 'more favorable reimbursement' scenario leads to a 14-fold increase in patient reach for Dx1 (Bac. vs other) in primary care, equating to around 125,000 more patients outside HICs being diagnosed and therefore – based on some estimates that 50%[107] of patients even in a hospital setting are unnecessary – potentially a large reduction in unnecessary prescriptions.

Of particular interest to the EAG during this study was the possibility of bringing the therapeutics and diagnostics streams together to see whether policy insights could be gained regarding the possible role of AMR diagnostics being used hand-in-hand with new antibiotics (often as complementary and/or companion diagnostics). In this scenario, the diagnostic is either supplied directly with, or made a condition of, a therapeutic prescription, such as with HIV and Hepatitis C virus (viral load testing and therapy). This is an ideal situation for the broader AMR response and is very much a reality in other therapeutic areas, such as oncology (the notable example being Herceptin and HER2+ breast cancer[108]).

However, interviews conducted as part of this study indicate that, due to the time-critical nature of the needs prioritized in this study and the specifications, e.g., invasive tissue sampling, the hoped-for transformative impact of such a solution might not be a viable near-term goal based on the current market landscape. Expert consultation indicated that a more viable goal in the medium term, would be for uptake of the increased number of narrow-spectrum candidates now evident in the pipeline[81] to be supported – not by a product-specific diagnostic but by a more general diagnostic

[107] (Burnham, Leeds, Nordmann, O'Grady & Patel, 2017)
[108] (American Cancer Society, Inc., 2021)

that would cover a range of bacterial identification and broad-susceptibility panels (a profile similar to our Dx2 [ID/susceptibility]).

Although bringing the therapeutic and diagnostic models, and therefore markets, together within the modeling itself was unfortunately beyond the initial scope of the study, this could nonetheless be a fertile area for future exploration. Specific, quantitative insights could be gained regarding the impact of 'diagnostic confirmation' (perhaps as a precondition for prescribing a branded Gram negative antibiotic)[109], on the various therapeutics and diagnostics market shares, revenues and reach. This would support investigations of whether such a scenario would facilitate therapeutic differentiation and uptake, improve revenue certainty on the diagnostics side or be market contracting (i.e., decreased volumes as a result of fewer 'incorrect' empiric prescriptions on the therapeutics side). In turn, this would aid understanding of whether enhanced cooperation between the therapeutic and diagnostic industry segments, and investment to support this goal, would be warranted despite the major challenges in pursuing this aim[110].

While the market attractiveness of diagnostics highlighted in this study are at the moment modest, a more positive message emerges from the scenario forecasting. The potential positive impacts – on the narrow value-framework of developer returns and patient reach – of improving diagnostic uptake and reimbursement prove to be substantial. The dearth of well-designed studies that demonstrate the clinical utility of advances in molecular diagnostics inhibits and slows their uptake. Additionally, the recent Covid-19 precedent, with reported 1,000-fold increases in molecular diagnostic uptake over 6-month periods, even in LMICs/LICs[69], may bolster policy-maker confidence in what can be achieved.

Overall, the study's breadth, yet specific terms of reference, has enabled the investigating group to reflect on the key gaps in data and knowledge, on future directions for this initial, foundational study and on recommendations for policy action.

[109] (FIND, 2018)
[110] (Dailey, Elbeik & Holodniy, 2020)

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6. LIST OF TABLES & FIGURES

7. APPENDIX

1. Epidemiology: Country Selection & Assumption Analysis

a. Therapeutics

For the selection of countries, the bidder should take the criteria in Table 1 into account and should justify the selection, based on their application or interpretation of these criteria:

Table 1. List of criteria for determining country selection ranked most to least important

1. Data availability (middle income countries where data are available for both Parts A and B)
2. Countries where patient numbers and/or potential revenues are particularly high
3. Countries with the greatest disparity between potential revenue and patient numbers
4. Country selection to represent geographical diversity - representation from all world regions

Geographic Scope of the project

- United States
- High-Income Countries
- Upper-Middle-Income Countries
- Lower-Middle and Lower-Income Countries combined

Countries selected within each income group :

- Meet specified EAG criteria on:
  - Data availability
  - Countries with high patient numbers / potential revenues
  - Countries with greatest disparity between patient numbers and revenues
  - Representation from all world regions
- Represent a range of AMR rates based on high level *E.coli* and *K.pneumoniae* resistance data from Pfizer ATLAS database
- Have a reasonable population size
- Have been noted to be of interest to EAG members during groupH interviews (in particular LMICs)
- Have other reasons to include (e.g. part of project scope / used to create epidemiology spreadsheet template due to good data availability)
- A 'nice-to-have' would be alignment also with commercial market data availability from IQVIA and the Revenue Potential Part of the project

Selected countries that meet EAG criteria and take into account additional factors such as population, AMR rates and EAG interest

Resistance	Population
<5%	< 25M
5 - <10%	> 25M <50M
10 - 25%	> 50M <100M
25 - 50%	>100M < 500M
≥50%	>500M

Legend for following 3 country selections

Selection Criteria		Proposed Countries				Other Potential Countries	
		North America	Europe	Middle East	Asia	Oceania	Europe
		USA	UK	Saudi Arabia	Japan	Australia	Italy
AMR Data Availability[1/2]		✓	✓	✓	✓	✓	✓
AMR %[2]	*E.coli* resistance to ceftazidime	◔	◔	◕	◔	◔	◔
	K.pneumoniae resistance to meropenem	○	◔	○	○	○	◔
Population		◔	◔	◔	◕	◔	◔
Interest Noted by EAG Members				✓	✓	✓	
Other Reasons to Include		Part of project scope	Used to create epi template due to good data availability			Southern Hemisphere Country	Combines High Income Country with High Resistance

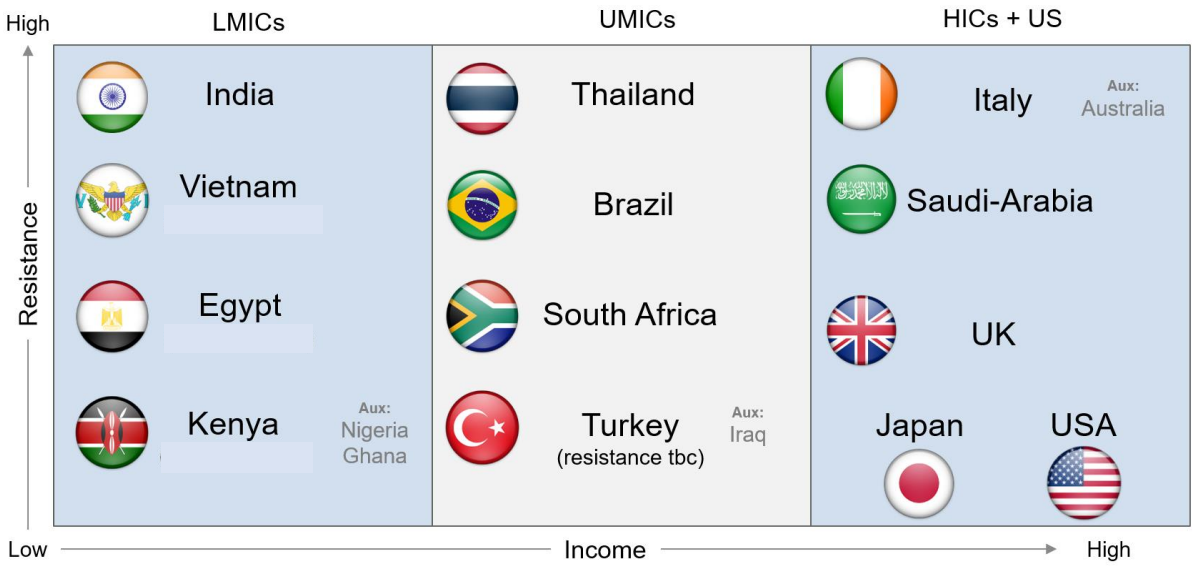
Selection: High-Income Countries. (Notes: [1] WHO 2020 GLASS report; [2] 2018 data sourced from Pfizer ATLAS surveillance database https://atlas-surveillance.com/)

Selection Criteria	Proposed Countries			Other Potential Countries	
	South America	Africa	Asia	Middle East	Asia
	Brazil	South Africa	Thailand	Iraq	Turkey
AMR Data Availability[1/2]	✓	✓	✓	✓	✓
AMR %[2] – *E.coli* resistance to ceftazidime	◑	◑	◕	Not available from 2	●
AMR %[2] – *K.pneumoniae* resistance to meropenem	◑	○	◑	Not available from 2	◑
Population	◕	◑	◑	◔	◑
Interest Noted by EAG Members	✓	✓	✓	✓	✓

Selection: Middle-Income Countries. (Notes: [1] WHO 2020 GLASS report; [2] 2018 data sourced from Pfizer ATLAS surveillance database https://atlas-surveillance.com/)

Selection Criteria		Proposed Countries			Other Potential Countries		
		Asia	Asia	Middle East	Africa		
		India	Vietnam	Egypt	Ghana	Kenya	Nigeria
AMR Data Availability[1/2]		✓	✓	✓	Not available from 1 or 2	Not available from 1 or 2	✓
AMR%[2]	*E.coli* resistance to ceftazidime	●	Not available from 2	Not available from 2	Not available from 1 or 2	Not available from 1 or 2	◕
	K.pneumoniae resistance to meropenem	●	Not available from 2	Not available from 2	Not available from 1 or 2	Not available from 1 or 2	◕
Population		●	◑	◕	○	◑	◕
Interest Noted by EAG Members		✓	✓	✓	✓	✓	

Selection: Low Middle- and Low-Income Countries. (Notes: [1] WHO 2020 GLASS report; [2] 2018 data sourced from Pfizer ATLAS surveillance database https://atlas-surveillance.com/)



Overview – Country Selection: Income / Resistance Matrix – Proposed Countries

HIC's (High Income Countries)

- Overall Italy was more 'popular' for inclusion than Australia as it represents a) a second (Southern) EU country very different to the UK and b) has a higher level of resistance compared to Australia and c) associated issues with stewardship
- Australia is attractive in its own right though, as it a) represents a geography not regularly covered and b) has good data and c) a large intensive livestock sector
- Both have good labs and academia

MICs (Middle Income Countries)

- Turkey was largely agreed on over Iraq because Turkey is reported to have overall better established systems and data and being a more robust state leaving less doubt as to what the reality in the country is and c) displaying one of the highest resistance rates in the EU region
- Iraq, on the other hand, has expressed interest in bring trained in antimicrobial consumption surveillance but has not started yet (WHO AMC report)

LMICs (Low to Middle Income Countries)

- Kenya received more 'votes' from the EAG than Nigeria
- Both countries have similar income GDP/capita rates
- Nigeria is the more populous country at ~200m (compared to Kenya at ~50m) and a key country in the African region
- Kenya is reported to have comparably good data and public information for an LMIC country and is 'much easier' to work in
- Kenya has just received a large grant for improving AMR resistance (ILRI involved) but has a porous border with Somalia (which imports drugs freely)

Country Selection Comments Summary

b. Diagnostics

Country prioritisation

- We assume that countries and third party donors will be very selective in providing funds for AMR - we have developed criteria for selecting countries from each income group with the highest need to combat AMR and the largest population
- For high income countries, analogue to drug markets, we selected key Western markets where diagnostics companies make the majority of their current revenue (US, EU5 + Japan) regardless of AMR burden
- To reduce complexity some assumptions are taken at country group level rather than by country. However, the underlying analysis may have country granularity where data was available

- Health Expenditure ($ per Capita) was mapped by traffic light for each country, to identify those with most need (red)

Health Expenditure Traffic Light			
	<	Medium	>
HIC	1000	1000-2000	2000
UMIC	350	350-500	500
LIC	75	75-125	125

- Additionally, surveillance was flagged as red or green according to inclusion in the GLASS study
- Finally, the status according to the National AMR Action Plan was heat mapped

Surveillance Levels Heat Mapping	
Rank	Explanation
1	None
2	Under Development
3	Developed
4	Govt. Approved; budgeted & monitoring
5	Govt. Approved; funded & implemented

Forecasting Dx1 and Dx2 – Market Assumptions: Market Assumptions 2020 - 2040 and rationale Global projected by region.

Income Region	Country	Population[1]	INCIDENCE LRT infection /100k[2]	LRT Patients	Severe Pneumonia	GN severe pneumonia patients	MDR[3]	MDR Patients	Country Share of Regional MDR Patients	Healthcare Expenditure per Capita ($)[5]	Surveillance Criteria 1[6]	Surveillance Criteria 2[7]	Include Country?
USA	US	332,639,102	4153.01	13,814,535	828,872	116,042	27%	30,751	100%	10,246	YES	5	Interim Proposed Country
HIC								**148,091**					**70% regional coverage**
HIC	Argentina	45,479,118	5,612.97	2,552,729	153,164	21,443	48%	10,185	7%	1,325	YES	3	Yes
HIC	Australia	25,466,459	2,647.77	674,293	40,458	5,664	17%	974	1%	5,332	YES	4	
HIC	Belgium	11,720,716	5,200.46	609,531	36,572	5,120	27%	1,398	1%	4,507	NO	3	
HIC	Canada	37,694,085	3,410.95	1,285,726	77,144	10,800	24%	2,614	2%	4,755	YES	3	
HIC	Chile	18,186,770	4,066.10	739,492	44,370	6,212	50%	3,081	2%	1,382	NO	4	
HIC	Croatia	4,227,746	3,633.54	153,617	9,217	1,290	48%	618	0%	902	YES	5	
HIC	Czech Republic	10,702,498	4,624.92	494,982	29,699	4,158	35%	1,443	1%	1,476	YES	4	
HIC	Finland	5,571,665	3,147.99	175,395	10,524	1,473	7%	96	0%	4,206	YES	4	
HIC	France	67,848,156	3,767.96	2,556,491	153,389	21,475	27%	5,841	4%	4,380	YES	4	Yes
HIC	Germany	80,159,662	3,601.18	2,886,694	173,202	24,248	23%	5,601	4%	5,033	YES	4	Yes
HIC	Greece	10,607,051	4,365.92	463,095	27,786	3,890	37%	1,432	1%	1,517	YES	3	
HIC	Hong Kong	7,249,907	0.00	0	0	0	29%	0	0%	n/a	n/a	n/a	
HIC	Hungary	9,771,827	3,743.13	365,772	21,946	3,072	36%	1,094	1%	981	NO	3	
HIC	Ireland	5,176,569	3,136.44	162,360	9,742	1,364	31%	427	0%	4,977	YES	4	
HIC	Italy	62,402,659	3,988.94	2,489,205	149,352	20,909	48%	10,036	7%	2,840	YES	4	Interim Proposed Country
HIC	Japan	125,507,472	3,572.56	4,483,830	269,030	37,664	15%	5,574	4%	4,169	YES	5	Interim Proposed Country
HIC	Korea, South	51,835,110	1,816.72	941,699	56,502	7,910	45%	3,536	2%	2,283	YES	5	
HIC	Kuwait	2,993,706	4,766.79	142,704	8,562	1,199	50%	602	0%	1,529	NO	1	
HIC	Latvia	1,881,232	7,741.20	145,630	8,738	1,223	41%	502	0%	930	YES	4	
HIC	Lithuania	2,731,464	8,478.55	231,589	13,895	1,945	45%	879	1%	1,078	YES	4	
HIC	Netherlands	17,280,397	3,070.71	530,631	31,838	4,457	16%	695	0%	4,911	YES	5	
HIC	Poland	38,282,325	4,181.51	1,600,779	96,047	13,447	56%	7,544	5%	907	YES	1	
HIC	Portugal	10,302,674	5,454.18	561,926	33,716	4,720	35%	1,662	1%	1,908	NO	3	
HIC	Russia	141,722,205	6,202.78	8,790,717	527,443	73,842	67%	49,253	33%	586	YES	4	Yes
HIC	Saudi Arabia	34,173,498	5,251.60	1,794,655	107,679	15,075	41%	6, 166	4%	1,166	YES	5	Interim Proposed Country
HIC	Singapore	6,209,660	2,750.75	170,812	10,249	1,435	24%	347	0%	2,619	YES	5	
HIC	Spain	50,015,792	3,248.99	1,625,008	97,500	13,650	33%	4,491	3%	2,506	NO	5	EU5???
HIC	Sweden	10,202,491	3,958.31	403,846	24,231	3,392	26%	868	1%	5,905	YES	5	
HIC	Switzerland	8,403,994	2,544.74	213,860	12,832	1,796	26%	458	0%	9,956	YES	5	
HIC	Taiwan	23,603,049	8,606.73	2,031,451	121,887	17,064	45%	7,696	5%	n/a	n/a	n/a	
HIC	UK	65,761,117	4,124.55	2,712,350	162,741	22,784	26%	5,924	4%	3,859	YES	4	Interim Proposed Country
HIC	Venezuela	28,644,603	6,033.20	1,728,186	103,691	14,517	49%	7,055	5%	94	NO	n/a	

Dx Country Selection, HICs

Income Region	Country	Population[1]	INCIDENCE LRT infection /100k[2]	LRT Patients	Severe Pneumonia	GN severe pneumonia patients	MDR[4]	MDR Patients	Country Share of Regional MDR Patients	Healthcare Expenditure per Capita ($)[5]	Surveillance Criteria 1[6]	Surveillance Criteria 2[7]	Include Country?
UMIC								**474,258**					**80% regional coverage**
UMIC	Belarus	9,477,918	5,256.79	498,234	29,894	4,185	47%	1,987	0%	342	NO	3	
UMIC	Bosnia	3,835,586	3,790.61	145,392	8,724	1,221	47%	580	0%	460	YES	n/a	
UMIC	Brazil	211,715,973	8,738.58	18,500,970	1,110,058	155,408	42%	64,650	14%	929	YES	4	Interim Proposed Country
UMIC	Bulgaria	6,966,899	4,790.83	333,772	20,026	2,804	47%	1,331	0%	664	NO	3	
UMIC	China	1,394,015,977	3,925.61	54,723,631	3,283,418	459,678	54%	250,065	53%	441	NO	5	Yes
UMIC	Colombia	49,084,841	5,597.67	2,747,607	164,856	23,080	36%	8,216	2%	459	NO	3	
UMIC	Costa Rica	5,097,988	6,629.07	337,949	20,277	2,839	32%	911	0%	869	NO	3	
UMIC	Dominican Republic	10,499,707	5,606.44	588,660	35,320	4,945	44%	2,171	0%	433	NO	n/a	
UMIC	Ecuador	16,904,867	7,054.71	1,192,589	71,555	10,018	47%	4,757	1%	518	NO	4	
UMIC	Iraq	38,872,655	4,681.29	1,819,742	109,185	15,286	47%	7,258	2%	210	YES	4	
UMIC	Jordan	10,820,644	4,591.81	496,863	29,812	4,174	54%	2,254	0%	341	YES	5	
UMIC	Kazakhstan	19,091,949	4,885.14	932,668	55,960	7,834	47%	3,720	1%	280	NO	3	
UMIC	Lebanon	5,469,612	5,523.21	302,098	18,126	2,538	47%	1,205	0%	719	YES	4	
UMIC	Malaysia	32,652,083	7,772.63	2,537,926	152,276	21,319	36%	7,589	2%	374	YES	5	
UMIC	Mexico	128,649,565	4,616.49	5,939,094	356,346	49,888	58%	29,035	6%	495	NO	n/a	
UMIC	Panama	3,894,082	6,674.91	259,926	15,596	2,183	46%	1,009	0%	1,112	NO	3	
UMIC	Peru	31,914,989	9,628.63	3,072,976	184,379	25,813	47%	12,257	3%	333	YES	5	
UMIC	Romania	21,302,893	5,943.81	1,266,203	75,972	10,636	51%	5,435	1%	555	NO	2	
UMIC	Serbia	7,012,165	3,648.20	255,818	15,349	2,149	47%	1,020	0%	529	NO	4	
UMIC	South Africa	56,463,617	8,699.33	4,911,956	294,717	41,260	44%	18,320	4%	499	YES	3	Interim Proposed Country
UMIC	Thailand	68,977,400	6,821.99	4,705,631	282,338	39,527	51%	20,080	4%	247	YES	5	Interim Proposed Country
UMIC	Tunisia	11,721,177	5,938.75	696,091	41,765	5,847	47%	2,777	1%	251	NO	4	
UMIC	Turkey	82,017,514	5,778.80	4,739,628	284,378	39,813	69%	27,630	6%	445	NO	3	Interim Proposed Country

Country Selection, UMICs

Income Region	Country	Population[1]	INCIDENCE LRT infection /100k[2]	LRT Patients	Severe Pneumonia	GN severe pneumonia patients	MDR[4]	MDR Patients	Country Share of Regional MDR Patients	Healthcare Expenditure per Capita ($)[5]	Surveillance Criteria 1[6]	Surveillance Criteria 2[7]	Include Country?
LMIC								1,032,815					80% regional coverage
LMIC	Bangladesh	162,650,853	6,738.69	10,960,537	657,632	92,069	59%	54,228	5%	36	YES	4	
LMIC	Egypt	104,124,440	7,063.90	7,355,246	441,315	61,784	59%	36,391	4%	106	YES	4	Interim Proposed Country
LMIC	Ghana	29,340,248	7,160.02	2,100,768	126,046	17,646	59%	10,394	1%	67	YES	5	
LMIC	Guatemala	17,153,288	7,383.19	1,266,460	75,988	10,638	54%	5,734	1%	260	NO	3	
LMIC	India	1,326,093,247	10,667.04	141,454,897	6,365,470	891,166	67%	599,755	58%	69	YES	4	Interim Proposed Country
LMIC	Indonesia	267,026,366	5,929.57	15,833,515	950,011	133,002	59%	78,338	8%	115	YES	5	
LMIC	Kenya	53,527,936	6,062.08	3,244,906	194,694	27,257	59%	16,054	2%	77	YES	4	Interim Proposed Country
LMIC	Morocco	35,561,654	5,775.66	2,053,920	123,235	17,253	52%	9,041	1%	161	YES	3	
LMIC	Nigeria	214,028,302	6,124.40	13,107,949	786,477	110,107	72%	78,947	8%	74	YES	4	Yes
LMIC	Pakistan	233,500,636	5,982.62	13,969,456	838,167	117,343	59%	69,115	7%	45	YES	5	Yes
LMIC	Philippines	109,180,815	7,568.21	8,263,033	495,782	69,409	38%	26,376	3%	133	YES	5	
LMIC	Sri Lanka	22,889,201	5,366.22	1,228,285	73,697	10,318	59%	6,077	1%	159	YES	4	
LMIC	Ukraine	43,922,939	6,760.91	2,969,590	178,175	24,945	70%	17,486	2%	177	NO	3	
LMIC	Vietnam	98,721,275	5,093.79	5,028,654	301,719	42,241	59%	24,880	2%	130	NO	4	Interim Proposed Country

Dx Country Selection, LMICs

Dx Country Selection Sources

1. Source for 2020 data: https://www.census.gov/data-tools/demo/idb/informationGateway.php. Accessed 17/11/2020
2. Source for 2019: http://ghdx.healthdata.org/gbd-results-tool, accessed November 2020
3. Source: groupH estimates. Note 4.5% was used in India
4. Source: ATLAS 2018 MDR - all GN pathogens combined, accessed November 2020
5. Source: Latest available of 2015-2017: https://apps.who.int/nha/database/ViewData/Indicators/en, accessed November 2020
6. Source: Proxy for Surveillance is enrolment in GLASS study at Feb 2020: https://docs.google.com/spreadsheets/d/14QJ4tUfqmS5YF60BOpXZzZffwr6cRlu_vEZ9_oYfpRA/edit#gid=0
7. Source: Proxy for Surveillance/Stewardship is ranking based on National AMR action Plan Survey 2019/20: http://amrcountryprogress.org/

2. Therapeutics (Commercial Context)

Tx1 Competitive Pipeline: GN BSI expected to see very few future launches, but as BSI is typically treated with products targeting the primary focus, new products with a BSI label might commercially be 'late entrants'

- Overall, there is limited interest by Big Pharma in GN BSI – only Pfizer remaining as a global multinational
- The pipeline of BSI is very limited; companies are targeting the primary infections sites of cUTI, HAP/VAP, cIAI either as indication-specific alone or targeting specific pathogens +/- resistances
  - BSI has previously been filed by some companies without success e.g. ZEMDRI (CRL received by Achaogen), AVICAZ/ZAVICEFTA (voted down by FDA advisory committee, but positive opinion by CHMP on BSI associated to cUTI, cIAI or HAP/VAP in June 2020)
  - For Shionogi's FETROJA there is an ongoing Ph 2 Investigator led study in BSI, NCT03869437 (but does not appear to be in development with Shionogi). Entasis' Ph 3 with SUL-DUR is targeting A. baumannii in an ongoing trial versus colistin in BSI, HAP/VAP, cUTI & surgical wounds patients; Other candidates are planning Phase 3 trials, incl. Pfizer's ATM-AVI targeting resistant pathogens
- Based on the pipeline for BSI and the experience with recent launches of branded products in the GN infection space, we expect probably no more than 1 or 2 approvals / launches for BSI over the next 5 years in the US, less in other HICs, and also less or even none in UMICs and LMICs
- However, we believe that a BSI label by itself will not lead to referred / earlier use in BSI vs. other products not specifically labelled for BSI; physicians are likely to continue to preferentially / initially use medications approved for primary sites of infection to also treat any BSI associated with that, and only refer to specific BSI drugs in later lines if the BSI cannot be controlled that way.
- In this situation, **we expect a limited patient share potential for new entrants with a label specific for BSI**

Summary of Commercial Analyis for Thereapeutic 1 (BSI).

Tx2 Competitive Pipeline: HAP/VAP market expected to see several further launches of relatively undifferentiated products, leading to a pronounced order of entry effect that would limit the share potential of late entrants

- Overall, there is limited interest by Big Pharma in GN pneumonia – only Merck & Pfizer remaining as global multinationals
- Nevertheless, there is considerable competitor activity for HAP/VAP by smaller companies
  - For GN infections, companies are mainly targeting HAP/VAP and cUTI, and to a lesser extent cIAI and only few target BSI; Many of the candidates are in development for several indications and this follows through to approval with the exceptions of ZEMDRI (cUTI alone) and XERAVA (cIAI alone)
  - The clinical pipeline for HAP/VAP is dominated by several β-lactam/BLI combinations - these do target key resistances such as CRE (carbapenem resistant Enterobacteriaceae), CRAB (carbapenem resistant A. baumannii), and CRPA (carbapenem resistant P. aeruginosa), but overall represent a low level of innovation – e.g. no new targets or new mechanism of action
- Based on the pipeline for HAP/VAP and the experience with recent launches for of branded products in the GN infection space, we expect several launches in US over next 5 years, but less in other HICs and even less in UMICs and LMICs. Therefore, we see the HAP/VAP market further evolving into a space with several launches of relatively undifferentiated products, which will be driven by costs and stewardship considerations
- In this situation, **we expect a pronounced order of entry effect with limited patient share potential for later entrants such as Tx2**

Summary of Commercial Analyis for Thereapeutic 2 (BSI).

Product	Company	Highest Phase	Indication	Class	RoA	Expected activity against							Innovation				
						CRE											
						Class A ESBL	Class A KPC	Class D OXA	Class B MBL	CRAB	CRPA	R	NCR	CC	T	MoA
ZERBAXA (Ceftolozane + tazobactam)	Merck	Launched	cUTI, cIAI, HAP/VAP	BL / BLI combo	IV	■	-	-	-	-	■	✓	-	-	✓	-
AVYCAZ/ZAVICEFTA (Avibactam + ceftazidime)	AbbVie/Pfizer	Launched	cUTI, cIAI, HAP/VAP	BL / BLI combo	IV	■	■	■	■	-	■	✓	-	-	-	-
VABOMERE (Vaborbactam + meropenem)	Melinta/Menarini	Launched	**BSI**, cUTI, cIAI, HAP/VAP	Boronate BLI + carbapenem	IV	■	■	?	-	-	-	✓	-	✓	-	-
RECARBRIO (Relebactam + cilastatin)	Merck	Launched	cUTI, cIAI, HAP/VAP	DBO-BLI + carbapenem	IV	■	■	?	-	-	■	✓	-	-	-	-
FETROJA (Cefiderocol)	Shionogi	Launched	cUTI, HAP/VAP	Siderophore cephalosporin	IV	■	■	■	■	■	■	✓	?	-	-	-
ZEMDRI (Plazomycin)	Cipla	Launched	cUTI	Aminoglycoside	IV	■	■	■	■	-	-	✓	-	-	-	-
Durlobactam (ETX-2514) + **sulbactam**	Entasis	Phase 3	**BSI**, cUTI, HAP/VAP	DBO-BLI / + β-lactam-BLI	IV	-	-	-	-	■	-	✓	-	-	-	-
Taniborbactam (VNRX-5133) + **cefepime**	VenatoRx	Phase 3	cUTI	Boronate-BLI + cephalosporin	IV	■	■	■	■	-	?	✓	?	✓	-	-
Enmetazobactam (AAI-101) + **cefepime**	Allecra	Phase 3	cUTI, HAP/VAP	β-lactam BLI + cephalosporin	IV	■	-	-	-	-	-	✓	-	-	-	-
Avibactam + Aztreonam (PF-06947387)	Pfizer / AbbVie	Phase 3	**BSI**, cUTI, cIAI, HAP/VAP	BL / BLI	IV	■	■	-	■	-	✓	✓	-	-	-	-
Zidebactam + cefepime (WCK-5222)	Wockhardt	Phase 3	cUTI, HAP/VAP	DBO-BLI + cephalosporin	IV	■	■	■	■	-	✓	✓	-	-	-	-
BOS-228 (LYS-228)	Boston	Phase 2	cUTI, cIAI	Monobactam	IV	■	■	■	■	-	✓	✓	-	-	-	-
Benapenem	Sichuan	Phase 2	cUTI	Carbapenem	IV	-	-	-	-	-	■	✓	-	-	-	-
ETX0282 + cefpodoxime	Entasis	Phase 1	cUTI	DBO-BLI + cephalosporin	oral	■	■	-	-	-	-	✓	-	-	-	-
SPR-206	Spero	Phase 1	HAP/VAP	Polymyxin	IV	■	■	■	■	■	■	✓	-	-	-	-
TP-6076	Tetraphase	Phase 1	HAP/VAP	Tetracycline	IV	■	?	?	?	■	-	✓	-	-	-	-

Symbols: ■ active (at least in vitro); ? possibly active; - not or insufficiently active or activity not assessed; **Abbreviations for innovation**: R = overcoming some resistance mechanisms, NCR = no cross-resistance; CC = new class; T = new target; MoA = new mechanism of action

Product for GN BSI

Key resistance mechanism in GN BSI (based on gH epidemiology work)

Product Attribute [Analogue] Analysis for Therapeutic 1 (BSI) profile. Source: WHO 2020, 2019 antibacterial agents in clinical development, downloaded from https://www.who.int/publications/i/item/9789240000193; Clarivate Analytics Cortellis; FDA; EMA

Product	Company	Highest Phase	Indication	Class	RoA	Expected activity against							Innovation				
						CRE				CRPA	CRAB	R	NCR	CC	T	MoA
						Class A ESBL	Class A KPC	Class D OXA	Class B MBL							
ZERBAXA (Ceftolozane + tazobactam)	Merck	Launched	cUTI, cIAI, **HAP/VAP**	BL / BLI combo	IV		-	-	-		-	✓	-	-	-	-
AVICAZ/ZAVICEFTA (Avibactam + ceftazidime)	AbbVie/ Pfizer	Launched	cUTI, cIAI, **HAP/VAP**	BL / BLI combo	IV						-	✓	-	-	-	-
VABOMERE (Vaborbactam + meropenem)	Melinta/Menarini	Launched	BSI, cUTI, cIAI, **HAP/VAP**	Boronate BLI + carbapenem	IV		?	?	-	-	-	✓	-	✓	-	-
RECARBRIO (Relebactam + cilastatin)	Merck	Launched	cUTI, cIAI, **HAP/VAP**	DBO-BLI + carbapenem	IV			?	-	-	-	✓	-	-	-	-
FETROJA (Cefiderocol)	Shionogi	Launched	cUTI, **HAP/VAP**	Siderophore cephalosporin	IV							✓	?	-	-	-
ZEMDRI (Plazomycin)	Cipla	Launched	cUTI	Aminoglycoside	IV					-	-	✓	-	-	-	-
Durlobactam (ETX-2514) + **sulbactam**	Entasis	Phase 3	BSI, cUTI, **HAP/VAP**	DBO-BLI / + β-lactam-BLI	IV	-	-	-	-			✓	-	-	-	-
Taniborbactam (VNRX-5133) + **cefepime**	VenatoRx	Phase 3	cUTI	Boronate-BLI + cephalosporin	IV					-	-	✓	?	✓	-	-
Enmetazobactam (AAI-101) + **cefepime**	Allecra	Phase 3	cUTI, **HAP/VAP**	β-lactam BLI + cephalosporin	IV		-	-	-	-	-	✓	-	-	-	-
Avibactam + Aztreonam (PF-06947387)	Pfizer / AbbVie	Phase 3	BSI, cUTI, cIAI, **HAP/VAP**	BL / BLI	IV			-		?	-	✓	-	-	-	-
Zidebactam + cefepime (WCK-5222)	Wockhardt	Phase 3	cUTI, **HAP/VAP**	DBO-BLI + cephalosporin	IV				?	?	-	✓	-	-	-	-
BOS-228 (LYS-228)	Boston	Phase 2	cUTI, cIAI	Monobactam	IV							✓	-	-	-	-
Benapenem	Sichuan	Phase 2	cUTI	Carbapenem	IV	-	-	-	-			✓	-	-	-	-
ETX0282 + cefpodoxime	Entasis	Phase 1	cUTI	DBO-BLI + cephalosporin	oral				-		-	✓	-	-	-	-
SPR-206	Spero	Phase 1	**HAP/VAP**	Polymyxin	IV							✓	-	-	-	-
TP-6076	Tetraphase	Phase 1	**HAP/VAP**	Tetracycline	IV			?				✓	-	-	-	-

Product Attribute [Analogue] Analysis for Therapeutic 2 (pneumonia) profile. Source: WHO 2020, 2019 antibacterial agents in clinical development, downloaded from https://www.who.int/publications/i/item/9789240000193; Clarivate Analytics Cortellis; FDA; EMA

Aspect		AVYCAZ ZAVICEFTA	FETOJA	VABOMERE	ZEMDRI	RECARBIO	ZERBAXA	BAXDELA	XERAVA	TYGACIL
General	API(s)	Avibactam + ceftazidime	Cefiderocol	Vaborbactam + meropenem	Plazomicin	Relebactam + Imipenem + cilastatin	Ceftolozane + tazobactam	Delafloxacin	Eravacycline	Tigecycline
	Active in GN	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pneumonia HAP/VAP	Approval	US & EU: HAP/VAP Rapid tissue distribution, incl. lung (Bassetti et al. 2020)	US only: HAP/VAP	EU	✗	US only: HAP/VAP	US & EU: HAP/VAP Rapid tissue distribution, incl. lung (Bassetti et al. 2020)	US only: CAP	✗	US: CAP JP: pneumonia
	Data supporting potential benefit if not approved				✓ Favorable lung penetration, good candidate for HAP/VAP (Karaiskos 2019)			? Approved for CAP, but role for treatment of GN pneumonia questionable (Nicolsen 2019)	? Lack of clinical data for pneumonia (Bassetti et al. 2020)	✗ Inadequate PK/PD for mono tx of pneumonia (Karaiskos 2019)
BSI	Approval	✗	✗	EU Efficacy in BSI with CRE shown in Tango II Ph 3 trial (Bassetti et al. 2020)	✗	✗	✗	✗	✗	✗
	Data supporting potential benefit if not approved	✓ Clinically useful in primary BSI (Bassetti et al. 2020) In EU, CHMP recommended to add BSI associated to above indications in Jun-2020)	✓ Ongoing trial investigating efficacy in BSI vs. BAT: GAMECHANGER, NCT03869437) Ph 2, n = 284	(✓) Assume some efficacy as for aminoglycosides in general. Also some weak evidence from pivotal CARE trial in BSI that was stopped early (Bassetti et al. 2020)	? No clear evidence found	(✓) Anecdotal evidence on successful off-label use in DTR / MDR BSI	? Potentiality some benefit in GP BSI, but role for GN BSI questionable (Nicolsen 2019)	? Lack of clinical data for BSI (Bassetti et al. 2020) Evidence not conclusive yet (Nicolsen 2019)	✗ Inadequate PK/PD for mono tx of BSI (Karaiskos 2019)	

Therapeutic Analogues: Label (License) Analysis. (Sources: Bassetti et al. 2020, treatment of Infections due to MDR gram-negative bacteria with difficult to treat resistance, Antibiotics 9: 632; Karaiskos et al. 2019, The ”old" and the ”new" antibiotics for MDR gram-negative pathogens: For whom, when, and how, Front Public Health 7:151)

Aspect	AVYCAZ ZAVICEFTA	FETROJA	VABOMERE	ZEMDRI	RECARBRIO	ZERBAXA	BAXDELA	XERAVA	TYGACIL
General									
API	Avibactam + ceftazidime	Cefiderocol	Vaborbactam + meropenem	Plazomicin	Relebactam + Imipenem + cilastatin	Ceftolozane + tazobactam	Delafloxacin	Eravacycline	Tigecycline
Active in GN	✓	✓	✓	✓	✓	✓	✓	✓	✓
Active in PN	✗	✗	✗	✗	(✓)	(✓)	✓	✓	✓
Gram negative									
Acinetobacter baumannii		✓			✓				(✓)
Burkholderia cepacia complex		(✓)							
Citrobacter freundii	✓	(✓)	(✓)	(✓)				✓	✓
Citrobacter koseri	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)		(✓)	(✓)
Enterobacter aerogenes	(✓)		(✓)	(✓)			(✓)	(✓)	(✓)
Enterobacter cloacae	✓	✓	✓	✓	✓	✓	✓	✓	✓
Escherichia coli	✓	✓	✓	✓	✓	✓	✓	✓	✓
Haemophilus influenzae	✓				✓	✓	✓		✓
Klebsiella aerogenes		(✓)			✓	(✓)			
Klebsiella oxytoca	✓	(✓)	(✓)	(✓)	✓	✓	(✓)	✓	✓
Klebsiella pneumoniae	✓	✓	✓	✓	✓	✓	✓	✓	✓
Legionella pneumophila									✓
Morganella morganii	(✓)	(✓)	(✓)			(✓)			
Pasteurella multocida					(✓)				(✓)
Proteus mirabilis	✓	✓	(✓)	✓		✓	(✓)		
Proteus spec.		(✓)		(✓)					
Providencia rettgeri	(✓)	(✓)				(✓)			
Providencia stuartii			(✓)	(✓)		(✓)			
Pseudomonas aeruginosa	✓	✓	(✓)		✓	✓	✓		
Serratia marcescens	✓	✓	(✓)	(✓)	✓	✓			(✓)
Stenotrophomonas maltophilia		(✓)							(✓)
Anaerobic GN – various (details in FDA leaflet)					✓	✓		✓	✓

✓ active against most isolates in vitro and in clinical infections

(✓) in vitro data available, but clinical significance unknown

Top 3 organisms for MDR/XDR GN BSI, current and in 2040

Therapeutic Analogues: Pathogen Activity Analysis for Need Profiles. (Source: FDA prescribing information downloaded from www.accessdata.fda.gov). ***NB:*** *Was also performed for Therapeutic 2 (pneumonia).*

Aspect		AVYCAZ ZAVICEFTA	FETROJA	VABOMERE	ZEMDRI	RECARBRIO	ZERBAXA	BAXDELA	XERAVA	TYGACIL
	API	Avibactam + ceftazidime	Cefiderocol	Vaborbactam + meropenem	Plazomicin	Relebactam + Imipenem + cilastatin	Ceftolozane + tazobactam	Delafloxacin	Eravacycline	Tigecycline
General	Active in GN	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Active in PN	✗	✗	✗	✗	(✓)	(✓)	✓	✓	✓
Gram negative	Acinetobacter baumannii		✓			✓				(✓)
	Burkholderia cepacia complex		(✓)							
	Citrobacter freundii	✓	(✓)	(✓)	(✓)				✓	✓
	Citrobacter koseri	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)		(✓)	(✓)
	Enterobacter aerogenes	(✓)		(✓)	(✓)			(✓)	(✓)	(✓)
	Enterobacter cloacae	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Escherichia coli	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Haemophilus influenzae	✓				✓	✓	✓		✓
	Klebsiella aerogenes		(✓)			✓	(✓)			
	Klebsiella oxytoca	✓	(✓)	(✓)	(✓)	✓	✓	(✓)	✓	✓
	Klebsiella pneumoniae	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Legionella pneumophila									✓
	Morganella morganii	(✓)	(✓)	(✓)			(✓)			
	Pasteurella multocida					(✓)				(✓)
	Proteus mirabilis	✓	✓	(✓)	✓		✓	(✓)		
	Proteus spec.		(✓)		(✓)					
	Providencia rettgeri	(✓)	(✓)				(✓)			
	Providencia stuartii			(✓)	(✓)		(✓)			
	Pseudomonas aeruginosa	✓	✓	(✓)		✓	✓	✓		(✓)
	Serratia marcescens	✓	✓	(✓)	(✓)	✓	✓			(✓)
	Stenotrophomonas maltophilia		(✓)							(✓)
	Anaerobic GN – various (details in FDA leaflet)					✓	✓		✓	✓

✓ active against most isolates in vitro and in clinical infections — Priority organisms for Tx2 (TPP)

(✓) in vitro data available, but clinical significance unknown

Therapeutic Analogues: Pathogen Activity Analysis for Exsiting Branded Antibiotics. Source: FDA prescribing information downloaded from www.accessdata.fda.gov) ***NB:*** *Was also performed for Therapeutic 1 (BSI)*

Aspect		AVYCAZ ZAVICEFTA	FETROJA	VABOMERE	ZEMDRI	RECARBRIO	ZERBAXA	BAXDELA	XERAVA	TYGACIL
General	API(s)	Avibactam + ceftazidime	Cefiderocol	Vaborbactam + meropenem	Plazomicin	Relebactam + Imipenem + cilastatin	Ceftolozane + tazobactam	Delafloxacin	Eravacycline	Tigecycline
	Active in GN	✓	✓	✓	✓	✓	✓	✓	✓	✓
MOA	Type	BL / BLI combo	BL	BL / BLI combo	Aminoglycoside	BL/ BLI combo	BL / BLI combo	Fluoroquinolone	Tetracycline	Tetracycline
	Impact	inhibition of cell wall synthesis	inhibition of cell wall synthesis	inhibition of cell wall synthesis	Inhibition of protein synthesis	inhibition of cell wall synthesis	inhibition of cell wall synthesis	inhibition of DNA synthesis	Inhibition of protein synthesis	Inhibition of protein synthesis
ESBL	**General**	B	F B	B	B	F B	B K N		B N	
	Class A (CTX-M, TEM, SHV)	F	F B W	B W		F B W				
CRE	**General**		F	N	N	B			N	
	Carbapenem resistant Enterobacteriaceae									
	OprD									
	Class A (KPC-2/3, IMI, SME)	F B	F B W	B W	B	F B W	B K		B	
	Class B MBLs (IMP, NDM, VIM)	B	F B W	B W N	B N	B	B K N		B	
	Class C (AmpC)		F			B				
	Class D (OXA-48)	F B	F B W	B W	B	B W	B K		B	
CRAB	**General**	B	F B W	B X N	B	B W	B N		B N	
	Carbapenem resistant A. baumannii									
	Class C (AmpC)		F							
	Class D (OXA)		F B	B						
CRPA	**General**	B	F B W	B W	B	B W	B K		B N	
	Carbapenem resistant P. aeruginosa		F			F	B K			
	OprD	F	F			F	B K			
	Efflux pumps (Mex)	F	F			F	B K			
	Class B MBLs (IMP, VIM)		F B			B				
	Class C (AmpC)	F	F			B	B K			
	Class D (OXA)					B				

F From FDA leaflet
B From Bassetti et al. 2020
W From WHO 2020
K From Karaiskos et al. 2019
N From Nicolsen & Strang 2019

green active
orange Perhaps active
red not active

Therapeutic Analogues: Resistance Mechanism Activity Analysis for Exsiting Branded Antibiotics.Source: FDA prescribing information downloaded from www.accessdata.fda.gov; Bassetti et al. 2020, treatment of Infections due to MDR gram-negative bacteria with difficult to treat resistance, Antibiotics 9: 632; Karaiskos et al. 2019, The ”old" and the ”new" antibiotics for MDR gram-negative pathogens: For whom, when, and how, Front Public Health 7:151; Nicolsen & Stang 2019, New antimicrobials: where they fit within the armamentarium, downloaded from https://www.idse.net; WHO 2020, 2019 antibacterial agents in clinical development, downloaded from https://www.who.int/publications/i/item/9789240000193)

Aspect		AVYCAZ ZAVICEFTA	FETOJA	VABOMERE	ZEMDRI	RECARBIO	ZERBAXA	BAXDELA	XERAVA	TYGACIL
General	API(s)	Avibactam + ceftazidime	Cefiderocol	Vaborbactam + meropenem	Plazomicin	Relebactam + Imipenem + cilastatin	Ceftolozane + tazobactam	Delafloxacin	Eravacycline	Tigecycline
	Active in GN	✓	✓	✓	✓	✓	✓	✓	✓	✓
cUTI	Approval	US & EU	US only	US & EU	US	US only, only if tx options limited	US & EU	✗	✗	✗
	At least NI vs. SOC / BAT	✓ NI vs. doripenem RECAPTURE 1 & 2	✓ NI vs. imipenem / cilastatin Ph2 APEKS-cUTI	✓ Superiority vs. pip/taz Ph 3 TANGO-1	✓ NI vs. meropenem Ph3 EPIC	✗ Approval based on limited clinical data, see below 'other'	✓ NI vs. levofloxacin 2 Ph3, CXA-cUTI-10-04, CXA-cUTI-10-05			
cIAI	Approval	US & EU	✗	EU	✗	US only, only if tx options limited	US & EU	✗	US & EU	US & EU & JP
	At least NI vs. SOC / BAT	✓ NI vs. meropenem Ph3 RECLAIM 1 & 2		See below under other indications		✗ Approval based on limited clinical data, see below 'other'	✓ metronidazole + NI vs. meropenem 2 Ph3, CXA-cIAI-10-08, CXA-cIAI-10-09		✓ NI vs. eftapenem (Ph3 INGITE-1) and NI vs. meropenem (Ph3 IGNITE 4)	✓ NI vs. imipenem / cilastatin, Study 301 Ph3 NCT00081744
Pneumonia HAP/VAP CAP	Approval	US & EU: HAP/VAP	US only: HAP/VAP	EU	✗	US only: HAP/VAP	US & EU: HAP/VAP	US only: CAP	✗	US: CAP JP: pneumonia
	At least NI vs. SOC / BAT	✓ NI vs. meropenem Ph3 REPROVE	✓ NI vs. meropenem Ph 3 APEKS-NP	✓ See below under other indications		✓ NI vs. piperacillin / tazobactam Ph3 RESTORE-IMI-2	✓ NI vs. meropenem Ph 3 ASPECT-NP	✓ NI vs. moxifloxacin Ph 3 ML-3341-306		✓ CAP: NI vs. levofloxacin Studies 308 & 313
BSI	Approval	✗	✗	✓ See below under other indications	✗	✗	✗	✗	✗	✗
	At least NI vs. SOC / BAT									
Other	Other	EU: infection with aerobic GN with limited tx options	EU: infection with aerobic GN with limited tx options	EU: infection with aerobic GN with limited tx options	n.a.	EU: infection with aerobic GN with limited tx options	n.a.	US only: ABSSSI	n.a.	US & EU & JP: cSSSI
	At least NI vs. SOC / BAT	✓ NI vs. BAT in ceftazidime-resistant cUTI and CIAI infections Ph3 REPRISE	✗ Approval based limited clinical data plus non-clinical data, incl. PK/PD and in vitro activity	✓ Superiority (mortality, cure, safety) vs. BAT in serious infections with CRE: incl. cUTI, cIAI, HAP/VAP and BSI (Ph 3 TANGO-2)		✗ Approval based on limited data, incl. Ph3 RESTORE-IMI-1 colistin + imipenem in imipenem resistant cUTI, cIAI, HAP/VAP		✓ NI vs. vancomycin and aztreonam, 2 Ph3, RX-3341-302, RX-3341-303		✓ NI vs. vancomycin and aztreonam, Study 305 Ph 3 NCT00228410

Therapeutic Analogues: Approval Pathway Analysis for Exsiting Branded Antibiotics. With few exceptions, analogue approvals were based on non-inferiority vs. current standard of care (SOC) or best available therapy (BAT) Source: Clarivate Analytics Cortellis; FDA; EMA

Product	Geography	Indication	Label	Comments
ZEMDRI Cipla	US	cUTI	June 2018	In pts 18 years or older for the treatment of cUTI, including pyelonephritis, caused by the following susceptible microorganism(s): E. coli, K. pneumoniae, P. mirabilis and Enterobacter cloacae; ZEMDRI should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms.	Filed for both cUTI and BSI; CRL for BSI (CARE study not sufficient evidence) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210303Orig1s000lbl.pdf
BLACK BOX WARNING	EU	cUTI	June 2020	Withdrawn	EMA concerns over sterilisation method
RECARBRIO Merck	US	cUTI cIAI	July 2019	In patients with limited or no alternative treatment options, for the treatment of cUTI, including pyelonephritis, and cIAI cased by the following GN: Enterobacter cloacae, Escherichia coli, Klebsiella aerogenes, K. pneumoniae, and P. aeruginosa.	https://www.merck.com/product/usa/pi_circulars/r/recarbrio/recarbrio_pi.pdf
		HAP/ VAP	June 2020	In adults, with HAP/VAP caused by : Acinetobacter calcoaceticus-baumannii complex, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella aerogenes, Klebsiella oxytoca, K. pneumoniae, P. aeruginosa, and S. marcescens.	Based on pivotal Ph 3 RESTORE-IMI-2
	EU	General	Feb 2020	Treatment of infections due to aerobic GNB in adults with limited treatment options	
FETROJA Shionogi	US	cUTI	Nov 2019	In adults who have limited or no alternative treatment options, for the treatment of cUTI , including pyelonephritis caused by susceptible GN: E. coli, K. pneumoniae, Proteus mirabilis, P. aeruginosa, and Enterobacter cloacae complex	Fast TRACK : Oct 2019
	US	HAP/VAP	Pre-Reg	Not yet approved	PDUFA Sep-2020 (APEKS-NP trial)
	EU	General	April 2020	Treatment of infections due to aerobic GNB in adults with limited treatment options	Filing was for GN infections with limited tx options
XERAVA Tetraphase	US	cIAI	Aug 2018	Treatment of cIAI in pts 18 years and older CAUSED BY SUSCEPTIBLE ORGANISMS: E. coli, K. pneumoniae, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, Enterococcus faecalis, Enterococcus faecium, S. aureus, Streptococcus anginosus group, Clostridium perfringens, Bacteroides species	based on data from the IGNITE 1 (NCT01844856) and IGNITE 4 (NCT02784704) phase III clinical trials
		cUTI	-	Failed at Phase 3 : IGNITE 3 (NCT03032510, vs. ertapenem)	
	EU	cIAI	Sep 2018	Indicated to treat complicated intra-abdominal infections in adults	Based on data from the IGNITE 1 trial

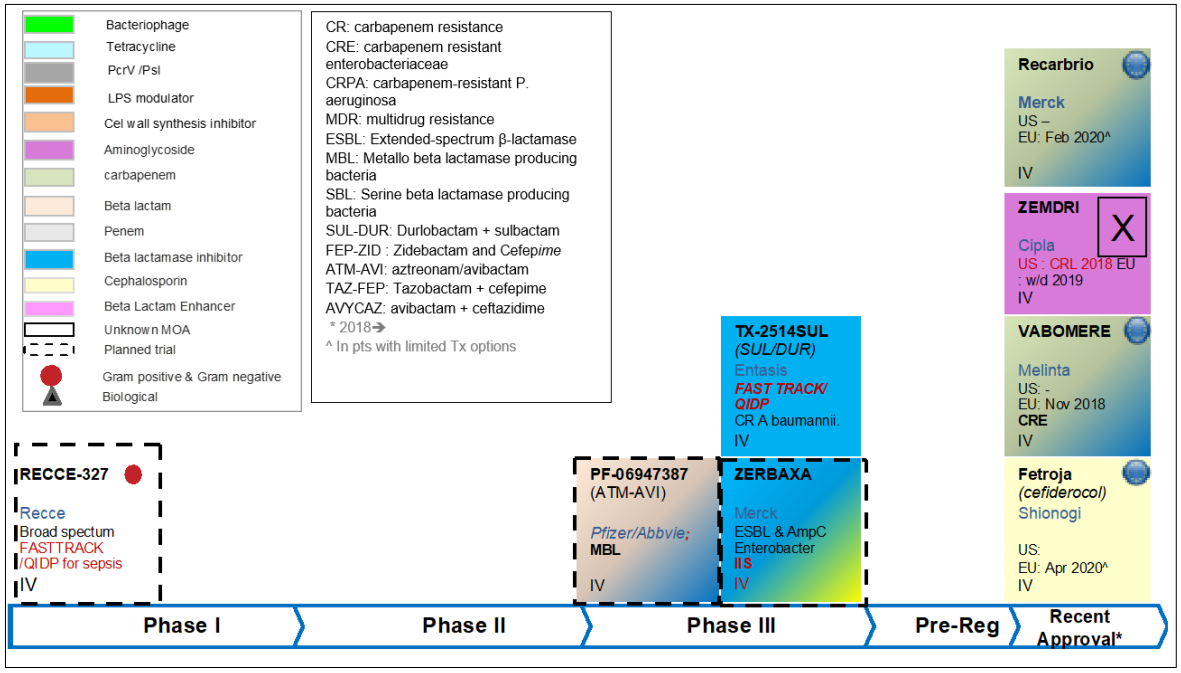
Therapeutic Analogues: Label (license) Analysis for Exsiting Branded Antibiotics (Part I). Source: Clarivate Analytics Cortellis; FDA; EMA

Product	Geography	Indication	Label	Comments
VABOMERE Melinta/ Menarini	US	cUTI	Aug 2017	In adults with cUTI including pyelonephritis caused by the following susceptible microorganisms: E. coli, K. pneumoniae, and Enterobacter cloacae species complex.	Based on TANGO-1 (cUTI & AP) and TANGO-2 (cUTI, HAP/VAP, BSI) data https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf US filed on TANGO-1 & supplementary data from TANGO-2
	EU	cUTI, cIAI HAP/VAP BSI	Nov 2018	Treatment of cIAI, cUTI (including pyelonephritis), HAP/VAP, and *bacteraemia that occurs in association with any of those infections* and infections due to aerobic Gram-negative organisms where treatment options were limited	
AVYCAZ ZAVICEFTA Pfizer/ AbbVie	US	cUTI	Feb 2015	In adults & paediatrics with cUTI/caused by susceptible Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Citrobacter freundii complex, Proteus mirabilis, and Pseudomonas aeruginosa. Paediatrics added Mar 2019	Initial approval "accelerated approval" HAP/VAP & BSI was also initial filing but voted down by advisory committee BSI not resubmitted
		cIAI	Feb 2015	In adults & paediatrics *in combo with metronidazole*, in cIAI caused by susceptible GNB: E. coli, K. pneumoniae, P. mirabilis, Enterobacter cloacae, Klebsiella oxytoca, Citrobacter freundii complex, and P. aeruginosa; Paediatrics added Mar 2019	
	EU	HAP/VAP	Feb 2018	In adults with HAP/VAP caused by the following susceptible GN microorganisms: K. pneumoniae, Enterobacter cloacae, E. coli, Serratia marcescens, Proteus mirabilis, Pseudomonas aeruginosa, and Haemophilus influenzae	Based on REPROVE study (initial filing with cUTI / cIAI was voted down by advisory committee
		cUTI, cIAI, HAP/VAP	June 2016	In adults with cIAI & cUTI, including pyelonephritis; and, the treatment of aerobic GN infections in adults who have limited treatment options; Paediatrics filed for cUTI & cIAI	Based on RECATURE-1 and -2 and REPROVE trials
ZERBAXA Merck	US	cUTI	Dec 2014	In adults with cUTI caused by: E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa.	
		cIAI	Dec 2014	In adults, *in combo with metronidazole*, in cIAI caused by following GNB and GPB: E. cloacae, E. coli, K. oxytoca, K. pneumoniae, P. mirabilis, P. aeruginosa, Bacteroides fragilis, S. anginosus, Streptococcus constellatus, and Streptococcus salivarius.	
	EU	HAP/VAP	June 2019	HAP/VAP in adults caused by GNB: Enterobacter cloacae, E. coli, H. influenzae, K. oxytoca, K. pneumoniae, P. mirabilis, P. aeruginosa, and S. marcescens)	
		cUTI, cIAI	Sep 2015	In adults for the treatment of cIAI, acute pyelonephritis, cUTI (designated susceptible microorganisms: E cloacae, E coli, K oxytoca, K pneumoniae, P mirabilis, P aeruginosa, S anginosus, S constellatus and S salivarius), and HABP/VABP	ASPECT-NP trial
		HAP/VAP	Aug 2019		

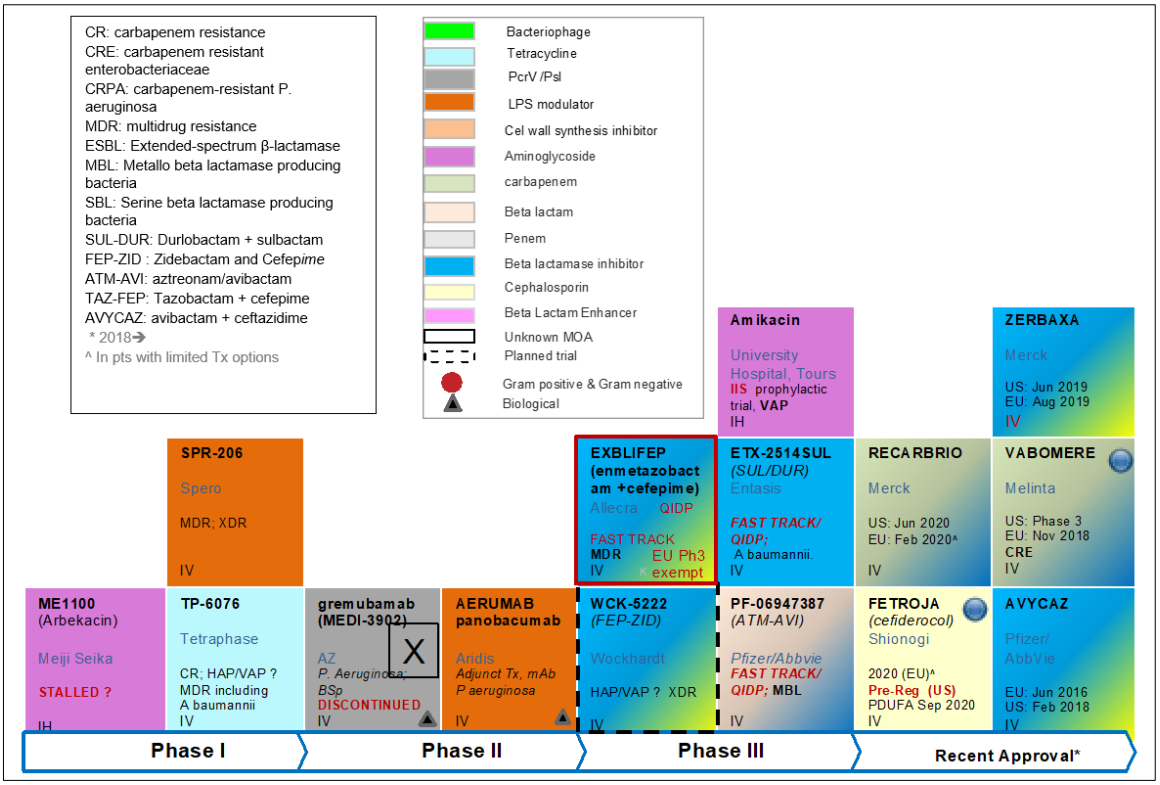
Therapeutic Analogues: Label (license) Analysis for Exsiting Branded Antibiotics (Part II). Source: Clarivate Analytics Cortellis; FDA; EMA

Product	Geography	Label	Comments
FORTAZ Ceftazidime GSK cephalosporin 1st launched in 1983	US	**Bacterial septicemia** caused by P. aeruginosa, Klebsiella spp., Haemophilus influenzae, E. coli, Serratia spp., Streptococcus pneumoniae, and Staphylococcus aureus (methicillin-susceptible strains).	Also indicated for: Lower Respiratory Tract Infections; SSSI, UTI (uUTI and cUTI); Bone and Joint Infections ; Gynaecologic Infections, IAI, CNS infections https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050578s061,050634s028lbl.pdf
	EU	**Bacteraemia** that is associated with in the labelled indications	Indicated for: hospital acquired pneumonia, complicated skin and soft tissue infections, bone and joint infections, chronic otitis media, complicated intra-abdominal infections, meningitis and complicated urinary tract infections https://www.ema.europa.eu/en/medicines/human/referrals/fortum
ROCEPHIN Ceftriaxone Roche cephalosporin 1st launched in 1982	US	**Bacterial septicemia** caused by S. aureus, Streptococcus pneumoniae, E. coli, Haemophilus influenzae or K. pneumoniae	Multiple indications: Lower respiratory tract infections; SSSI; UTI, uncompl. gonorrhoeae, pelvic inflammatory infections; bone & joint infections; IAI, meningitis & surgical prophylaxis https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/0550585s063lbl.pdf
	EU	**Bacteraemia** suspected to be caused by any of the labelled indications	Indicated for HAP, CAP, acute otitis media, IAI, cUTI incl. pyelonephritis ;infections of bones and joints; complicated skin and soft tissue infections; STIs gonorrhoea and syphilis; bacterial endocarditis; https://www.ema.europa.eu/en/medicines/human/referrals/rocephin
PRIMAXIN imipenem and cilastatin Merck Broad spectrum US initial approval in 1985	US	**Bacterial Septicemia :** indicated for the treatment of bacterial septicemia caused by susceptible strains of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing isolates), Enterobacter species, E. coli, Klebsiella species, P. aeruginosa, Serratia species, Bacteroides species	Also indicated for: Lower respiratory tract Infections, SSSI, UTI (uUTI and cUTI), bone & joint infections, gynaecologic Infections, IAI, Endocarditis https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050587s074lbl.pdf
	EU	Treatment of bacteraemia that is associated with or suspected to be associated with the indicated infections	Indicated for: cIAI, severe pneumonia including HAP and VAP, intra- and post-partum infections, cUTI, complicated skin and soft-tissue infections, use for fever in neutropenic patients when infection is suspected

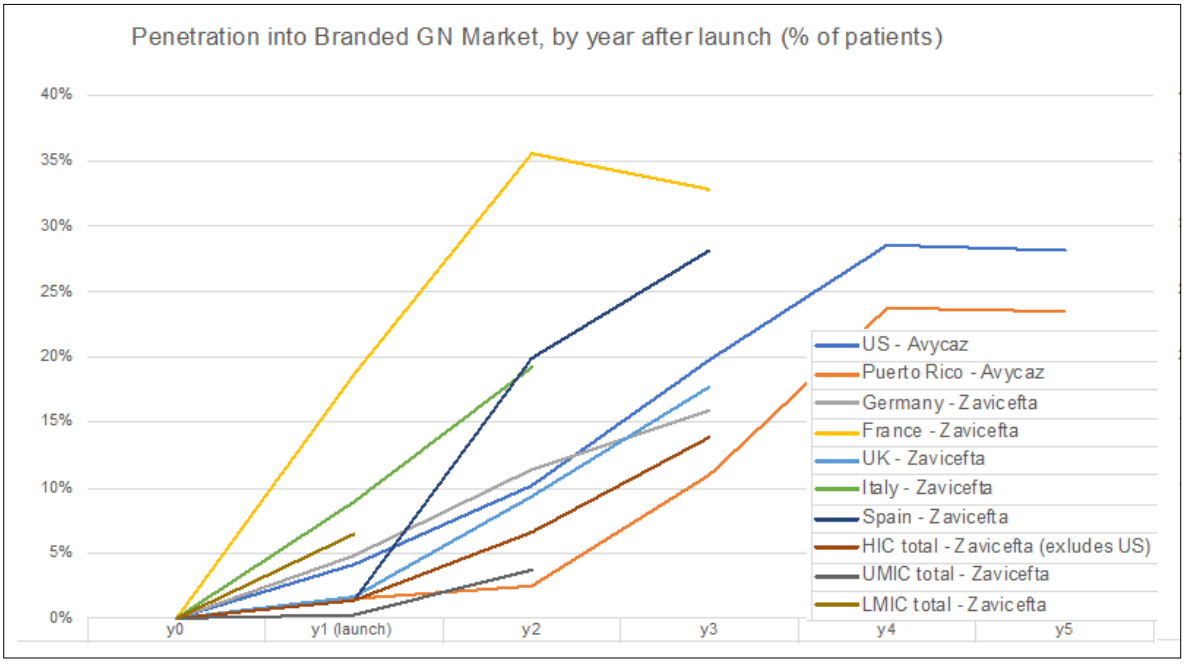
Therapeutic Analogues: Label (license) Analysis for Older Antibiotics Used In Critically Ill Patients. Source: Timsit et al Intensive Care Med. 2020; 46(2): 266–284.; FDA and EMA

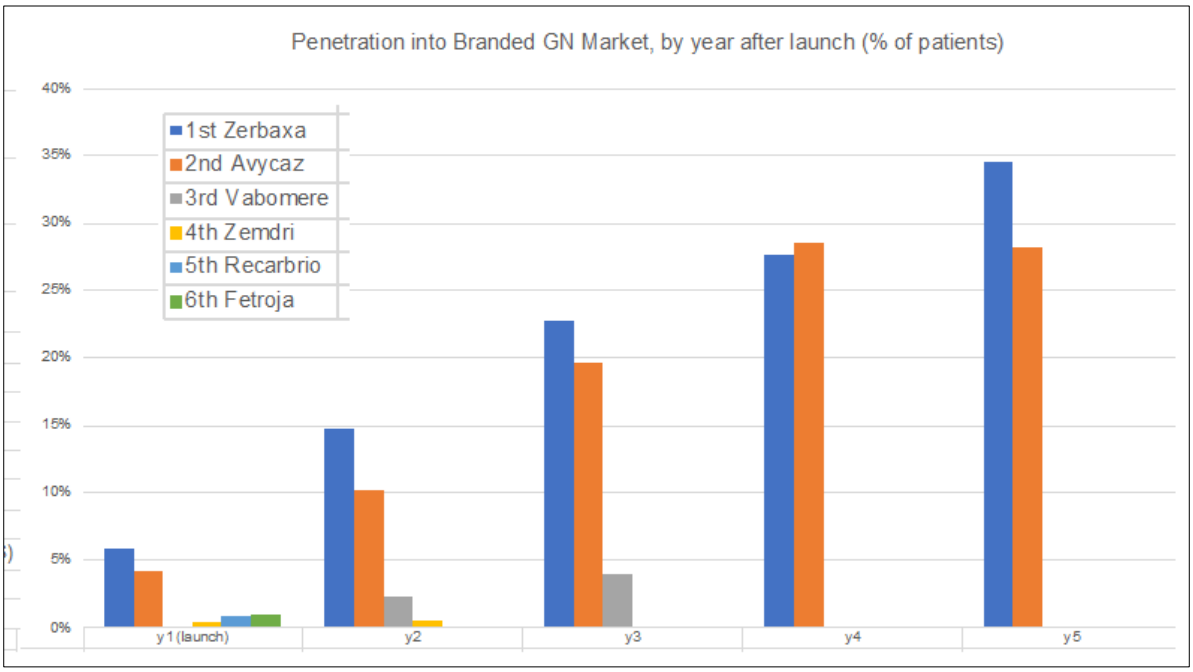


Commercial Context: Clinical Development Landscape (therapeutic 1, BSI).. Source: Clarivate Analytics' Cortellis; www.clinicaltrials.gov; www.clinicaltrialsregister.eu/

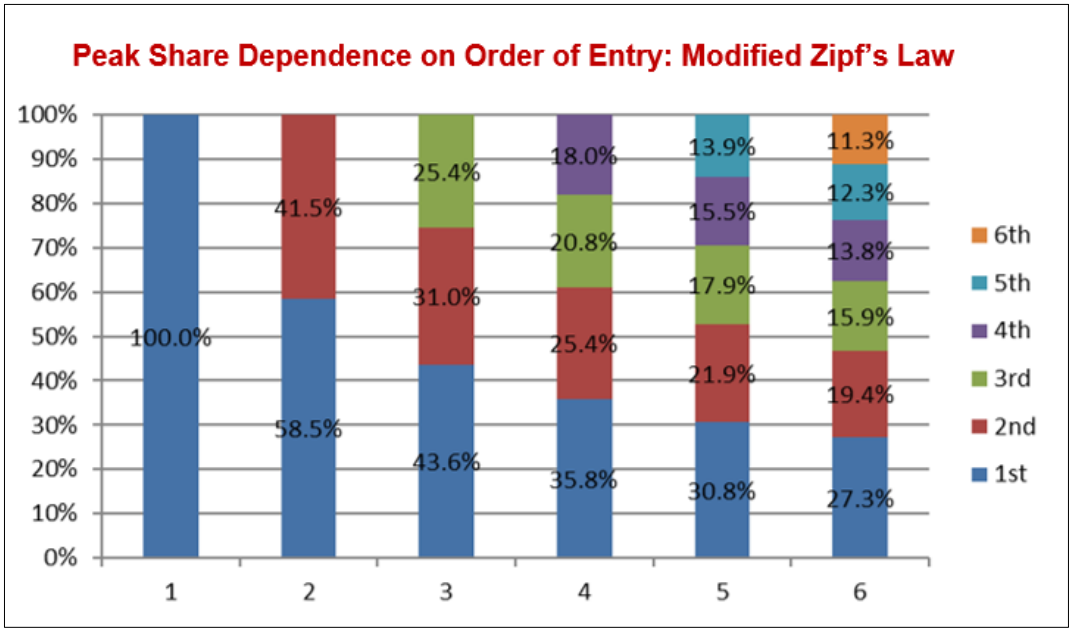


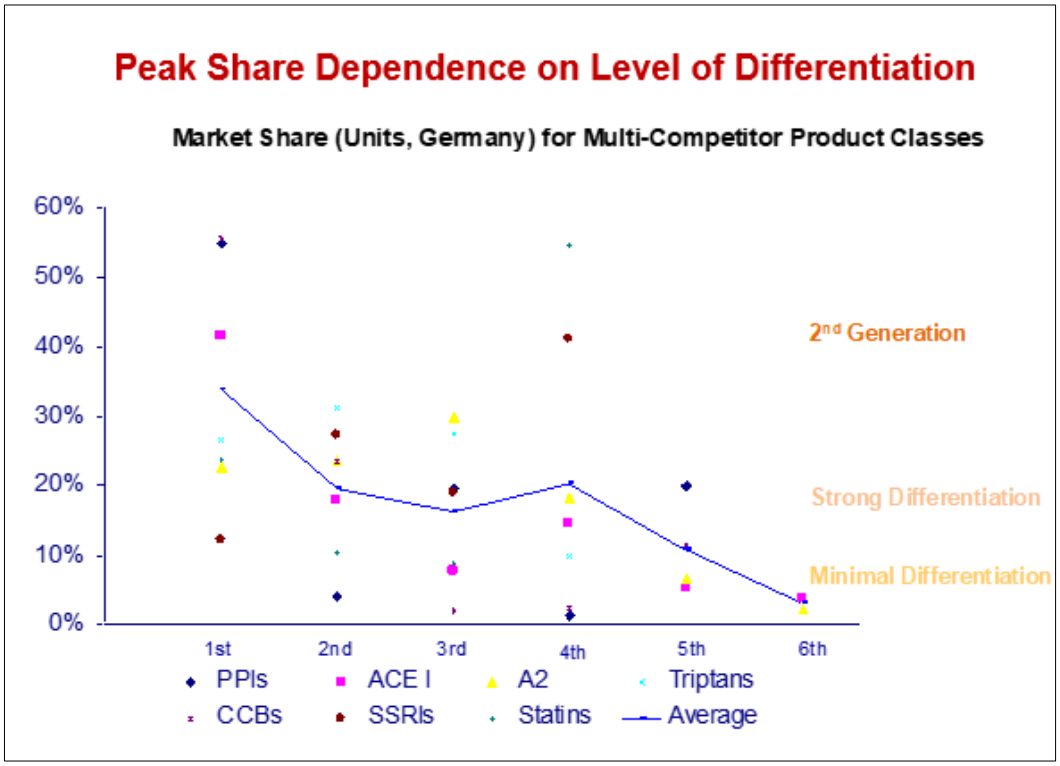
Commercial Context: Clinical Development Landscape (therapeutic 2, GN HAP/VAP). Source: Clarivate Analytics' Cortellis; www.clinicaltrials.gov; www.clinicaltrialsregister.eu/





Commercial Context: Commercial Differentiation and Positioning (US market: Order of Entry (top) & Uptake Effects (bottom). Source: IQVIA data





Commercial Context: Commercial Differentiation and Positioning (US market: Peak Share Dependence by OOE (top) & Level of Differentiation (bottom). Sources: https://business.illinois.edu/working_papers/papers/02-0125.pdf; http://www.celforpharma.com/insight/5-most-useful-sales-forecasting-techniques-pharmaceutical; Arzneimittelverordnungsreport 2003, Wood Mackenzie PharmaView

Commercial Context: Tx 1 (BSI) Assumptions for Modeling Derived from Analysis.

Geography	Price / pt / year		Peak share in GN branded market (% of patients)		Launch Year		Time to peak share & adoption curve	
	Value	Rationale	Value	Rationale	Value	Rationale	Value	Rationale
US	**$10,000**	▪ Based on average $/Pt/year of Avycaz, Vabomere, Recarbrio, and Fetroja in 2020	**5%**	▪ High level assumption by groupH, based on the following considerations (for details see prior slide): ▪ 25% is upper limit for early entrant targeting later line MDR/XDR with broad label (Avycaz) ▪ Few current and future competitors with label in BSI; However, Tx1 TPP does not assume clinical superiority ▪ We therefore assume restriction to late lines based on costs and stewardship considerations - e.g. use only for difficult to treat resistance (DTR) BSI that has proven to be refractory to products targeting the primary site of infection	**2025**	▪ gH high level assumption	**4 years, linear**	▪ Based on uptake of Avycaz in US
Other HIC (excl. US)	**$4,500**	▪ Based on average $/Pt/year of Zavicefta and Vabomere in 2020	**7%**	▪ Higher than in US, assumes fewer launches, e.g. less competition	**2026**	▪ 1 year delay vs. US	**5 years, linear**	▪ Time to peak longer due to sequential launches
UMIC	**$4,500**	▪ Same as in HIC, based on Zavicefta situation 2020	**10%**	▪ Higher than in US and HIC, assumes fewer launches, e.g. less competition	**2027**	▪ 2 year delay vs. US	**7 years, linear**	▪ Time to peak longer due to sequential launches
LMIC	**$3,000**	▪ 30% less than UMIC, based on Tygacil and Avycaz pricing difference in 2020	**12%**	▪ Higher than in US, HIC, and UMIC, assume fewer launches, e.g. less competition	**2028**	▪ 3 year delay vs. US	**7 years, linear**	▪ Time to peak longer due to sequential launches

Commercial Context: Tx 2 (pneumonia) Assumptions for Modeling Derived from Analysis.

Geography	Price / pt / year		Peak share in GN branded market (% of patients)		Launch Year		Time to peak share & adoption curve	
	Value	Rationale	Value	Rationale	Value	Rationale	Value	Rationale
US	**$10,000**	▪ Based on average $/Pt/year of Avycaz, Vabomere, Recarbrio, and Fetroja in 2020	**3%**	▪ High level assumption by groupH, based on the following considerations (for details see prior slide): ▪ 25% is upper limit for early entrant targeting later line MDR/XDR with broad label (Avycaz) ▪ Several current and future competitors with label in GN pneumonia; Tx2 TPP does not assume clinical superiority ▪ We therefore assume restriction to late lines based on costs and stewardship considerations – e.g. use only for difficult to treat resistance (DTR) GN pneumonia that has proven to be refractory to several earlier lines of therapy	**2025**	▪ gH high level assumption	**4 years, linear**	▪ Based on uptake of Avycaz in US
Other HIC (excl. US)	**$4,500**	▪ Based on average $/Pt/year of Zavicefta and Vabomere in 2020	**5%**	▪ Higher than in US, assumes fewer launches, e.g. less competition	**2026**	▪ 1 year delay vs. US	**5 years, linear**	▪ Time to peak longer due to sequential launches
UMIC	**$4,500**	▪ Same as in HIC, based on Zavicefta situation 2020	**7.5%**	▪ Higher than in US and HIC, assumes fewer launches, e.g. less competition	**2027**	▪ 2 year delay vs. US	**7 years, linear**	▪ Time to peak longer due to sequential launches
LMIC	**$3,000**	▪ 30% less than UMIC, based on Tygacil and Avycaz pricing difference in 2020	**10%**	▪ Higher than in US, HIC, and UMIC, assume fewer launches, e.g. less competition	**2028**	▪ 3 year delay vs. US	**7 years, linear**	▪ Time to peak longer due to sequential launches

Aspect	AVYCAZ ZAVICEFTA	FETROJA	VABOMERE	ZEMDRI	RECARBRIO	ZERBAXA	BAXDELA	XERAVA	TYGACIL	CUBICIN	ZYVOX
API	Avibactam + ceftazidime	Cefiderocol	Vaborbactam + meropenem	Plazomicin	Imipenem + relebactam + cilastatin	Ceftolozane + tazobactam	Delafloxacin	Eravacycline	Tigecycline	Daptomycin	Linezolid
Company	Pfizer, AbbVie	Shionogi	Melinta / Menarini	Cipla	Merck	Merck	Melinta / Menarini	Tetraphase Pharma	Pfizer	Merck	Pfizer
FDA leaflet revision	03/2019	09/2020	08/2017	06/2018	06/2020	06/2019	10/2019	08/2018	01/2020	03/2017	09/2013
FDA leaflet dosage (normal kidney function, creatine clearance >50 mL/min)	1 pack with 0.5g / 2g every 8 hours	For cUTI (incl. PN) and HABV/VAP): 2 g every 8 h	cUTI & PN: 2 packs with 1g/1g each (=2g/2g) every 8 h	cUTI: 15 mg/kg every 24 h	For all indications: 1 pack with 1.25g (500/500/250) every 6 h	cUTI and cIAI: 1 pack with 1g/0.5g every 8h HAP/VAP: 2 pack with total 2g / 1g every 8h	300 mg IV OR 450mg Tablet every 12 h	1mg/kg every 12 h	50 mg every 12h	cSSSI: 4mg/kg every 24h S. aureus BSI: 6mg/kg every 24h	Adults: 600mg IV or oral very 12 h Pediatric: 10mg/kg IV or oral very 8h
Per day	3 packs with 0.5g / 2g	6 packs with 1 g each / d	6 packs with 1g/1g each	For 70 kg adult: ~1000mg/day corresponding to 20 ml of 50mg/ml per day (= 2 x vial with 10ml each)	4 packs with 1.25 g (500/500/250) each	cUTI and cIAI: 3 packs with 1g/0.5g each HAP/VAP: 6 packs with 1g/0.5g each	2 packs with 300 mg each IV / d OR 2 tablets with 450mg each / d	For 70Kg adult: ~3 packs with 50 mg each (total 140 mg, 2 x 70 mg) / d	2 packs with 50 mg each / d	For 70Kg adult: cSSSI: 280mg / d, ~1 pack with 350mg / d S. aureus BSI: 420 g / d, ~1 pack with 350mg / d	Adults: 300 ml IV with total 600 mg or 2 tablets with 600mg each
FDA label Recommended duration of tx	cUTI & PN: 7-14d cIAI: 5-14d HAPB/VAPB: 7-14 d	7-14 d	cUTI & PN: up to 14 d	cUTI: 4-7 d	4-14 d	cUTI & PN: 7 d cIAI: 4-14 d HAP/VAP: 8-14 d	ABSSSI: 5-14 d CABP: 5-10 d	cIAI: 4-14 d	cIAI: 5-14 d CAP: 7-14 d	cSSSI: 7-14 d S. aureus BSI: 2-6 weeks	CAP, HAP/VAP incl. BSI, SSSI: 10-14d Vancomycin-resistant E. faecium infections, incl. BSI: 14-28d

Commercial Context: Assumptions Used for Therapeutic Patient Conversionns.

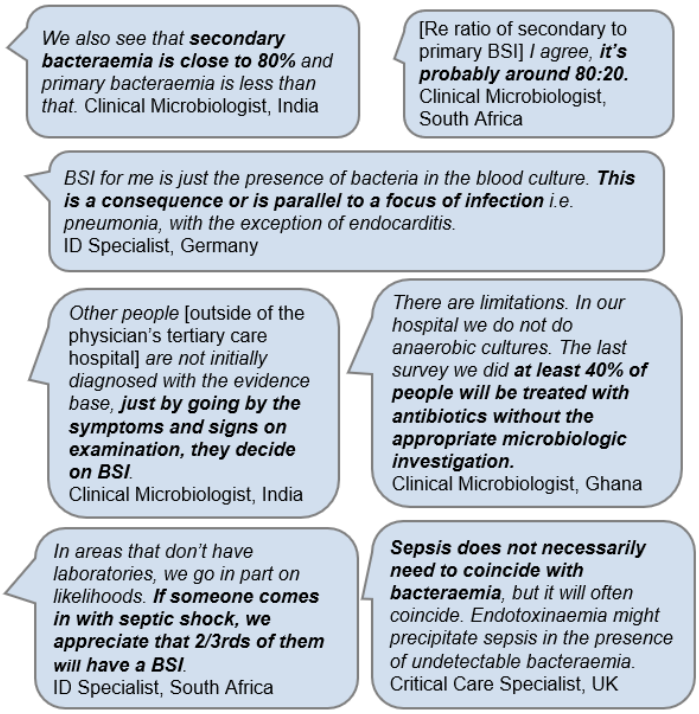
Primary Research

Introductions and data source interviews with 15 EAG members completed	✓
13 local expert HCPs contacted by groupH for data sourcing or validation	✓
2 Online 90 min 'BSI label' - Boards with 7 HCPs in HICs and LMICs	✓
10 Dx + Tx industry executives and 7 clinicians in HIC and LMIC interviewed	✓
2 Public Sector Donor (Global Fund) Representatives interviewed	✓

Overview- Delivered Content, Key Activities & Market Research.

- **The vast majority of BSIs are secondary to another focus of infection**
  - Primary BSIs occur in relatively few (~ 20%) cases and are mostly Gram +ve (including *S.aureus* line infections and non-typhi salmonella in HIV patients)
- **Being a 'side finding' of another focus of infection, BSI is not perceived to be a syndrome in its own right like other infections e.g. pneumonia but indicating a particular severity in a patient**
  - Knowledge of the presence of a BSI may impact duration of treatment but not treatment itself
  - In higher resource settings BSI will also trigger further investigation for the primary infection sources
- **Diagnosis of BSI in low resource settings without access to microbiology will often be made on clinical signs alone i.e. fever, chills, abnormal vital signs, septic shock**
  - A significant proportion of patients in these settings will be treated with antibiotics without appropriate microbiological investigation
- **There is a degree of overlap between BSI and sepsis**
  - Whilst patients presenting with sepsis are more likely to have had bacteraemia at some point, a BSI does not inevitably result in sepsis

Commercial Context: Secondary Research Insights – All Income Groups Clinician Prespectives on Need Profiles & Particualrly BSI label.



Summary Insights from HIC & LMIC Infectious Disease and Clinical Microbiology Specialists Source: Online expert advisory boards @ 90 minutes each have been conducted in HICs (n = 3 respondents from UK, US, Germany) and LMICs (n = 4 respondents from India, Ghana and South Africa).

3. Diagnostics (Clinical & Commercial Context)

3a Diagnostic 1 (Bacterial versus. Other)

Dx1 – Analogue Analysis

- groupH found only two currently existing relevant analogues for Dx1
  - **MeMed BV** – 3 protein markers, qualitative, algorithm, result read by instrument (Sensitivity 91%, Specificity 94%)
  - **RPS FebriDx** – 2 markers, RDT (Sensitivity 80-95%, Specificity 76-94%)
- Both include CRP as one of their markers; determine bacterial vs. viral, NOT bacterial vs. non-bacterial
- Both assays have insufficient sensitivity and specificity to "give users the confidence to act upon its result (to eliminate harmful treatment decisions and inform more targeted antibiotic use)."
- Not widely used, even in HIC
- MeMed technology has the capability needed to potentially meet the EAG TPP requirements: multiplex, quantitative, and algorithm, but will require an instrument – limiting uptake in resource limited settings

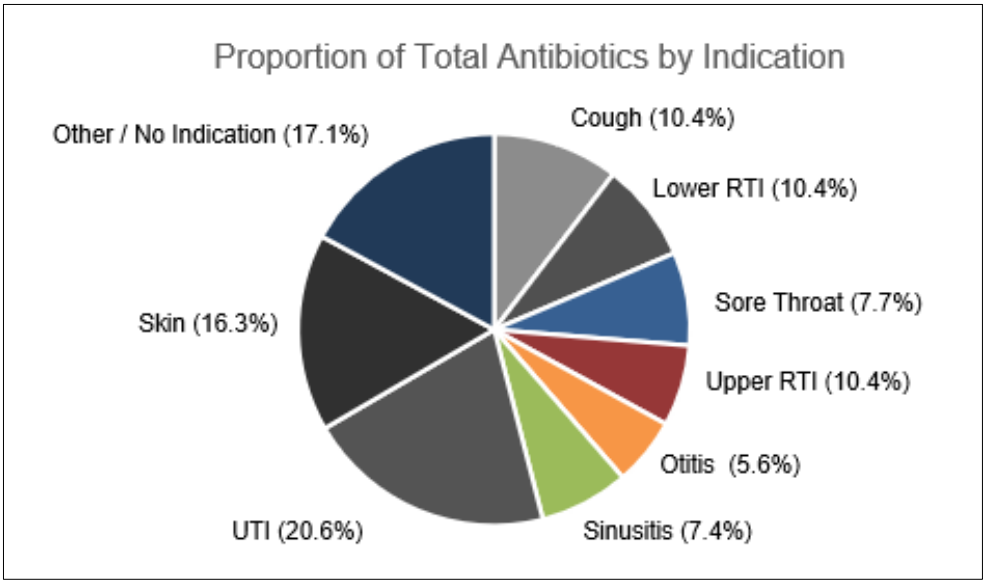
Summary of Analogue Analyis for Product Attribtes of Diagnostic 1.

Dx1 Analogues

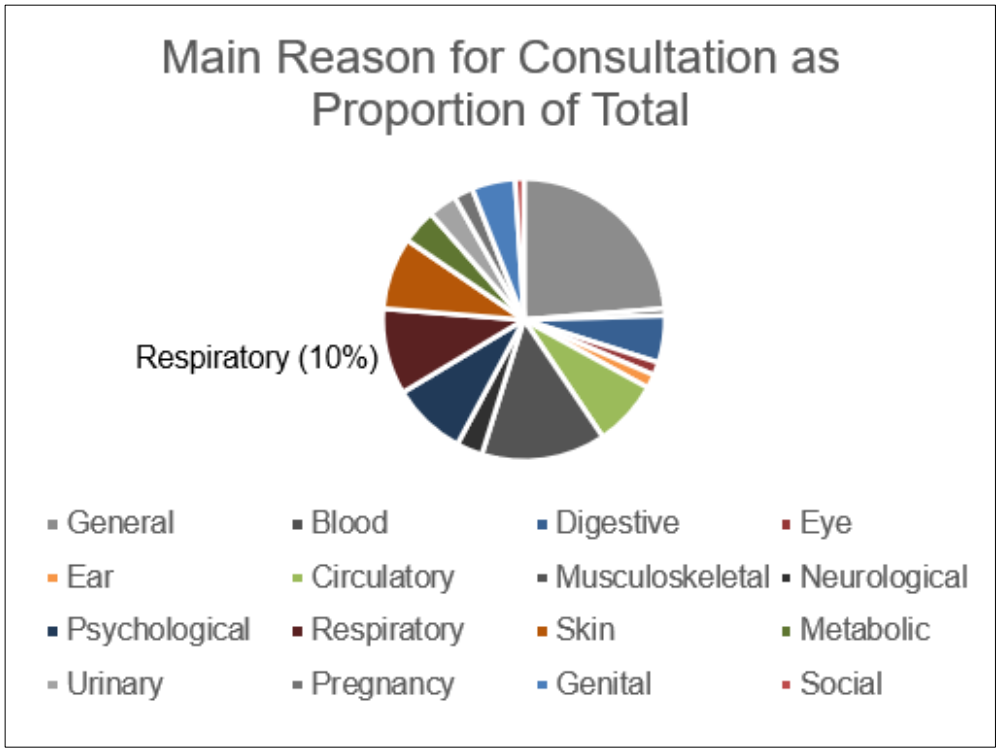
Criteria	Dx1	MeMed Dx – MeMed BV	RPS - FebriDx	Comments
Technical				
Target Indication	Acute febrile illness; respiratory infection in patients > 2 months	●	◕	RI only for FebriDx
Intended Use	Determine if infection is bacterial or not bacterial (not bacterial vs. viral); reduce use of antibiotics	◔	◔	Bacterial vs. viral only
Assay Type	Multiplex, quantitative, algorithm to interpret results	●	○	
Time to Result	<15 minutes	●	●	
Performance	High sensitivity (≥95%) and specificity (≥98%); confidence to act on result	◔	○	Major gap, both tests
Specimen type	Minimally invasive, easily obtained (e.g. capillary blood)	●	●	
Operational	Minimal storage reagents, training, easy to use and interpret	◕	●	
Commercial				
Target Geographies	All; must be usable in resource limited settings	◑	●	MeMed requires power
Target Markets	Public and private	◑	◕	
Target Setting	Point-of-care test all settings including community health setting	◕	●	FebriDx is RDT
Target User	Physicians, nurses, pharmacists, CHW, and medical support staff	◕	◑	MeMed requires interpretation
Cost per test	$5 ($1-3 for LMICs, aspirational)	Not known	●	FebriDx: £11.25
Instrument cost	$5,000	Not known	●	FebriDx: no reader
Overall Fit		◑	◔	Gaps: performance and intended use

Very High ● High ◕ Medium ◑ Low ◔ Very Low ○

Summary of Dx1 Analogue Analysis.



Diagnostic 1 (clinical context). Illustrative figure. Dx1 will be most useful in respiratory consultations In HICs & UMICS. Source: Analysis based on Journal of Antimicrobial Therapy 2018.



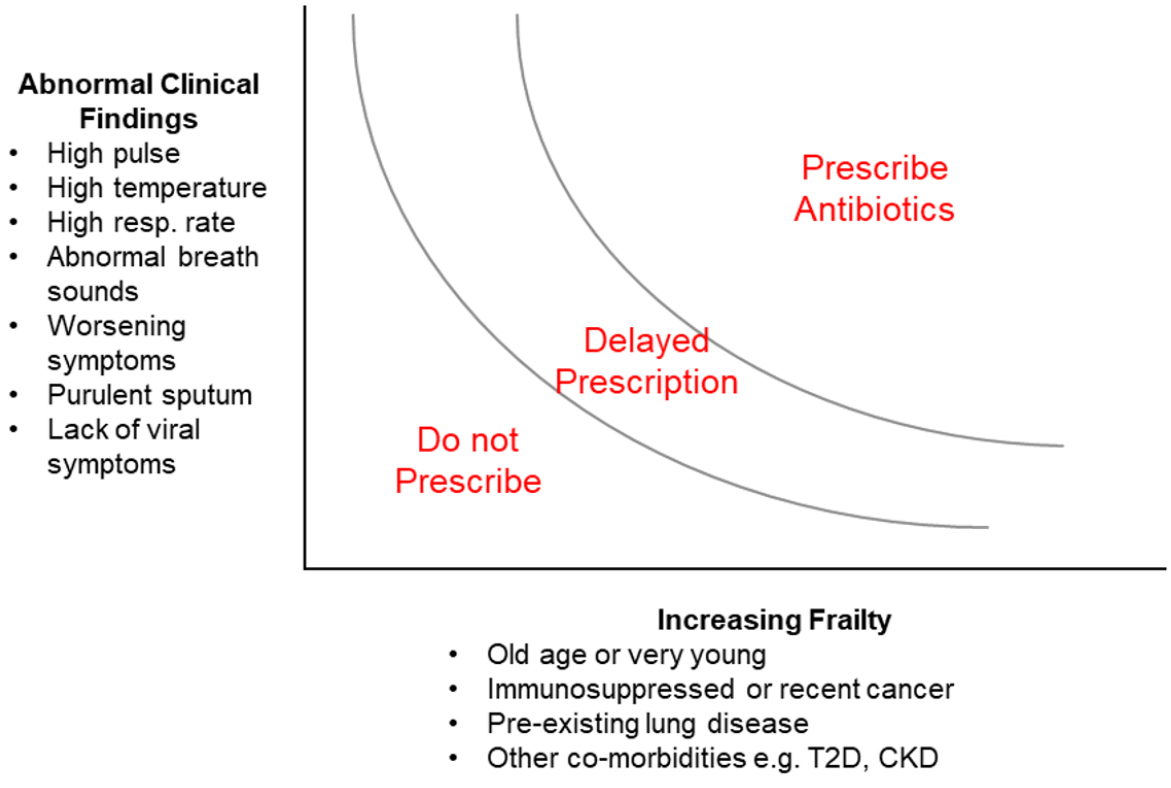
Diagnostic 1 (clinical context). Illustrative figure. Dx1 Frequency of Use in Primary Care. Source: Analysis based on Scandinavian Journal of Primary Health Care, NHS Digital

Indication	Clinical Utility	Comments
LRTI	**H**	• Treat if unwell or at risk e.g. COPD
URTI	**M**	• Mostly viral, self-limiting
Sinusitis	**M**	• Often mixed infection
Otitis Media	**L**	• Usually bacterial but self-limiting, treat if systemically unwell
Otitis Externa	**L**	• Usually bacterial but self-limiting, treat if systemically unwell
UTI	**L**	• Dipstick testing rapid & cheap, often self-limiting,
Other	**M**	• Undiagnosed fever treated if unwell or at risk

Dx1 use likely

Dx1 may be used

Dx1 use unlikely



Diganostic 1 (clinical utility research behind assumptions). Use case.

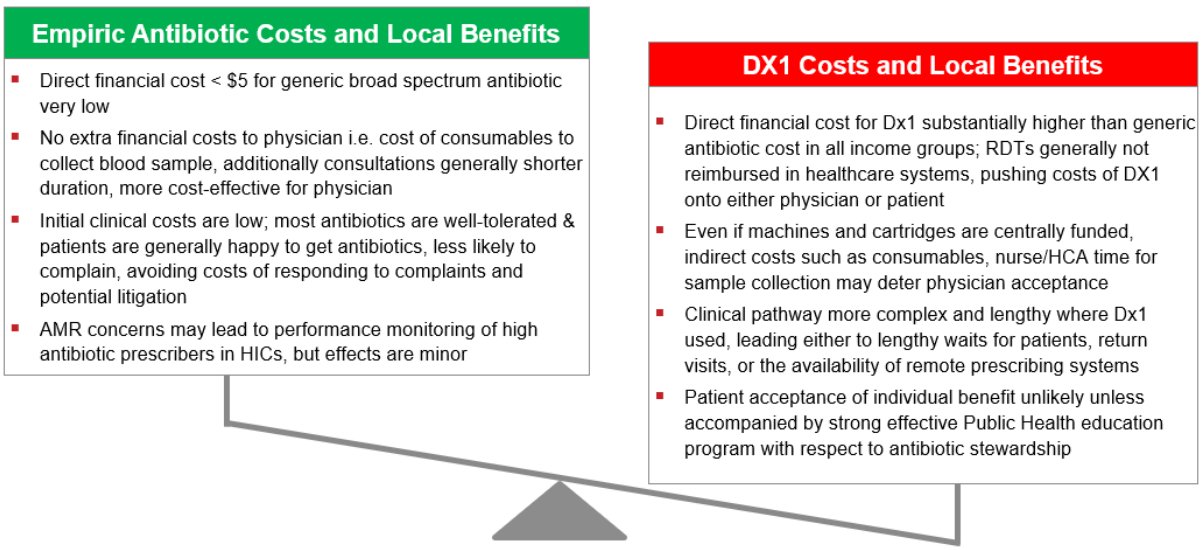
#	Income Region	Country	Bundle	# of GPs/PCPs (WHO, Eurostat, Other)	Source
1	USA	US	US	223,125	
2	HIC	Argentina	HICs	30,766	groupH estimate
3	HIC	France	EU5	94,923	
4	HIC	Germany	EU5	82,290	
5	HIC	Italy	EU5	53,742	
6	HIC	Japan	HICs	102,457	Working in clinics (not hospitals), Ministry of Health Source 2016
7	HIC	Russia	HICs	72,732	
8	HIC	Saudi Arabia	HICs	11,692	
9	HIC	Spain	EU5	35,798	
10	HIC	UK	EU5	49,569	
11	UMIC	Brazil	UMICs	153,832	
12	UMIC	China	UMICs	308,740	
13	UMIC	South Africa	UMICs	17,000	BMJ Global Health 2018
14	UMIC	Thailand	UMICs	17,199	
15	UMIC	Turkey	UMICs	48,688	
16	LMIC	Egypt	LMICs	30,000	
17	LMIC	India	LMICs	126,564	Government report 2018 public and community health centres + groupH estimate of private primary care
18	LMIC	Kenya	LMICs	5,602	
19	LMIC	Nigeria	LMICs	71,508	
20	LMIC	Pakistan	LMICs	110,000	Journal of Pakistan Medical Association 2015
21	LMIC	Vietnam	LMICs	10,000	groupH estimate, Health Statistics Year Book (government source), Primary Healthcare Centres

Dx1 Other Forecast Assumptions - # of primary care consultations (1).

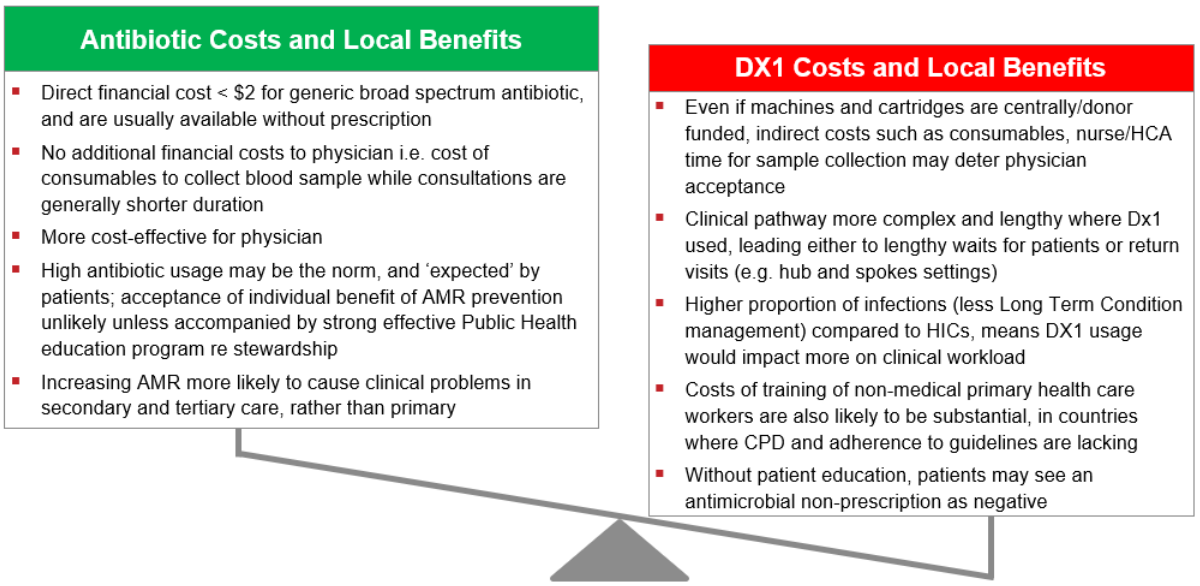
# of Consultations and Assumptions

Geography	# of GPs/PCPs (WHO, Eurostat, Other)	2019					2040		
		% in Clinical Practice*	Consultations per Day**	Consultation Days per Year***	Consultations per Year	% Consultations Online****	Consultations per Day	Consulting Days per Year
USA	223,125	60%	40	235	1,258,425,000	30%	52	235
HIC – EU5	316,322	60%	40	235	1,784,056,080	30%	52	235
Other HIC	217,647	60%	40	235	1,227,531,336	30%	52	235
UMIC	545,459	60%	30	235	2,307,291,570	30%	39	235
LMIC	353,674	60%	27	245	1,733,002,600	20%	33	245

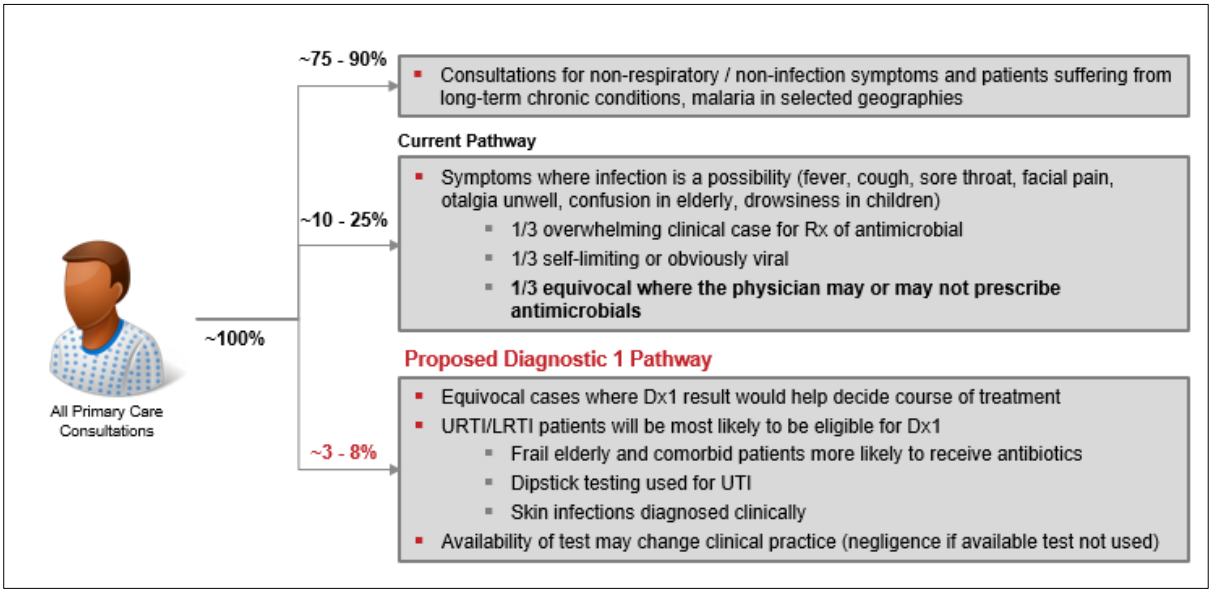
Dx1 Other Forecast Assumptions - # of primary care consultations (2). Source: *groupH estimate, **groupH estimate, POSEIDON study: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(15)00152-7/fulltext and includes assumption that ~60% of GP time is spent with direct patient consultation in HICs, http://www.bristol.ac.uk/news/2016/april/gps-workload-increase.html, ***groupH estimate, ****groupH estimate



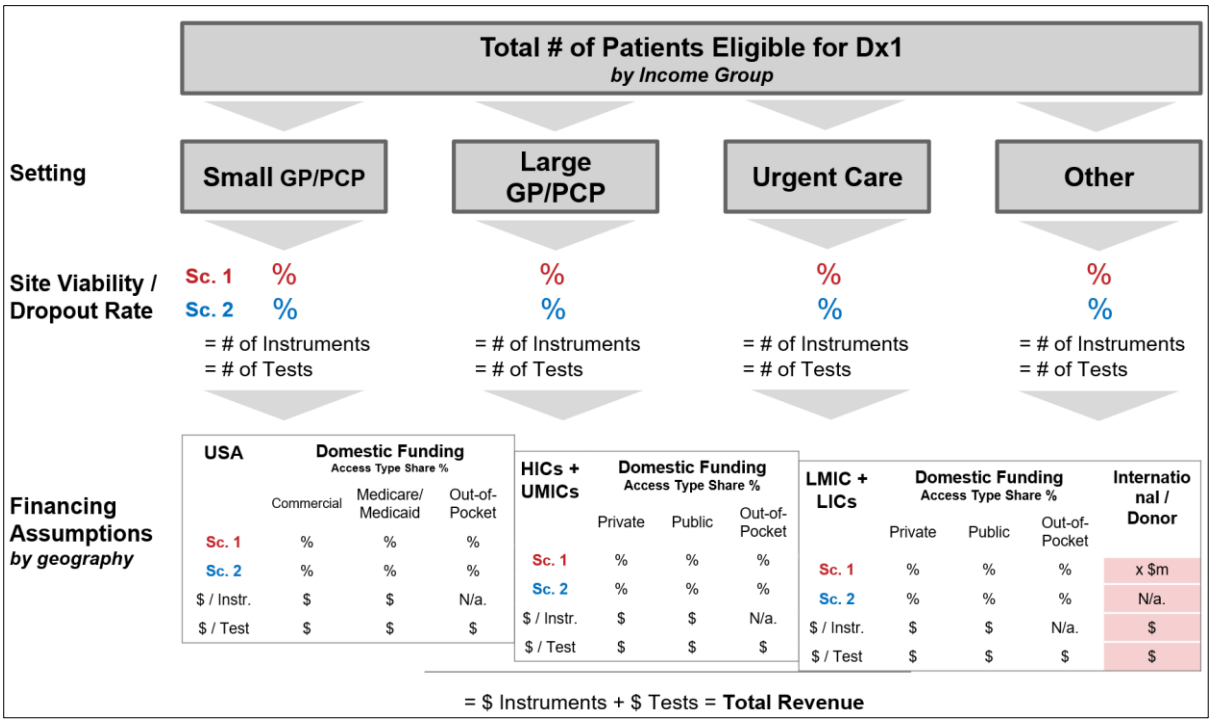
Dx1 Local Use Case HICs and UMICs.



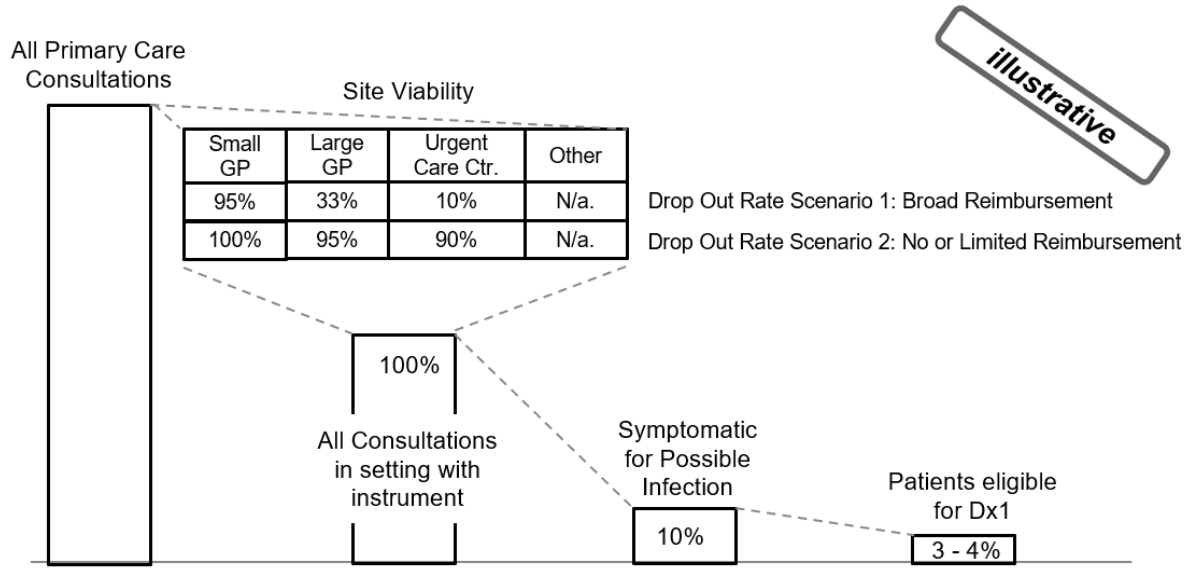
Dx1 Local Use Case LMICs. Source: FIND report on CRP launch in LMICs



Forecasting Dx1 – Use Case HICs and UMICs.

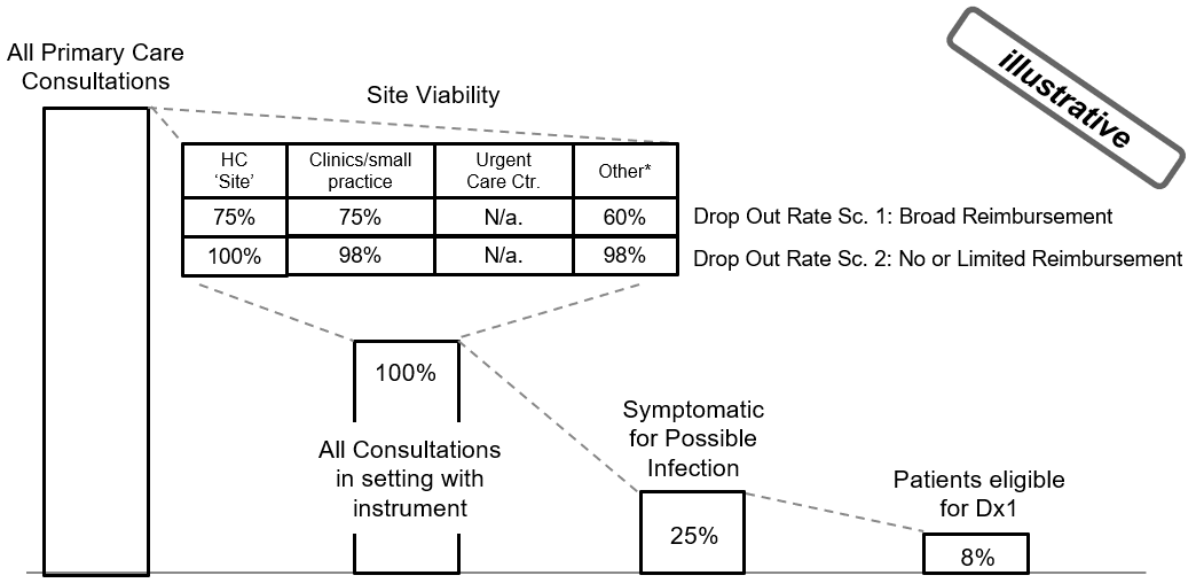


Other Forecast Assumptions: Total number of Patients Eligible for Dx1.



Dx1 (clinical Context). Use Cases in HICs and UMICS. It is assumed that in HICs 3 – 4% of all consultations in settings where testing is viable a patient will be eligible for Dx1; a negative local use case mandates broad reimbursement and a public health campaign to facilitate uptake. Source:
Note: # of instruments calculated based on # of viable sites per scenario.

Dx1 Local Use Case - LMICs



Dx1 (clinical Context). Use Cases in LMICs: Third party donor and public funding is key to adoption and broad use in low-income settings.Source: see Appendix 4 for Febrile Illness analysis in LMIC for assumption support, *POSEIDON

Dx1 – 'Site Viability' Assumptions						
US						**Comments**
		Small GP/PCP	Large GP/PCP	Urgent Care	Other	
Drop Out Rate (investment not viable)	Sc. 1 – Broad Reimbursement	95%	33%	10%	N/a.	groupH estimates, following challenging local use case we assume that even if broadly endorsed, Dx1 won't be viable in small PCP practices. If not endorsed and reimbursed we assume Dx1 only to be available in a small number of settings
	Sc. 2 – Current Status Quo	100%	95%	90%	N/a.	
Other HICs (and EU5)						
		Small GP/PCP	Large GP/PCP	Urgent Care	Other	
Drop Out Rate (investment not viable)	Sc. 1 – Broad Reimbursement	95%	33%	10%	N/a.	Same assumptions as for US
	Sc. 2 – Current Status Quo	100%	95%	90%	N/a.	
UMICs						
		Small GP/PCP	Large GP/PCP	Urgent Care	Other	
Drop Out Rate (investment not viable)	Sc. 1 – Broad Reimbursement	95%	33%	10%	N/a.	Same assumptions as for HICs but higher drop out rates for scenario 2
	Sc. 2 – Current Status Quo	100%	95%	90%	N/a.	
LMICs						LMICs particularly driven by domestic and international budget not by 'site viability'
		HC Workers	Clinics/small practice	Urgent Care	Other	
Drop Out Rate (investment not viable)	Sc. 1 – Broad Reimbursement	75%	75%	N/a.	60%	Very heterogenous landscape in primary care across countries. Assuming 'hub and spokes' type setting for Sc. 1 but TB analogue suggests only minority of settings offering access. For Sc. 2, access will be the exception
	Sc. 2 – Current Status Quo	100%	98%	N/a.	98%	

Summary - Site Viability/Drop Out' assumptions for Dx1 Scenario 1/2.

Scenario 1 – Broad Reimbursement and Funding								
US								**Comments**
Commercial	Medicare/Medicaid	Out-of-pocket						
60%	30%	10%						US general population health-care financing sources
Other HICs (and EU5)								
Private	Public	Out-of-pocket (or Other)						groupH estimate of general health-care financing sources in HICs. Note: for HICs and UMIC, overall revenue is driven by site viability and # of tests/instruments x price (not budget)
10%	89%	<1%						
UMICs								
	Domestic		International Funding					
Private	Public	Out-of-pocket						Population weighted average of populous UMICs TB financing (China, Brazil, Turkey, Thailand, South Africa) and groupH estimates. Small share of international funding driven by South Africa
10%	88%	<1%	2%					
LMICs								
	Domestic		International Funding **$50m/year**, Global budget = **$250m/year**					Note: For LMIC **overall budget** is driven by International Funding budget plus a roll-up for domestic, for comparison TB yearly global budget for concessioned Xpert cartridges in 2018 = ~$120m (see groupH analysis)
Private	Public	Out-of-pocket						
5%	75%	0%	20%					Population weighted average of populous LMICs TB financing (India, Pakistan, Nigeria, Egypt, Vietnam, Kenya) and groupH estimates

Financing assumptions for Dx1 Scenario 1 – Summary (refers to financing of Dx1 not healthcare delivery setting).

Scenario 2 – Current Status Quo (no reimbursement or int. funding)						
US						**Comments**
Commercial	Medicare/Medicaid	Out-of-pocket				
60%	30%	10%				US general population health-care financing sources
Other HICs (and EU5)						
Private	Public	Out-of-pocket (or Other)				
80%	10%	10%				groupH estimate for HICs, from the few patients tested most will be from the private sector/private insurance
UMICs						
Domestic			International Funding			
Private	Public	Out-of-pocket				
80%	10%	10%	0%			groupH estimate for UMICs, from the few patients tested most will be from the private sector/private insurance
LMICs						
Domestic			International Funding			
Private	Public	Out-of-pocket	**No funding**			
95%	2.5%	2.5%	0%			Note: For LMIC in this scenario revenue is driven by site viability and # of tests/instruments x price and the few patients tested are likely to have private insurance and are tested in the private sector

Financing assumptions for Dx1 Scenario 2 – Summary (refers to financing of Dx1 not healthcare delivery setting).

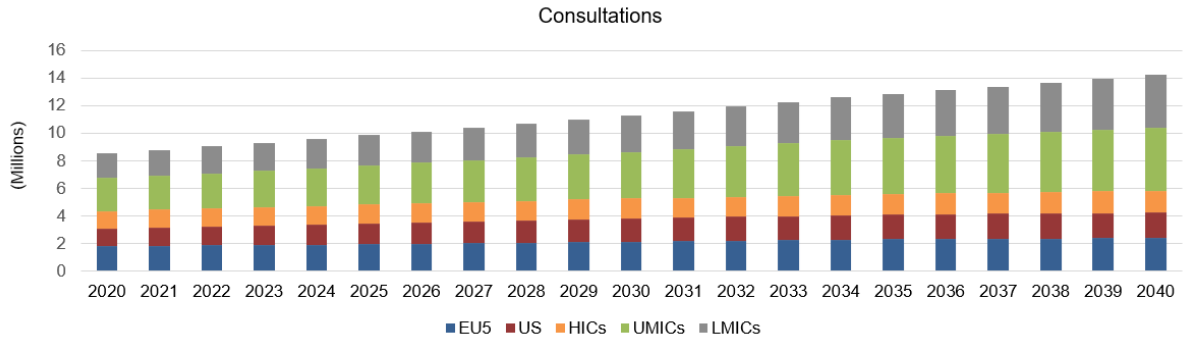
US						Comments
	Commercial	Medicare/Medicaid	Out-of-pocket			
Test	$25	$25	$25			We assume that in US and HICs costs per test and instrument costs are up to 4 x higher than sponsored tests and instruments for LMICs
Instrument	$10,000	$10,000	N/a.			
Other HICs (and EU5)						
	Private	Public	Out-of-pocket (or Other)			
Test	$25	$10	N/a.			See US assumptions
Instrument	$10,000	$10,000	N/a.			
UMICs						
	Domestic			International Funding		
	Private	Public	Out-of-pocket			
Test	$25	$10	$25	$5		For out-of-pocket we assume only 20% of pts. Max. would pay for Dx1 if offered, following local use case. Most instruments assumed to be paid by domestic public financing
Instrument	$10,000	$10,000	N/a.	$5,000		
LMICs						
	Domestic			International Funding		
	Private	Public	Out-of-pocket			
Test	$25	$5	$25	$5		Vast majority of Dx1 assumed to go through public channel supported by international funding
Instrument	$10,000	$5,000	N/a.	$5,000		

Pricing assumptions for Dx1 Scenario 1/2 - Summary.

- The consultations for each region was projected from 2020 through to 2040 using lifecycle growth rates at 5-year intervals

	2019 Consultations	2020-2024	2025-2029	2030-2034	2035-2040	2040 Consultations
EU5	1.8b	1.6%	1.9%	1.6%	0.9%	2.4b
USA	1.3b	3.1%	2.4%	1.3%	0.7%	1.8b
HIC	1.2b	1.7%	1.4%	0.8%	1.2%	1.6b
UMIC	2.4b	3.5%	3.6%	3.9%	2.5%	4.6b
LMIC	1.8b	3.9%	4.0%	3.9%	3.6%	3.8b

- Allowing for a global universe of ~16.2 billion consultations by in 2029



Projecting the Eligible Consultation Universe for Dx1.

3b. Diagnostic 2 (pathogen ID/AST)

Dx2 – Analogue Analysis

- Pneumonia analogue: **BioMerieux Biofire pneumonia panel**
  - Direct detection of most priority pathogens but limited resistance markers
  - Expensive instrument and assays designed for HIC
- Blood Stream Infection analogue: **T2 Biosciences Bacteria panel and Resistance Panel**
  - Direct detection from blood – CE-IVD and FDA
  - Currently limited panel for ID (5) and resistance markers
  - Very expensive and complex instrument (magnetic resonance)
- No good analogues for direct detection and then real AST (as opposed to resistance gene detection)
- Cepheid GeneXpert MTB/Rif is an analogue for modest success in rollout of a complex technology in LMIC (highly subsidized)
  - Not for pneumonia or for blood stream infections
  - Commercial analogue not a technical or indication analogue

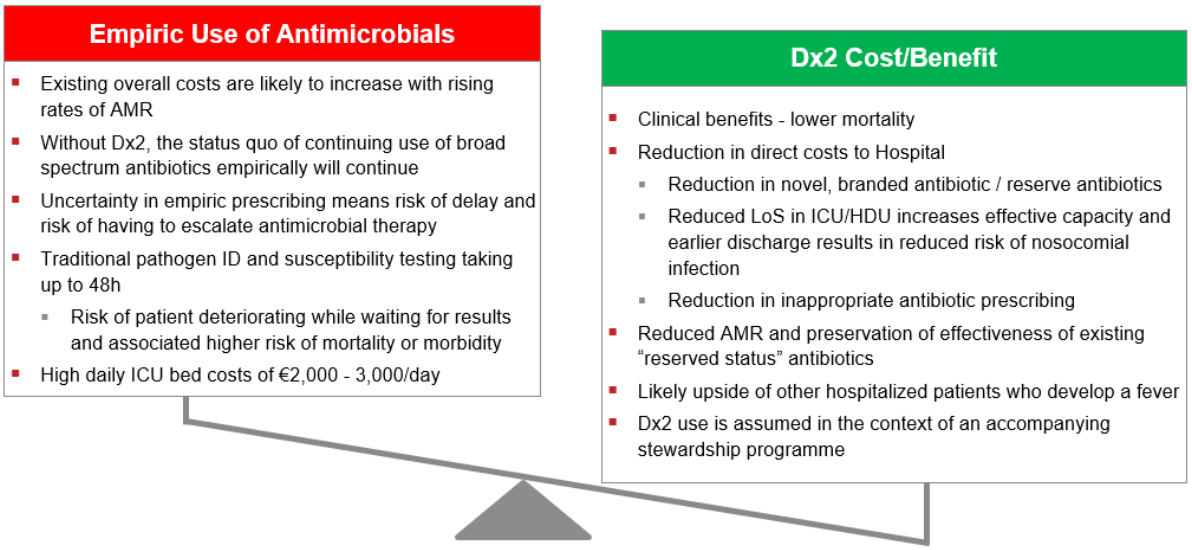
Summary of Product Attribute Analogue Analysis for Dx2. Source: *see analogue analysis in the Appendix 3a

Dx2 Analogues

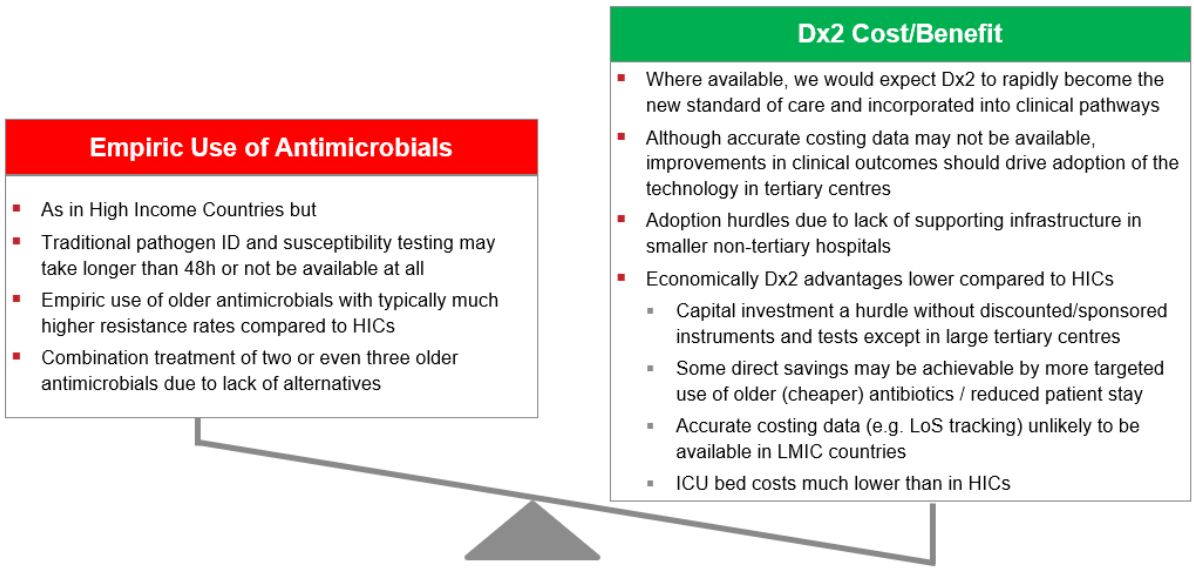
Criteria	Dx2	BioMerieux – Biofire pneumonia	T2 Bio – Bacteria & Resistance	Cepheid – GeneXpert MTB/Rif	Comments
Technical					
Target Indication	Pneumonia or BSI	●	●	○	GeneXpert for tuberculosis
Intended Use	Rapid ID and AST/Resistance wide panel of WHO priority pathogens: targeted Rx initiation or transition in critically ill patients	◑	◔	○	Limited resistance panels; T2 limited bacteria
Assay Type	Highly multiplexed; direct from specimen – culture independent	●	◕	◔	
Time to Result	<4 hours	●	◕	●	
Performance	High sensitivity (≥95%) and specificity (≥98%)	●	●	●	Performance in limited panels only
Specimen type	Respiratory sample (BAL) or blood	●	●	●	
Operational	Minimal storage reqts., training, easy to use and interpret	◔	○	◕	
Commercial					
Target Geographies	All; must be usable in resource limited settings	◔	○	◕	GeneXpert is used in RLS
Target Markets	Public and private	◑	◑	●	
Target Setting	Near patient testing, hospitalized patients	◔	○	◑	Gap; all mainly used in laboratory
Target User	Trained laboratory personnel	●	●	●	
Cost per test	$5 ($1-3 for LMICs, aspirational)	○	○	◔	GeneXpert: subsidized price
Instrument cost	$5,000	○	○	◔	GeneXpert: subsidized price
Overall Fit		◑	◔	◔	

Very High ● High ◕ Medium ◑ Low ◔ Very Low ○

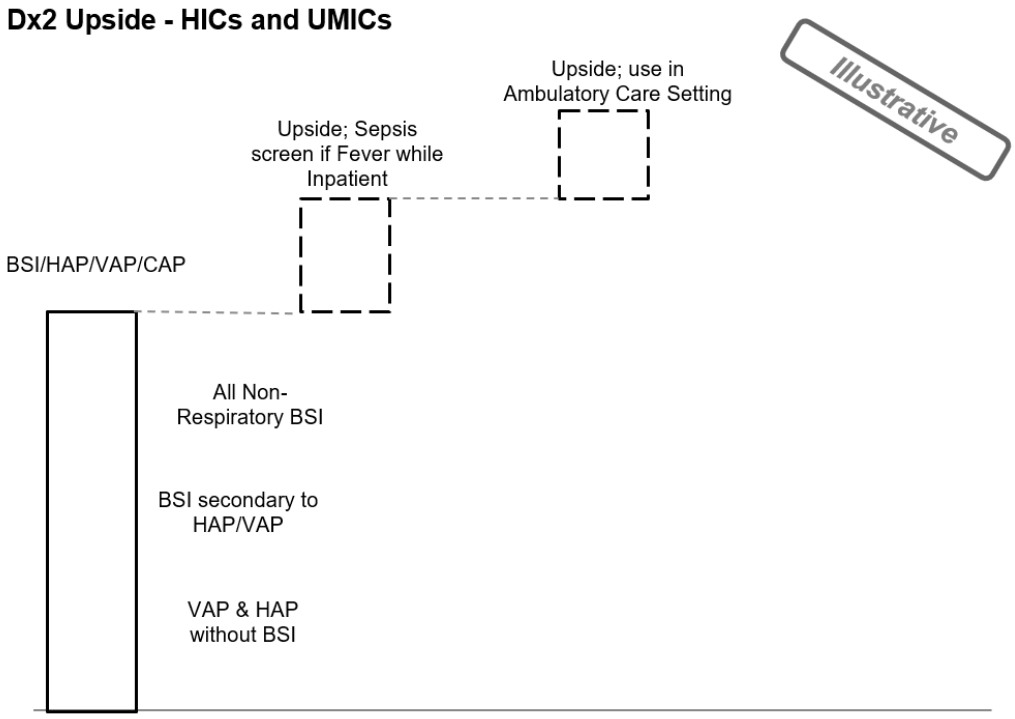
Summary of Dx2 Analogue Analysis.



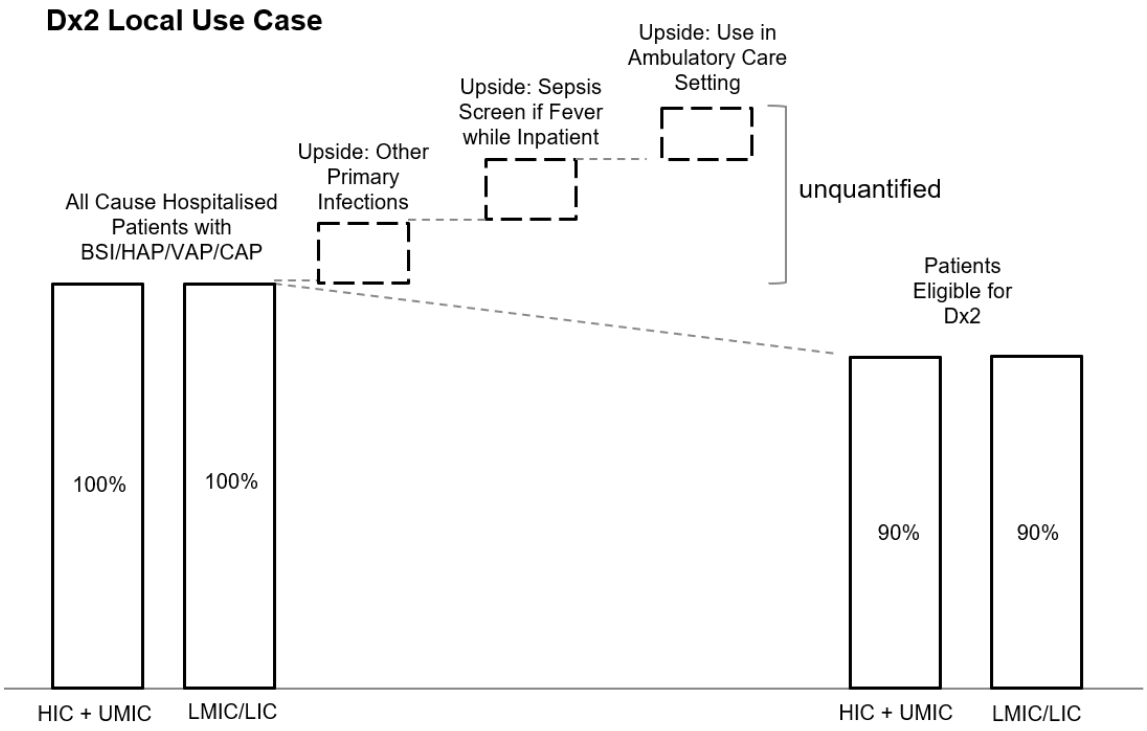
Dx2 Local Use Case HICs and UMICs. In US, HICs and UMICs the use of Dx2 is very likely to pay for itself over time due to its clinical benefits and financial cost savings Source: groupH analysis & interviews



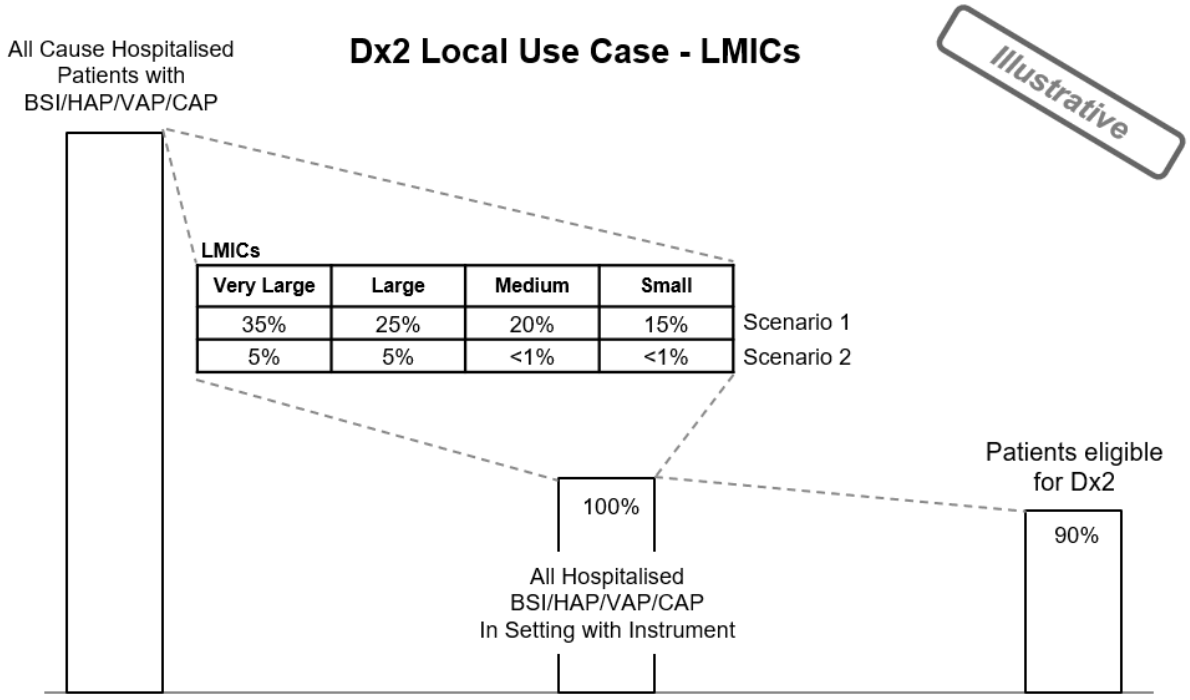
Dx2 Local Use Case LMICs. In LMICs, there is still the same unmet clinical need for rapid accurate pathogen identification and antibiotic sensitivity, but the cost would need to be subsidized.



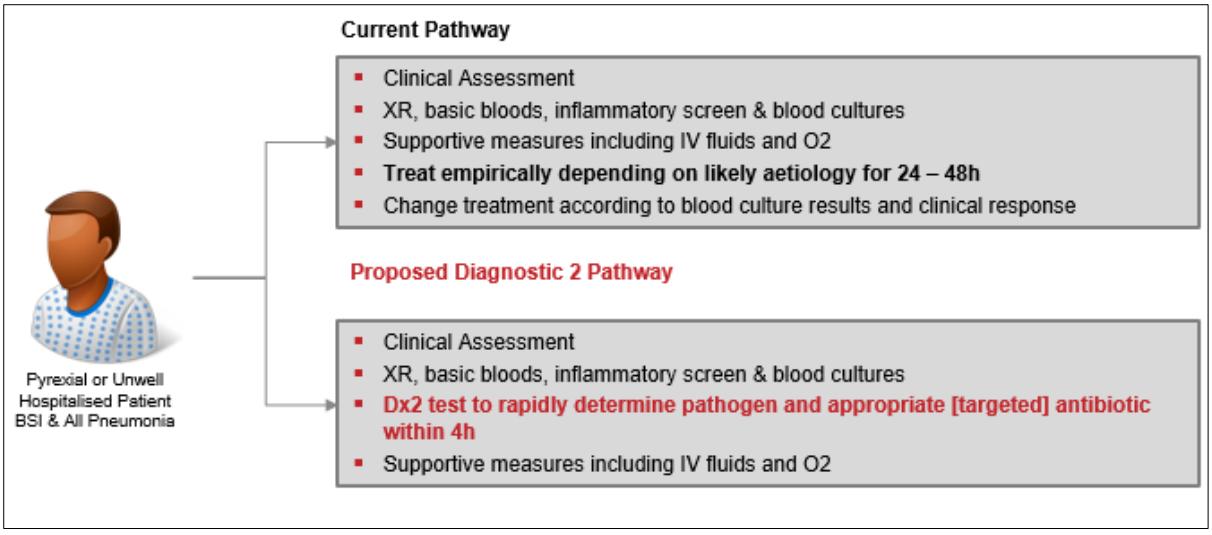
For HICs Dx2 will become an integral part of pathways for patients with BSI/Pneumonia, then may be used more widely in other clinical settings.



Dx2 Local Use Case.

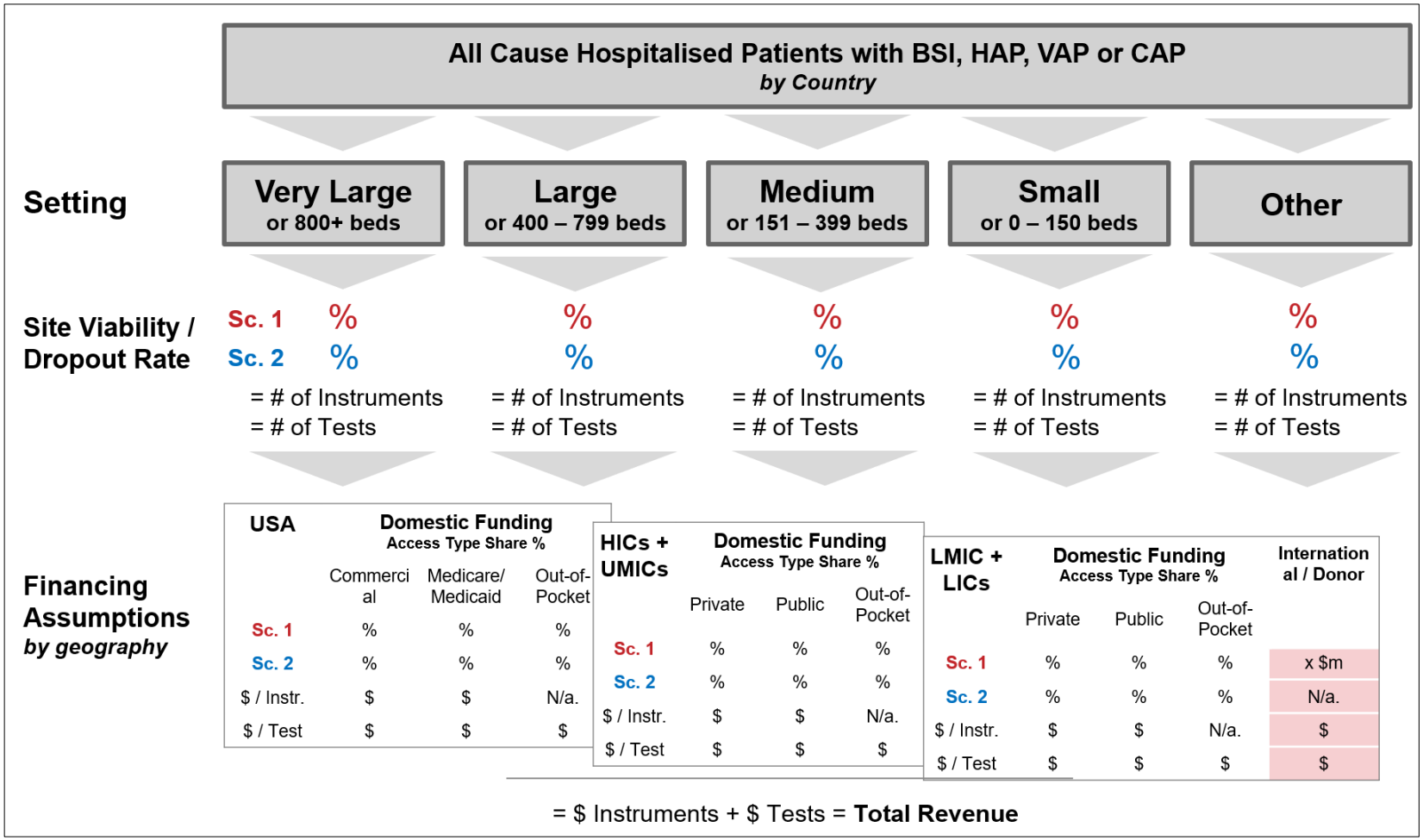


LMICS there is the same unmet need, but DX2 adoption will depend more on public and donor funding, as for *GeneXpert* in TB.



Forecasting Dx2 – Use Case HICs and UMICs.

Dx2 Clinical Context. Summary of Use Cases. Dx2 addresses a very real unmet need and will be widely used once available, justifying its cost by reducing other hospital direct costs next to wider societal benefits.



Forecasting Dx2 – Other Forecast Assumptions.

Dx2 – 'Site Viability' Assumptions						
US						**Comments**
		800+ beds	400 – 799 beds	151 – 399 beds	0 – 150 beds	
Site Viability Rate	Sc. 1 – Broad Reimbursement	66%	60%	50%	40%	Following positive local use case we assume high viability in most settings for Sc. 1 (the larger the more viable due to capital investment) and still good viability even without broad reimbursement for Sc. 2.
	Sc. 2 – Current Status Quo	45%	40%	30%	5%	
Other HICs (and EU5)						
		Very Large	Large	Medium	Small	
Site Viability Rate	Sc. 1 – Broad Reimbursement	66%	60%	50%	40%	Same as for US
	Sc. 2 – Current Status Quo	45%	40%	30%	5%	
UMICs						
		Very Large	Large	Medium	Small	
Site Viability Rate	Sc. 1 – Broad Reimbursement	45%	40%	30%	20%	Same as for HICs but overall somewhat lower capacity to afford investment in UMIC
	Sc. 2 – Current Status Quo	25%	20%	10%	2%	
LMICs						
		Very Large	Large	Medium	Small	
Site Viability Rate	Sc. 1 – Broad Reimbursement	40%	30%	20%	10%	Similar to UMIC but overall somewhat lower capacity to afford investment in LMIC
	Sc. 2 – Current Status Quo	10%	10%	<1%	<1%	

Summary - 'Site Viability' assumptions for Dx2 Scenario 1/2.

Summary - Financing assumptions for Dx2 Scenario 1 (refers to financing of Dx2 not healthcare delivery setting).

Scenario 1 – Broad Reimbursement and Funding				
US				**Comments**
Commercial	Medicare/Medicaid	Out-of-pocket		
60%	30%	10%		US general population health-care financing sources
Other HICs (and EU5)				
Private	Public	Out-of-pocket (or Other)		groupH estimate of general health-care financing sources in HICs
10%	90%	0%		
UMICs				
	Domestic		International Funding	
Private	Public	Out-of-pocket		
10%	88%	0%	2%	Population weighted average of populous UMICs TB financing (China, Brazil, Turkey, Thailand, South Africa) and groupH estimates. Small share of international funding driven by South Africa
LMICs				
	Domestic		International Funding **$10m/year**, Total LMIC budget = **$31m/year**	Note: For LMIC **overall budget** is assumed driven by International Funding budget plus a roll-up for domestic, for comparison TB yearly global budget for concession Xpert cartridges in 2018 = ~$120m (see groupH analysis). Population weighted average of populous LMICs TB financing (India, Pakistan, Nigeria, Egypt, Vietnam, Kenya) and groupH estimates ~25% Int. funding share on average for TB. We estimate that Int. funding share for instruments and cartridges only to be at least 67%
Private	Public	Out-of-pocket		
5%	33%	0%	62%	

Scenario 2 – Current Status Quo (no reimbursement or int. funding)							
US							**Comments**
Commercial		Medicare/Medicaid		Out-of-pocket			
60%		30%		10%			US general population health-care financing sources
Other HICs (and EU5)							
Private		Public		Out-of-pocket (or Other)			
80%		10%		10%			groupH estimate for HICs, from the few patients tested most will be from the private sector/private insurance
UMICs							
		Domestic			International Funding		
Private		Public		Out-of-pocket			
80%		10%		10%	0%		groupH estimate for UMICs, from the few patients tested most will be from the private sector/private insurance
LMICs							
	Domestic				International Funding		
Private		Public		Out-of-pocket			
95%		2.5%		2.5%	0%		Note: For LMIC in this scenario revenue is driven by site viability and # of tests/instruments x price and the few patients tested are likely to have private insurance and are tested in the private sector

Summary - Financing assumptions for Dx2 Scenario 2 (refers to financing of Dx2 not healthcare delivery setting).

US						**Comments**
	Commercial	Medicare/Medicaid	Out-of-pocket			
Test	$150	$150	$120			We assume that in US and HICs costs per test and instrument costs are up to 4 x higher than sponsored tests and instruments for LMICs
Instrument	$50,000	$50,000	N/a.			
Other HICs (and EU5)						
	Private	Public	Out-of-pocket (or Other)			
Test	$120	$100	$120			See US assumptions
Instrument	$50,000	$50,000	N/a.			
UMICs						
	Domestic			International Funding		
	Private	Public	Out-of-pocket			
Test	$120	$60	$120	$60		Positive local use case for Dx2. Most instruments assumed to be paid by domestic public financing
Instrument	$50,000	$50,000	N/a.	$50,000		
LMICs						
	Domestic			International Funding		
	Private	Public	Out-of-pocket			
Test	$120	$5	$120	$5		Positive local use case for Dx2 but in LMIC we acknowledge that costs for patients going through ICU not always tracked. Costs as per TPP, sponsored/discounted costs seen as very aspirational
Instrument	$50,000	$5,000	N/a.	$5,000		

Summary - Pricing assumptions for Dx2 Scenario 1/2.

Geography	Launch Year	Average Time to Instrument Ramp-Up
EU5	from 2025	5 years
USA	2025	5 years
Other HICs	from 2025	7 years
UMIC	from 2025	8 years
LMIC	from 2025	10 years

Dx2 Other Forecast Assumptions. Source: HIC: High Income Countries, UMIC: Upper Middle, LMIC: Low Middle- and Low-Income Countries combined

# of Hospitals per Country

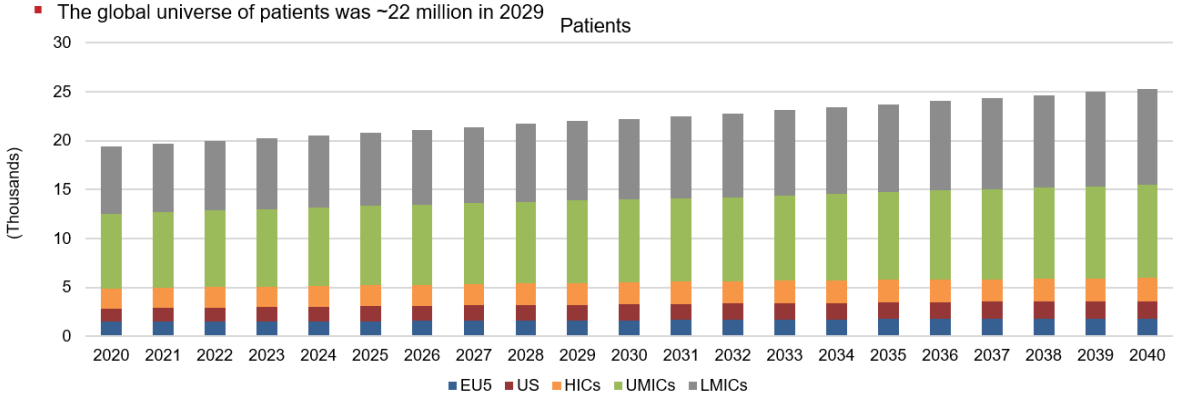
#	Income Region	Country	Bundle	# of Hospitals	# of Hospital Beds	Average Beds per Hospital
1	USA	US	US	6,146	931,203	152
2	HIC	Argentina	HICs	5,178	227,400	44
3	HIC	France	EU5	3,042	395,670	130
4	HIC	Germany	EU5	3,084	661,448	214
5	HIC	Italy	EU5	1,298	189,753	146
6	HIC	Japan	HICs	8,442	1,641,407	194
7	HIC	Russia	HICs	5,400	1,044,875	193
8	HIC	Saudi Arabia	HICs	355	76,540	216
9	HIC	Spain	EU5	815	139,061	171
10	HIC	UK	EU5	1,910	165,844	87
11	UMIC	Brazil	UMICs	6,154	456,291	74
12	UMIC	China	UMICs	33,009	6,120,500	185
13	UMIC	South Africa	UMICs	544	117,841	217
14	UMIC	Thailand	UMICs	1,269	144,837	114
15	UMIC	Turkey	UMICs	1,271	231,913	182
16	LMIC	Egypt	LMICs	645	148,892	231
17	LMIC	India	LMICs	69,265	710,761	10
18	LMIC	Kenya	LMICs	786	74,928	95
19	LMIC	Nigeria	LMICs	3,534	134,000	38
20	LMIC	Pakistan	LMICs	1,237	140,100	113
21	LMIC	Vietnam	LMICs	1,293	256,672	199

Dx2 Other Forecast Assumptions – Hospitals, Beds & Sector Data. Source: WHO, OECD, World Bank, EUROSTAT, Government sources (Ministry of Health Year Books etc.), Associations (e.g. AHA for US, https://www.aha.org/statistics/fast-facts-us-hospitals), Literature searches

- The BSI and pneumonia patients for each region were obtained from publicly available sources* for 2020-2040

	2020 Patients	2025 Patients	2030 Patients	2035 Patients	2040 Patients
EU5	1.5m	1.6m	1.7m	1.8m	1.8m
USA	1.4m	1.5m	1.6m	1.7m	1.8m
HIC	2.1m	2.2m	2.2m	2.3m	2.4m
UMIC	7.7m	8.1m	8.5m	9m	9.5m
LMIC	6.9m	7.5m	8.2m	9m	9.8m

- The global universe of patients was ~22 million in 2029



Projecting the Eligible Patient Universe for Dx2. Source:* = country-reported data and modelled estimates (US all-cause PNM sourced from HCUPnet i.e hospital discharge statistics, and US all-cause BSI from GBD Sepsis Study - which uses hospital admissions and death records)

4. Epidemiology

4a. National Level Epidemiology Results

Gram-Negative BSI Patient Numbers		2020		2025		2030		2035		2040	
		Total Cases	MDR Cases	Total Cases	MDR Cases	Total Cases	MDR Cases	Total Cases	MDR Cases	Total Cases	MDR Cases
HICs	UK	68,785	3,602	73,342	5,364	79,037	8,100	83,968	11,996	87,036	16,047
	US	261,825	27,995	290,372	40,380	315,145	57,255	331,679	79,032	342,582	105,491
	S. Arabia	27,225	14,565	29,364	17,315	32,354	20,621	35,959	23,545	40,297	27,143
	Japan	100,159	19,200	101,225	24,601	101,717	26,456	102,201	27,334	103,391	28,545
	Italy	31,578	8,937	33,060	10,733	35,280	13,225	37,609	16,497	39,631	18,367
UMICs	Brazil	303,087	114,496	312,429	127,781	324,208	140,589	332,990	153,594	339,440	167,099
	Thailand	95,603	39,314	97,235	44,591	98,643	50,634	99,663	57,457	100,340	60,920
	S. Africa	77,452	36,852	80,022	41,021	82,195	45,675	84,588	51,274	87,604	56,708
	Turkey	51,569	19,591	55,258	23,668	60,050	28,457	65,043	34,246	70,439	40,755
LMICs / LICs	India	1,587,250	1,214,077	1,659,301	1,287,741	1,737,844	1,370,008	1,824,426	1,462,886	1,916,085	1,564,932
	Kenya	86,168	43,313	94,822	52,189	105,312	62,152	116,933	71,431	129,753	82,151
	Vietnam	120,566	56,882	125,360	64,827	131,411	73,105	137,498	80,848	144,131	86,775
	Egypt	107,217	69,085	117,020	77,231	126,171	85,320	137,126	95,046	149,499	106,252

Antibiotic Resistant Gram-Negative BSI - Estimated Patient Numbers Estimates for Current and Projected Total Cases and MDR Cases of Gram-Negative BSI.

Gram-Negative Pneumonia Patient Numbers		2020		2025		2030		2035		2040	
		Total Cases	MDR Cases	Total Cases	MDR Cases	Total Cases	MDR Cases	Total Cases	MDR Cases	Total Cases	MDR Cases
HICs	UK	30,294	1,096	32,011	1,746	33,927	2,795	36,329	4,416	38,405	5,418
	US	149,908	25,509	164,682	34,146	177,601	45,193	186,213	52,844	191,887	59,371
	S. Arabia	26,218	7,584	28,743	9,871	31,483	12,691	34,121	15,464	36,697	18,834
	Japan	88,734	11,237	90,928	13,732	90,922	14,865	90,624	15,711	90,670	16,767
	Italy	12,637	4,073	13,019	4,574	13,541	5,194	14,376	6,096	15,243	6,733
UMICs	Brazil	101,045	26,658	109,191	30,826	118,830	35,205	129,172	40,223	138,335	45,350
	Thailand	20,927	7,463	21,825	8,889	23,070	10,736	24,370	12,965	25,594	14,375
	S. Africa	55,941	28,063	59,986	32,010	64,206	36,215	68,196	40,268	72,077	44,285
	Turkey	36,732	16,794	38,979	19,572	41,782	22,418	45,130	25,990	48,334	29,406
LMICs / LICs	India	727,714	467,515	785,014	521,769	845,745	583,351	910,227	653,652	979,112	734,584
	Kenya	29,292	13,650	32,914	16,212	36,879	19,257	41,253	22,906	45,954	27,220
	Vietnam	14,724	7,254	15,823	8,607	17,308	10,044	18,937	11,644	20,351	12,829
	Egypt	91,677	48,663	102,030	56,691	112,522	65,517	123,598	75,501	135,725	87,087

Antibiotic Resistant Gram-Negative Pneumonia - Estimated Patient Numbers. Estimates for Current and Projected Total Cases and MDR Cases of Gram-Negative Pneumonia.

4b. Epidemiology data gaps

Gram negative BSI Data Gaps		*For more details please refer to the individual country epi workbooks.*
HIC	UK	
	US	Pediatric studies that have full quantification of GN pathogens. There is no etiology data for Acinetobacter from the studies found - is it a really small proportion of US Gram-negative BSI or is it just not detected?
	Saudi Arabia	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
	Japan	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
	Italy	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
MIC	Brazil	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
	Thailand	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
	South Africa	Better etiology breakdown of bacteraemia including for Enterobacter spp. which is missing. National surveillance shows very low numbers of ESKAPE pathogens as a percentage of BSI isolates with positive culture which needs checking, but no other data found. Also notes that blood testing is under-utilised in the public sector leading to lower cases than expected.
	Turkey	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
LIC	India	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
	Kenya	Lack of national surveillance data - etiology has been taken from a study in a tertiary care hospital which includes community-acquired and hospital-acquired BSI and may not be representative of the population as a whole.
	Vietnam	National BSI figures that may be more accurate than our estimations from the GBD Sepsis study
	Egypt	Good comprehensive BSI etiology for Egypt.

Gram negative BSI Data Gaps

Resistant Gram negative BSI Data Gaps		*For more details please refer to the individual country epi workbooks.*
HIC	UK	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii* and *E.cloacae*.
	US	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii* and *E.cloacae*.
	Saudi Arabia	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii and E.cloacae*. National rates that may be more representative of the country as a whole vs Pfizer Atlas data.
	Japan	MDR rates in neonates only for E.coli, *K.pneumoniae, P.aeruginosa, A.baumannii and E.cloacae*. National MDR and XDR data as the only available data is through Pfizer ATLAS.
	Italy	MDR and XDR rates for *E.cloacae* (not available from SENTRY). Also national data rather than SENTRY data that may be more representative of the population as a whole.
MIC	Brazil	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii and E.cloacae*. Also national MDR / XDR data that may be more representative of the population as a whole versus Pfizer's Atlas data.
	Thailand	MDR and XDR rates for *A.baumannii* and *E.cloacae* as well as MDR rates in neonates for our pathogens of interest.
	South Africa	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii and E.cloacae*.
	Turkey	MDR rates in neonates only for E.coli, *K.pneumoniae, P.aeruginosa, A.baumannii* and *E.cloacae*. Also MDR / XDR rates for *E.cloacae* (not enough isolates in SENTRY).
LIC	India	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii and E.cloacae*. National MDR and XDR data as the only available data is through Pfizer ATLAS. Some MDR data has been received but it doesn't seem to correlate with resistance to individual antibiotic class data.
	Kenya	More recent MDR / XDR data - MDR and DTRs data is sourced from Pfizer's ATLAS database - the data is available for 2013 and 2014 only.
	Vietnam	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii and E.cloacae*. Also MDR / XDR rates for *E.cloacae* (not enough isolates in SENTRY).
	Egypt	MDR rates in neonates only for *E.coli, K.pneumoniae, P.aeruginosa, A.baumannii and E.cloacae*. National rates that may be more representative of the country as a whole vs Pfizer Atlas data.

Resistant Gram negative BSI Data Gaps.

Gram negative Pneumonia Data Gaps		*For more details please refer to the individual country epi workbooks.*
HIC	UK	Incidence data for hospitalised pneumonia caused by *A.baumanii, S. marcescens and Enterobacter spp.* (ICD-10 diagnosis code J15.6 groups together 'other GNs' which include *S. marescens, Enterobacter spp., Achromobacter* and *Proteus miribilis* without further data split).
	US	Incidence of all-cause hospitalised pneumonia for 2018 (and 2015).
	Saudi Arabia	Incidence data for hospitalised pneumonia that may be more accurate than the Global Burden of Disease modelled estimates. More recent & complete etiology breakdown for all-cause hospitalised pneumonia than 2003 that also includes *E.coli, A.baumanii, S. marcescens* and *Enterobacter spp*.
	Japan	More recent data for all-cause annual pneumonia incidence and etiology.
	Italy	National pneumonia hospital discharge data seems a little low compared to similar-sized countries i.e. UK. Would be good to locate another source for hospitalised pneumonia incidence to double-check. Also incidence of all-cause pneumonia caused by *S. marcescens* and *Enterobacter* spp.
MIC	Brazil	
	Thailand	Incidence of all-cause pneumonia caused by A.*baumannii, S.marcescens* and *Enterobacter* spp. Incidence data for additional years (data only found online for 2018).
	South Africa	Official figures for the incidence of all-cause pneumonia and a more recent etiology breakdown.
	Turkey	
LIC	India	National pneumonia incidence estimates that may be more accurate than the Global Burden of Disease modelled estimates and the India Government official figures, the latter which underestimate the incidence in the population that does not have access to medical facilities.
	Kenya	All-cause pneumonia incidence that may be more accurate than our figure derived from the Global Burden of Disease modelled estimates.
	Vietnam	Incidence of all-cause pneumonia that is attributable to *E.coli, A.baumannii, S. marcescens* and *Enterobacter* spp. Incidence of all-cause pneumonia by age groups.
	Egypt	All-cause pneumonia incidence that may be more accurate than our figure derived from the Global Burden of Disease modelled estimates.

Gram negative Pneumonia Data Gaps

Resistant Gram negative Pneumonia Data Gaps		*For more details please refer to the individual country epi workbooks.*
HIC	UK	
	US	
	Saudi Arabia	MDR and XDR % data for the GN pathogens of interest from national sources (data taken from Pfizer Atlas but this is from 1 site only).
	Japan	MDR and XDR data from national sources (data taken from SENTRY and Pfizer ATLAS).
	Italy	
MIC	Brazil	National AMR surveillance data source for GN pathogens (only comprehensive source found is SENTRY surveillance database and Pfizer ATLAS). No MDR or XDR data for *E.cloacae*.
	Thailand	National data source for MDR / XDR data (current data is taken from SENTRY for all sample sites as otherwise number of isolates too low).
	South Africa	National MDR / XDR data for our GN pathogens of interest (Data is extracted from Pfizer Atlas database in the absence of national NCID figures).
	Turkey	National data source for XDR data (current data is taken from SENTRY). MDR / XDR data for *E.cloacae*.
LIC	India	National data source for MDR and XDR rates that is more in line with national resistance to single antibiotic classes. MDR and DTR data taken from Pfizer Atlas.
	Kenya	MDR and XDR data from national sources and for more recent years than Pfizer Atlas (2013 and 2014).
	Vietnam	MDR / XDR data from national sources (current data is taken from SENTRY for all sample sites as otherwise number of isolates too low).
	Egypt	MDR and XDR data from national sources. MDR and DTR data is currently taken from Pfizer Atlas.

Resistant Gram negative Pneumonia Data Gaps

4c. Detailed Data Source Assessment (across the breadth of the epidemiology)

Country	Secondary Data Sources			Primary Sources
	Pneumonia	BSI	AMR	
Brazil	• Brazil Ministry of Health DATASUS database • Luna CM et al. Community-acquired pneumonia: etiology, epidemiology, and outcome at a teaching hospital in Argentina. Chest. 2000 Nov 1;118(5):1344-54. [used in the absence of Brazil-specific data giving comprehensive etiology breakdown of hospitalized CAP] • Gales AC et al. Antimicrobial susceptibility of gram-positive bacteria isolated in Brazilian hospitals participating in the SENTRY Program (2005-2008). Brazilian Journal of Infectious Diseases. 2009 Apr;13(2):90-8.[Includes GN bacterial]	• Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11 • Diekema DJ et al. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrobial agents and chemotherapy. 2019 Jul 1;63(7):e00355-19	• Pfizer Atlas surveillance database	• No Brazil / Latin American contact within EAG
Egypt	• Global Burden of Disease data for lower respiratory tract infections accessed at: http://ghdx.healthdata.org/gbd-results-tool • El-Sokkary RH et al. Community acquired pneumonia among adult patients at an Egyptian university hospital: bacterial etiology, susceptibility profile and evaluation of the response to initial empiric antibiotic therapy. Infection and drug resistance. 2018;11:2141	• Used in absence of Egypt BSI etiology papers: Bandy A, Almaeen AH. Pathogenic spectrum of blood stream infections and resistance pattern in Gram-negative bacteria from Aljouf region of Saudi Arabia. Plos one. 2020 Jun 9;15(6):e0233704 • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• WHO GLASS dashboard • Pfizer ATLAS surveillance database	• Ministry of Health and Population contacted for pneumonia incidence

Selected secondary data sources and primary sources used to derive GN pneumonia and BSI epi data…1/7

Country	Secondary Data Sources			Primary Sources
	Pneumonia	BSI	AMR	
India	• Central Bureau of Health Intelligence - India National Health Profiles • Global Burden of Disease data for lower respiratory tract infections accessed at: http://ghdx.healthdata.org/gbd-results-tool • Gupta D et al. Guidelines for diagnosis and management of community-and hospital-acquired pneumonia in adults: Joint ICS/NCCP (I) recommendations. Lung India: Official Organ of Indian Chest Society. 2012 Jul;29(Suppl 2):S27 • Para et al. Microbial etiology in hospitalized North Indian adults with community-acquired pneumonia. Lung India 2018 35(2) P108-115	• Indian Council of Medical Research Annual AMR Surveillance Report 2018 • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• Indian Council of Medical Research Annual AMR Surveillance Reports • Pfizer ATLAS surveillance database	• MDR data for India from Dr Kamini Walia, Indian Council for Medical Research and Dr Jyoti Joshi, CDDEP (introduced by EAG member Dr Saiyed)
Italy	• EUROSTAT datasets for hospital inpatients discharge data by diagnosis • Aliberti S et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. Clinical infectious diseases. 2012 Feb 15;54(4):470-8	• EUROSTAT datasets for hospital inpatients discharge data by diagnosis • Giannella M et al. Prognostic utility of the new definition of difficult-to-treat resistance among patients with gram-negative bloodstream infections.Open forum infectious diseases 2019 Dec (Vol. 6, No. 12, p. ofz505) • Rudd KE et al. Global, regional and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020.18;395(10219) • Luzzaro F et al. Prevalence and epidemiology of microbial pathogens causing bloodstream infections: results of the OASIS multicenter study. Diagnostic microbiology and infectious disease. 2011 Apr 1;69(4):363-9	• ECDC ATLAS Surveillance system (EARS-net) • SENTRY surveillance system	

Selected secondary data sources and primary sources used to derive GN pneumonia and BSI epi data…2/7

Country	Secondary Data Sources			Primary Sources
	Pneumonia	BSI	AMR	
Japan	• Kobayashi M. PRM71-ESTIMATION OF THE NUMBER OF PNEUMONIA PATIENTS IN JAPAN USING PUBLIC REAL-WORLD DATA. Value in Health. 2018 Oct 1;21:S367 • Morimoto K et al. Adult Pneumonia Study Group-Japan (APSG-J). The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. PLoS One 2015 Mar 30;10(3):e0122247 • For age data: Global Burden of Disease data for lower respiratory tract infections accessed at: http://ghdx.healthdata.org/gbd-results-tool	• Hattori H et al. Epidemiology and risk factors for mortality in bloodstream infections: A single-center retrospective study in Japan. American journal of infection control. 2018 Dec 1;46(12):e75-9 • Japan Nosocomial Infections Surveillance (JANIS) - Annual Open report 2019 • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11 • To give indication of age group breakdown for septicaemia in HIC: HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality. https://hcupnet.ahrq.gov/	• Japan Nosocomial Infections Surveillance (JANIS) - Annual Open reports • Pfizer ATLAS surveillance database	
Kenya	• Global Burden of Disease data for lower respiratory tract infections accessed at: http://ghdx.healthdata.org/gbd-results-tool • Nyawanda BO et al. Comparison of respiratory pathogen yields from Nasopharyngeal/Oropharyngeal swabs and sputum specimens collected from hospitalized adults in rural Western Kenya. Scientific reports. 2019 Aug 2;9(1):1-6.	• Maina D et al. Spectrum of microbial diseases and resistance patterns at a private teaching hospital in Kenya: implications for clinical practice. PLoS One. 2016 Jan 25;11(1):e0147659 • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• Wangai FK et al. Bridging antimicrobial resistance knowledge gaps: The East African perspective on a global problem. PloS one. 2019 Feb 11;14(2):e0212131. • Pfizer ATLAS surveillance database	• AMR data request to John Kiiru, KEMRI and Arshnee Moodley, ILRI (introduced by EAG member Prof Randolph) • Kenya Health Information System Tracker service desk contacted for pneumonia statistics • BSI online panel member Dr Alex Owusu-ofori emailed for contacts working in MoH / other for pneumonia incidence and AMR

Selected secondary data sources and primary sources used to derive GN pneumonia and BSI epi data…3/7

Country	Secondary Data Sources			Primary Sources
	Pneumonia	BSI	AMR	
Saudi Arabia	• Ministry of Health Statistical Yearbook • Kurashi NY et al. Community acquired acute bacterial and atypical pneumonia in Saudi Arabia. Thorax. 1992 Feb 1;47(2):115-8 • Balkhy HH et al. Hospital- and community-acquired infections: a point prevalence and risk factors survey in a tertiary care center in Saudi Arabia. Int J Infect Dis. 2006 Jul;10(4):326-33. doi: 10.1016/j.ijid.2005.06.013	• Bandy A et al. Pathogenic spectrum of blood stream infections and resistance pattern in Gram-negative bacteria from Aljouf region of Saudi Arabia. Plos one. 2020 Jun 9;15(6):e0233704. • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• Ministry of Health Summary Report of Antibiogram Data from MOH Hospitals • Pfizer ATLAS surveillance database	• Hospitalised pneumonia data request forwarded to Saudi MoH contact via EAG Secretariat • MDR data request emailed to Prof Shibl, Saudi local network organiser for ANSORP
South Africa	• Global Burden of Disease data for lower respiratory tract infections accessed at: http://ghdx.healthdata.org/gbd-results-tool • Feldman C et al. The aetiology of severe community-acquired pneumonia and its impact on initial, empiric, antimicrobial chemotherapy. Respiratory medicine. 1995 Mar 1;89(3):187-92	• McKay R, Bamford C. Community-versus healthcare-acquired bloodstream infections at groote schuur hospital, cape town, South Africa. South African Medical Journal. 2015 Dec 8;105(5):363-9. • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• National Department of Health government report on South African AMR surveillance and consumption of antibiotics • National Health Laboratory Service (NHLS) and National Institute for Communicable Diseases (NCID) AMR Dashboard • Pfizer ATLAS surveillance database	• Prof Cheryl Cohen at NCID request for pneumonial incidence • Prof Adrian Brink, clinical microbiologist involved in CAP treatment guidelines request for more recent aetiology breakdown. • MDR data request to Prof Koleka Mlisana at NHLS (contact from EAG member Sabiha Essack); forwarded on to Prof Perovic

Selected secondary data sources and primary sources used to derive GN pneumonia and BSI epi data…4/7

Country	Secondary Data Sources			Primary Sources
	Pneumonia	BSI	AMR	
Thailand	• Thailand Ministry of Public Health Annual Surveillance Reports • Reechaipichitkul W et al. Burden of adult pneumonia in Thailand: a nationwide hospital admission data 2010. J Med Assoc Thai. 2014 Mar 1;97(3):283-92.	• Antimicrobial resistance of blood samples from NARST accessed at http://narst.dmsc.moph.go.th. • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• National Antimicrobial Resistance Surveillance Center, Thailand (NARST) reports • SENTRY surveillance system • Pfizer ATLAS surveillance database	• MDR data request forwarded to Prof Visanu Thamlikitkul, Thailand local network organiser for ANSORP
Turkey	• EUROSTAT datasets for hospital inpatients discharge data by diagnosis • Kara S et al. Comparative analysis of the patients with community-acquired pneumonia (CAP) and health care-associated pneumonia (HCAP) requiring hospitalization. Tuberkuloz ve toraks. 2019 Jun;67(2):108-15	• EUROSTAT datasets for hospital inpatients discharge data by diagnosis • Diekema DJ et al. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrobial agents and chemotherapy. 2019 Jul 1;63(7):e00355-19 • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• CAESAR (Central Asian and European Surveillance of Antimicrobial Resistance network) • SENTRY surveillance system	

Selected secondary data sources and primary sources used to derive GN pneumonia and BSI epi data…5/7

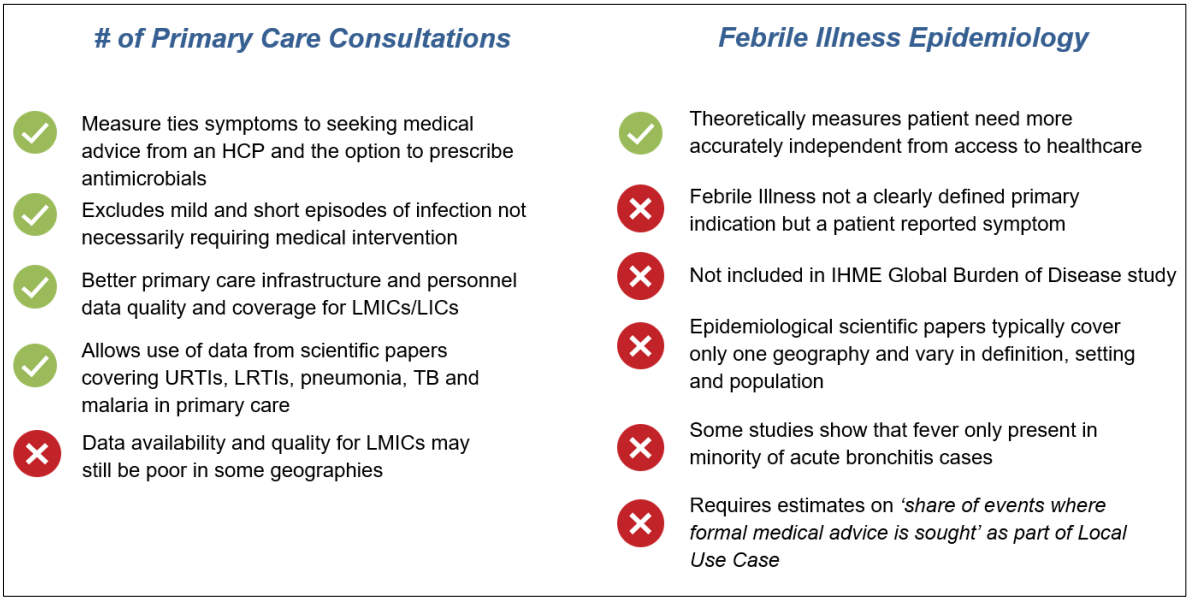
Country	Secondary Data Sources			Primary Sources
	Pneumonia	BSI	AMR	
UK	• NHS England hospital statistics admitted patient care • Chalmers JD et al. Epidemiology, antibiotic therapy, and clinical outcomes in health care–associated pneumonia: a UK cohort study. Clinical infectious diseases. 2011 Jul 15;53(2):107-13 • Leven M et al. Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. Clinical Microbiology and Infection. 2018 Nov 1;24(11):1158-63.	• PHE Laboratory surveillance of Pseudomonas and Stenotrophomonas spp. bacteraemia in England Wales and Northern Ireland • PHE Laboratory surveillance of Klebsiella spp. bacteraemia in England Wales and Northern Ireland • PHE Laboratory surveillance of Escherichia coli bacteraemia in England, Wales and Northern Ireland • PHE report - Laboratory surveillance of acinetobacter spp. bacteraemia in England, Wales and Northern Ireland: 2018 • PHE report - Laboratory surveillance of enterobacter spp. bacteraemia in England, Wales and Northern Ireland: 2018 • PHE Annual epidemiological commentary: Gram-negative bacteraemia, MRSA bacteraemia, MSSA bacteraemia and C. difficile infections, up to and including financial year April 2018 to March 2019	• PHE Laboratory surveillance reports for all GN pathogens listed under BSI • SENTRY surveillance system	

Selected secondary data sources and primary sources used to derive GN pneumonia and BSI epi data…6/7

Country	Secondary Data Sources			Primary Sources
	Pneumonia	BSI	AMR	
US	• HCUPnet (Healthcare Cost and Utilization Project) database • Sader HS et al. Comparison of ceftazidime-avibactam and ceftolozane-tazobactam in vitro activities when tested against gram-negative bacteria isolated from patients hospitalized with pneumonia in United States medical centers (2017–2018). Diagnostic Microbiology and Infectious Disease. 2020 Mar 1;96(3):114833	• Sader HS et al. Frequency of occurrence and antimicrobial susceptibility of bacteria isolated from patients hospitalized with bloodstream infections in United States medical centers (2015–2017). Diagnostic microbiology and infectious disease. 2019 Nov 1;95(3):114850 • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11 • Age data for septicaemia as an indication for HICs from HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. https://hcupnet.ahrq.gov/.	• SENTRY surveillance system	• Request for more recent hospital admissions data for pneumonia and statistics for all diagnoses to HCUPnet
Vietnam	• Ministry of Health metolazone Statistics Yearbooks • Takahashi K et al. The incidence and aetiology of hospitalised community-acquired pneumonia among Vietnamese adults: a prospective surveillance in Central Vietnam. BMC infectious diseases. 2013 Dec 1;13(1):296 • Vu TV et al. Antimicrobial susceptibility testing and antibiotic consumption results from 16 hospitals in Viet Nam: The VINARES project 2012–2013. Journal of global antimicrobial resistance. 2019 Sep 1;18:269-78	• Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, Jones RN. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrobial agents and chemotherapy. 2019 Jul 1;63(7):e00355-19 • Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11	• CDDEP Resistance Map • SENTRY surveillance system	• AMR data request to OUCRU Vietnam (introduced via EAG member Prof Baker)

Selected secondary data sources and primary sources used to derive GN pneumonia and BSI epi data…7/7

4d. Febrile Illness Data Assessment



Number of [primary care setting] consultations chosen as the basis for Dx1 patient numbers; febrile illness epi does not seem a suitable measure.

Country	Usefulness for Dx Epidemiology	Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
USA	• Fever only counted if Principal RFE – hence likely to be grossly under represented • No incidence only absolute numbers • Community Health Centres are a subset of US Primary Care	Fever = 1.16% of All Primary Care Visits in Community Health Centres	RVC Code 'Fever'* Only Principal Diagnosis	NHCS, National Ambulatory Medical Care Survey, 2014 = https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2014_namcs_chc_web_tables-508.pdf	2014	• Total = 58,528,000 ambulatory care visits including physician and non-physician visits
USA	• Only Fever as Principal Diagnosis counted	1.6% of visits estimate RFE – rural 3.1% of visits RFE – urban	ICD-9 Only Principal Diagnosis	Probst et al. Rural-urban differences in visits to primary care physicians. Fam Med 2002;34(8):609-15.	2002 using data from 1996/97	• An estimated 792 million visits were made to primary care physicians' offices in the 2-year period of 1996 – 1997 (of these, 624 million in urban areas and 167 million in rural areas)
Global	• Report provides ranking of RFV** but no absolute numbers or incidences • In 18 studies Fever reported by patients but not physicians	Ranking by physicians and patients and for Developed and Developing countries	'Fever' Consolidated from 18 individual studies with varying definitions	Finley et al. What are the most common conditions in primary care? Canadian Family Physician November 2018, 64 (11) 832-840 – a systematic review	2018	• Provides evidence that LMIC incidence of respiratory conditions in primary care higher (not quantifiable) • Illustrates that 'Fever' is reported by patients but not by physicians

Key: High Medium Low

Febrile Illness Epidemiology - US. Source: RFE = Reason for Encounter, *RVC = "A Reason for Visit Classification for Ambulatory Care (RVC)" defined in the 2014 National Ambulatory Medical Care Survey Public Use File Documentation, **RFV = Reason for Visit

Country	Usefulness for Dx Epidemiology	Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
Saudi Arabia	• Study covered only two centres in the private sector • No incidence, only absolute numbers	5,285 out of 24,816 outpatient clinic visits (21.3%) presented with fever (50% under 15 years with majority in under 5s, 40.5%)	Not mentioned	El-Gamal et al . Causes and clinical aspects of fever in patients visiting primary healthcare . World Family Medicine. 2020; 18(1): 23-29. DOI: 10.5742MEWFM.2020.93724	2 years 2017 – 2018	• 84% of those with fever had acute respiratory tract infection (URTI 62.4%, LRTI 21.6%) • 50% of the patients with fever needed investigations to conclude the diagnosis (14% special investig.) • The majority of patients with fever (63%) received antibiotics • Fever was present in only 32.8% of the patients with acute bronchitis
Japan	• Single centre (outpatient department of small community hospital) • No incidence, only absolute numbers	215 of 2,292 RFE (1,515 cases) = 9.5%	ICPC-2 coded	Takeshima et al . Reasons for encounter and diagnoses of new outpatients at a small community hospital in Japan: an observational study. Int J Gen Med. 2014; 7 259–269	2010 - 2011	• Small community hospitals (<200 beds) = 70% of all hospitals in Japan • Respiratory highest reason for visit and highest diagnosis

Key: High Medium Low

Febrile Illness Epidemiology – High Income Countries. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care

Country	Usefulness for Dx Epidemiology	Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
Japan	• Japanese language paper	Unknown	unknown	Yamada T, Yoshimura M, Nago N, et al. What are common diseases and common health problems? The use of ICPC in the community-based project. Japanese Journal of Primary Care. 2000;23:80–89	2000	• None
Netherlands	• Only paediatrics (GP out-of-hours service) • No incidence, only absolute numbers	5,343 of 17,170 contacts (31.1%) were fever related (70.0% resulted in a GP consultation)	ICPC coded	De Bont et al. Workload and management of childhood fever at general practice out-of-hours care: an observational cohort study. BMJ Open. 2015; 5(5): e007365	2012	• One in four consultations resulted in an antibiotic prescription
Other HIC papers (not further explored at this point) • Moth G, Olesen F, Vedsted P. Reasons for encounter and disease patterns in Danish primary care: changes over 16 years. Scand J Prim Health Care. 2012;30(2):70–75 • Okkes IM, Polderman GO, Fryer GE, et al. The role of family practice in different health care systems: a comparison of reasons for encounter, diagnoses, and interventions in primary care populations in The Netherlands, Japan, Poland, and the United States. J Fam Pract. 2002;51(1):72–73						

Key: High Medium Low

Febrile Illness Epidemiology – High Income Countries. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care

Country	Usefulness for Dx Epidemiology	Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
Thailand	• Data from one Northern province (not national data) • Only public PCUs included (not private clinics or GPs in provincial hospitals) • No incidence, only absolute numbers	• 29,246 (35.3%) patients presented with a history of fever • 10,508 (13.7%) had a temperature of more than 37.5°C at presentation • 8,871 (11.6%) patients had both a history of fever and a temperature at presentation	Not mentioned	Greer et al. Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ Open 2018;8 e022250. doi 10.1136	2018	• 762,868 patients attended the PCUs between 1 January 2015 and 31 December 2016 • Antibiotics were prescribed for 81,691 (97.7%) illness episodes; 37,011 (44.2%) patients were prescribed an antibiotic during their first visit • 13.8% of patients (11, 547) were prescribed antibiotics without a temperature, history of fever or ICD 10 code for infection
Vietnam	• Data from only Southern Vietnam Community Primary Health Facilities • No incidence, only absolute numbers	• Fever = 12.5% of consultations	Axillary temperature ≥ 38.0 °C	Phuong et al. Dengue virus infections in Vietnam: Tip of the iceberg. Dengue Bulletin. 2006;30:15–25	2006	• 688,220 patient consultations • On average 17 consultations per health post per day • A total of 86,449 patients had fever

Key: High Medium Low

Febrile Illness Epidemiology – UMIC. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care

Country	Usefulness for Dx Epidemiology	Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
South Africa	• No incidence, only absolute numbers • Limited coverage of population due to limited access to doctors • Four provinces only but representing 32% of SA population	• 869 of 31,357 RFEs = 2.8% presented with fever	Not mentioned ICPC-2 coded	Mash et al. (2012) A Morbidity Survey of South African Primary Care. PLoS ONE 7(3) e32358.	2012	• In SA about 16% of the population has insurance and makes use of the private sector • Remaining 84% of the population is dependent on the public sector • Fever starts at a peak in the under-5s, falls rapidly over the next 5-years and then levels out to decline more slowly over the adult years • Nurses saw 16,238 (86.1%) and doctors 2,612 (13.9%) of patients
South Africa	• Febrile illness not included, only respiratory • Limited coverage of population due to limited access to doctors	• N/a.	Not mentioned ICPC-2 coded	Brueton et al. . Primary care morbidity in Eastern Cape province. S Afr Med J 2010;100(5):309-12	2010	• 4,383 patient encounters • Data for 4,379 patients • 6,856 symptoms recorded • Most contacts at the clinic (97%) and the health centre (80%) were with a nurse

Key: High Medium Low

Febrile Illness Epidemiology – UMIC. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care.

Country	Usefulness for Dx Epidemiology		Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
Brazil	• No incidence, only absolute numbers • Limited coverage of population • PHC units of a medium sized Brazilian City, same day appointments		• 30 out of 1,220 RFEs = 2.5% presented with fever (RFEs not number of patients)	Not mentioned ICPC coded	Landsberg et al. Analysis of demand for family medical care in Brazil using the International Classification of Primary Care. Science & Collective Health ; Rio de Janeiro Vol. 17, Iss. 11, (Nov 2012): 3025-3036	2012	• 1,220 RFEs and 562 cases in total
Other UMIC papers (not further explored at this point) • https://academic.oup.com/fampra/article-abstract/37/5/648/5820801							

Key: High Medium Low

Febrile Illness Epidemiology – UMIC. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care

Country	Usefulness for Dx Epidemiology	Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
India	• No incidence, only absolute numbers • Only one health centre	• Pyrexia of unknown origin: 4.7% of 6,838 patients	Pyrexia of unknown origin	Kumari et al . Morbidity Profile and Seasonal Variation of Diseases in a Primary Health Center in Kanpur District: A Tool for the Health Planners. J Family Med Prim Care. 2012 Jul-Dec; 1(2) P86–91.	2012	• 6,838 patients • 1 year study from June 2007 to July 2008 • Primary Health Centre in Patara in Kanpur District, India
India	• One day Point prevalence • No incidence, only absolute numbers	• Fever (35.5%) was the most common presenting symptom	Not mentioned ICD-10 code	Salvi et al. Symptoms and medical conditions in 204 912 patients visiting primary health-care practitioners in India: a 1-day point prevalence study (the POSEIDON study) Lancet Glob Health. 2015;3(12):e776–84.	2011	• 7,400 health-care practitioners; 204,912 patients, who presented with 554,146 reasons for visit • 142,619 patients (69.6% attended a private clinic, 41,802 pts (20.4%) attended private hospitals and 20,491 pts (10%) were seen by health-care practitioners from government hospitals • Number of patients seen per doctor: private clinics: 27, private hospitals: 28, government hospitals: 29

Key: High Medium Low

Febrile Illness Epidemiology – LMIC. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care

Country	Usefulness for Dx Epidemiology		Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
Kenya	• Only paediatrics included • Limited physician access / coverage • No incidence, only absolute numbers		• Fever in 86% of sick child visits (<5 years)	Not mentioned	Van Hemelrijck et al. Trends observed during a decade of paediatric sick visits to peripheral health facilities in rural western Kenya, 1997-2006 Trop Med Int Health . 2009 Jan;14(1):62-9. https://pubmed.ncbi.nlm.nih.gov/19017311/	2009	• No physicians worked regularly in the clinics (Physician assistants) • 64,394 Sick Child Visits were made (average rate of 0.70 SCVs per child-year) • Fever and cough were the most common symptoms, reported, on average, in 86% and 67% of SCVs • Most common infections: malaria, pneumonia, GI infections and URTI
Nigeria	• No incidence, only absolute numbers • Only one general hospital (outpatient department) • Small sample size (402 patient encounters)		• 17.2% of patients with symptoms of fever • Of these 48.9% diagnosed with malaria; 5.4% URTI; GI infection 2.2%; cystitis 2.2%; cough 2.2%; others 39% • Diagnosis in general (not related to fever above): Malaria = 18%, URTI = 3.2%	Not mentioned ICPC-2 coded	Olagundoye et al. International Classification of Primary Care-2 coding of primary care data at the general out-patients' clinic of General Hospital, Lagos, Nigeria. J Family Med Prim Care. 2016 Apr-Jun; 5(2): 291–297	2016	• Out-patients' clinic of a family medicine department at a single hospital (physician led) • Small sample size: 401 patient encounters • Analysis on randomly selected patient encounters by systematic sampling until the minimum sample size of 384

Key: High Medium Low

Febrile Illness Epidemiology – LMIC. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care

Country	Usefulness for Dx Epidemiology	Febrile Illness Measure	Febrile Illness Definition	Source / URL	Date	Comments
Pakistan	• Single Health Centre only • No incidence, only absolute numbers • Study performed during winter (potential seasonal bias)	• Pyrexia of unknown origin = 3.8% of all consultations	Not mentioned (Patients categorised on basis of symptoms into organ systems involved)	Khan et al 2018. Demographic and disease patterns at a primary healthcare setting. Annals of King Edward Medical University, 24(1): 69-74	2018	• In Punjab there are 2,500 Basic Health Units which are the first point of contact between the patient and physician • Single Health centre with 60-100 patients daily • Study: 2,357 patients (4.4% of population) during 1st January 2017 to 30th June 2017 • Study performed during Winter
Tanzania	• Focus on respiratory symptoms and diagnosis (fever not quantified) • Only paediatrics • No incidence, only absolute numbers	• 62.2% of all had an acute respiratory infection (5% radiologically confirmed pneumonia)	Temperature ≥ 38°C	D'Acremont et al Beyond Malaria — Causes of Fever in Outpatient Tanzanian Children. N Engl J Med 2014; 370:809-817	2014	• Febrile Children <10y • Two outpatient clinics - one rural and one urban • 70.5% = viral disease, 10.9% = parasitic disease, 22.0% = bacterial disease • Systemic infection other than malaria or typhoid found in 13.3% • Malaria = 10.5%, Gastroenteritis = 10.3%, UTI = 5.9%, Typhoid fever = 3.7% • Nasopharyngeal viral infection (without respiratory symptoms or signs) in 11.9%

Other LMIC papers (not further explored at this point)

- Naville et al. Scope of health problems managed by general practitioners in Mali and France: awaiting practice transition in sub-Saharan Africa? Family Practice, Volume 37, Issue 5, October 2020, Pages 668–674
- There is an ongoing observational study to help address information gaps: Hopkins et al. Febrile Illness Evaluation in a Broad Range of Endemicities (FIEBRE): protocol for a multisite prospective observational study of the causes of fever in Africa and Asia. BMJ Open 2020;10:e035632.
- 5 community health centres

Key: High Medium Low

Febrile Illness Epidemiology – LMIC. Source: RFE = Reason for Encounter, *ICPC: International Classification of Primary Care

Table 2: Fever presentation among outpatient visits due to Lower respiratory disorders

Variables	Fever				Chi Square (p)
	Yes		NO		
	Number	%	Number	%	
- Acute respiratory failure	0	00.0%	2	100.0%	
- Asthma	154	14.6%	898	085.4%	
- Asphyxia	0	00.0%	1	100.0%	
- Bronchiectasis	0	00.0%	15	100.0%	
- Bronchiolitis	9	24.3%	28	075.7%	
- Bronchitis	586	32.8%	1199	067.2%	
- Broncho pneumonia	219	55.2%	178	044.8%	
- Cancer lung	0	00.0%	1	100.0%	
- COPD	3	12.5%	21	087.5%	
- Croup	58	79.5%	15	020.5%	
- DIPF	0	00.0%	1	100.0%	
- Hemothorax	0	00.0%	2	100.0%	
- Haemoptysis	0	00.0%	1	100.0%	407.870
- Pertussis	19	76.0%	6	024.0%	(< 0.00)
- Pleural effusion	0	00.0%	6	100.0%	
- Pleurisy	0	00.0%	26	100.0%	
- Pneumonia	84	42.9%	112	057.1%	
- Pneumothorax	0	00.0%	15	100.0%	
- Pulmonary oedema	1	06.3%	15	093.8%	
- Pulmonary embolism	0	00.0%	7	100.0%	
- Recurrent laryngeal nerve injury.	0	00.0%	1	100.0%	
- Respiratory distress syndrome	0	00.0%	4	100.0%	
- TB	7	35.0%	13	065.0%	

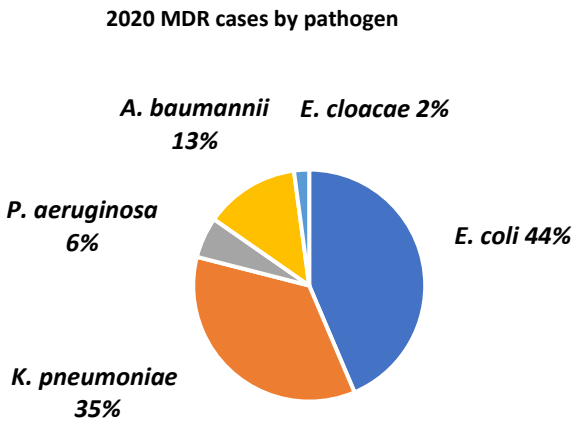
Table 3: Fever presentation among outpatient visits due to upper respiratory tract disorders

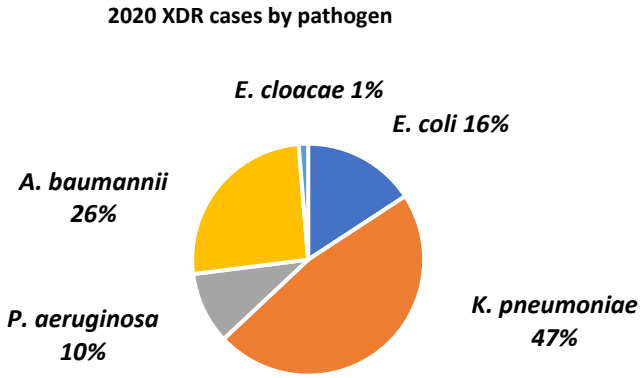
Variables	Fever				Chi Square (p)
	Yes		No		
	Number	%	Number	%	
-Allergic Rhinitis	32	18.8%	138	081.2%	
- Allergic sinusitis	11	18.3%	49	081.7%	
- Common cold	296	46.6%	339	053.4%	
- Epiglottitis	0	00.0%	14	100.0%	
- Epistaxis	1	16.7%	5	083.3%	
- Influenza	115	78.8%	31	021.2%	581.561
- OM	124	42.2%	170	057.8%	(< 0.00)
- Otitis externa	0	00.0%	22	100.0%	
- Pharyngitis	2153	69.5%	946	030.5%	
- Tonsillitis	564	74.0%	198	026.0%	
- Vertigo	3	05.1%	56	094.9%	

- Respiratory tract infections are the most common cause of fever among outpatient visits in private hospitals in Saudi Arabia
- As shown in the tables not all present with fever (Pneumonia 42.9%; Broncho-pneumonia 55.2%)

Febrile illness in RTI in Primary Care – Saudi Arabia. Source : El-Gamal et al. Causes and clinical aspects of fever in patients visiting primary healthcare. World Family Medicine. 2020; 18(1): 23-29

4e. MDR/XDR cases per pathogen - BSI



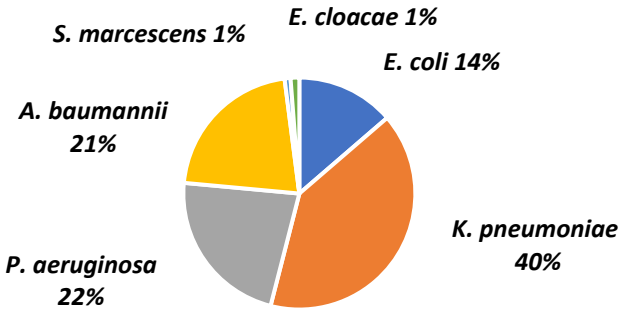


***E. coli, K. pneumoniae* and *A. baumannii* are the top 3 Gram negative pathogens contributing to MDR & XDR Gram negative BSI cases**

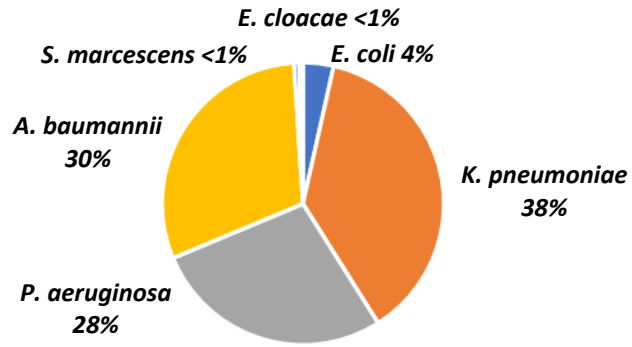
- In 2020, the top 3 pathogens contributing to MDR and XDR/DTR Gram negative BSI for the 13 countries are ***E. coli, K. pneumoniae and A.baumannii*** highlighting the **greater contribution to BSI from *E. coli*** as compared to Gram negative pneumonia where *K. pneumoniae* and *P. aeruginosa* dominate
- Despite the dominance of *E.coli* in BSI, there is an increased proportion of XDR/DTR Gram negative BSI that is due to *A. baumannii* and *K. pneumoniae* (versus MDR), reflecting greater XDR resistance rates for these pathogens compared to *E. coli*, resistance rates of the latter which are relatively low across the 13 countries
- Looking to 2040, ***E. coli*, *K. pneumoniae* and *A. baumannii* are forecast to remain the top 3 pathogens in Gram negative BSI**
- MDR and XDR/DTR data by country has been extracted from SENTRY and Pfizer's ATLAS surveillance databases. **MDR**: Multi-drug resistance defined as three or more antibiotic drug classes have a non-susceptible drug. **XDR:** Extensively drug resistant defined as resistance to all but 2 or fewer antibiotic classes. **DTR**: Difficult-to-treat resistance defined as defined as resistance to ≥1 FQ + ≥1 3GC + ≥1 CBP first line Tx.

4f. MDR/XDR cases per pathogen - Pneumonia

2020 MDR cases by pathogen



2020 XDR cases by pathogen



- In 2020, the top 3 pathogens contributing to MDR and XDR/DTR Gram negative pneumonia for the 13 countries are ***K. pneumoniae*, *P. aeruginosa* and *A. baumannii***
- There is an increased proportion of *A.baumannii* and *P.aeruginosa* contributing to XDR Gram negative cases (versus MDR), reflecting greater XDR resistance rates in most countries (along with *K. pneumoniae*) as compared to the other Gram negative pathogens of interest; in contrast XDR / DTR resistance proportions for *E.coli* are relatively low across most countries
- Looking to 2040, ***K. pneumoniae*, *P. aeruginosa* and *A .baumannii* are forecast to remain the top 3 pathogens in Gram negative pneumonia**
- MDR and XDR/DTR data by country has been extracted from SENTRY and Pfizer's ATLAS surveillance databases.
- **MDR**: Multi-drug resistance defined as three or more antibiotic drug classes have a non-susceptible drug. **XDR:** Extensively drug resistant defined as resistance to all but 2 or fewer antibiotic classes. **DTR**: Difficult-to-treat resistance defined as defined as resistance to ≥1 FQ + ≥1 3GC + ≥1 CBP first line Tx.

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