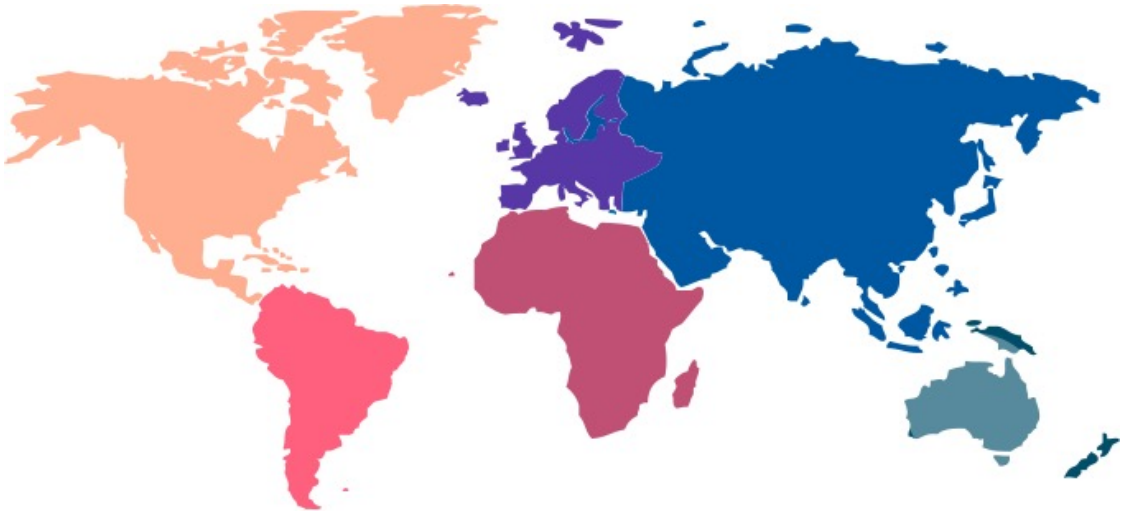
Aestimo
Innovator's Briefing

Antibiotics:
Bacterial Sepsis



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About Sepsis

Epidemiology

(data extracted from Rudd K. E. et al 2020, Lancet: see Annex for adapted table data)

	Direct infection		Non-Communicable Disease		Tissue injury	
Location	**Incident sepsis cases**	**Sepsis ASIR per 100,000 population**	**Incident sepsis cases**	**Sepsis ASIR per 100,000 population**	**Incident sepsis cases**	**Sepsis ASIR per 100,000 population**
EU27/EEA	644,745	86.9	644,195	76.8	50,331	8.9
North America	652,213	138.3	480,673	97.2	49,221	12.3
LATAM	2,812,914	258.3	1,630,600	144.4	195,728	16.4
Asia	14,766,112	322.8	7,350,511	157.5	858,512	17.1
Africa	14,757,635	696.45	3,947,527	258.75	730,168	52.2

- Sepsis-3 definition (2016): A life-threatening organ failure or dysfunction caused by a dysregulated response to an infection, of which septic shock is a subset. Following infection, within endothelial cells pro-coagulation factors are activated, releasing inflammatory mediators into the circulation leading to a systemic inflammatory response.

- If misdiagnosed or untreated, the patient can perish in less than 12 hours, with the paradigm that delaying antibiotics increases mortality by up to 10% every hour.

- It can be caused by bacteria (87%), virus (1%), fungi (12%) or parasite (rare), each with its own mechanism: bacterial types are the most frequent (values on global averages, in LMIC viral based sepsis has been reported to have a higher frequency). However, it can also be mimicked in response to other acute conditions without any infectious material detectable.

- ***Top 5 leading causes of incidence***: diarrhoeal diseases, LRTI, maternal disorders (childbirth in less than optimal conditions), neonatal disorders, malaria

- ***Top 5 leading causes of death***: LRTI, diarrhoeal diseases, neonatal disorders, stroke (9^{th} by incidence), cirrhosis (8^{th} by incidence)

- Up to 42% of sepsis presentations are culture negative, suggesting a non-bacterial cause. However bacterial related sepsis does not always involve bacterial migration into the blood stream (bacteremia): the results is modern perspectives of sepsis are based on clinical manifestations, requiring a suspicion of infection at initial presentation.

- Adults with cardiovascular disease, diabetes, or viral infections are more susceptible to opportunistic sepsis, specifically, antibiotic-resistant organisms.

- Sepsis may be caused by one agent, but sequelae often involve additional infectious agents i.e. a bacterial sepsis can facilitate a viral infection and further sepsis

- Previously, sepsis was divided into three stages, but 'severe sepsis' has been removed, with 'Sequential Organ Failure Assessment' (SOFA) integrated into the diagnosis.
- SOFA is a 6 organ systems assessment (respiratory, coagulation, liver cardiovascular, CNS and renal): each system is given a point value from 0 to 4, corresponding to normal to high tissue dysfunction. The higher the cumulative score, the greater the prediction of mortality (e.g. SOFA score 10-12 = 40-50% mortality, SOFA score 16-24 = >90% mortality)
- The patient is monitored at 24 hours and then every 48 hours: scores increasing or decreasing contribute to the prognosis: in the ICU setting SOFA pertinence has been questioned as patients typically present with organ failure and that a significant number of them have no infection. The ramification being '***do you or do you not prescribe antibiotics?***'.
- More recently, using computer algorithms, other teams have divided sepsis into 4 types (SENECA project definition 2019)

Stages of Sepsis
(2016 definition)*

stage	***description***
Sepsis	Clinical life-threatening organ dysfunction caused by a dysregulated response to infection
Septic shock	Significant/critical circulatory, cellular and metabolic abnormalities associated with greater risk of mortality. Can be identified by need to maintain arterial pressure and serum lactate levels

**severe sepsis that fell between sepsis and septic shock has been removed: however not all practicing healthcare workers use this terminology*

Types of Sepsis
(2019 SENECA definition)

Type	***Description****
alpha	33% of patients, lowest organ dysfunction and lowest death rate
beta	27% of patients, older with chronic illness and kidney dysfunction
gamma	Same as beta, but with added elevated indicators of inflammation and pulmonary dysfunction
delta	13% of patients: liver dysfunction and shock with high in-hospital death rate

**inclusion in the definition required combination of antibiotic administration and body fluid culture*

The Patient Journey

Patient manifests

- Nausea/vomiting
- Severe breathlessness
- Change in mental state
- Dizziness/feeling feint
- Muscle pain
- Pale or mottled skin
- Diarrhoea and reduced urine production

Patient is assessed

- Blood tests (infection, coagulation issues)
- Liver/Kidney function assessment
- Urine, wound or respiratory secretion assessment
- X-ray imaging (X-ray, ultrasound, MRI)
- SOFA assessment

Confirmation and staging

Treatment

- Systemic or IV antibiotics depending on stage, location and severity
- Vasopressors if blood pressure low
- IV fluids
- Possible surgery if infected tissue observed
- Location specific interventions (airway or renal support, lavage, drainage)

Follow up
patient care and management

Routinely and frequently (at least every 2 - 3 months) due to possible recurrence, reinfection and organ function assessment: specifics dependent on infectious agent and organs affected

Recurrence, refraction or relapse:

- Possible post sepsis syndrome (affects 50% of sufferers: physical and psychological effects)
- Common hospital readmission (nearly 30% within 90 days of hospital discharge)
- Increasing evidence that treating with 3rd or 4th generation antibiotics, disrupts the microbiota and can result in severe sepsis

Treatment approach

The approach for antibiotic prescription differs between professional societies, reimbursement entities and practitioners, however, overall, the general approach is to prescribe antibiotics as soon as possible.

Step 1: while waiting for culture tests, IV application of broad acting empiric antibiotics within 60 minutes of the patient entering the hospital

The aim of empiric antibiotics is to target as many likely causative agents as possible: the selection of the antibiotic(s) is based on clinical manifestations and characteristics (which organs are failing, medical history of patient, patient biometrics, risk of drug resistance) and infectious agents that are known to cause the organs to fail.

If patient entering septic shock, combination therapies can be considered if bacteria is gram-negative

Step 2: as knowledge of the infectious agent becomes more evident, and clinical manifestations potentially decrease in severity, narrow down antibiotic usage. If infection is not cause of symptoms, cease antibiotics immediately

Step 3: once exact cause of sepsis known, reduce antibiotics (narrowing or de-escalation) to those known to act precisely on the pathogen to increase efficacy, reduce possible resistance and emergence of drug resistant bacteria and adverse drug effects.

Key experiences and insights obtained:

- Incorrect empiric antibiotic usage can significantly reduce patient survival
- In septic shock patients with multiple organ dysfunction higher mortality rates have been reported because of inappropriate empiric antibiotic usage
- Between 11% and 55% of treatments are only ever de-escalated due to health care worker concerns for patient deterioration or further infection
- Prescription of incorrect or inadequate empiric antibiotics is occurring up to 40% of the time
- Duration of antibiotic treatment is still ill defined: one week to ten days of treatment results in a lower emergence of resistant strains. Shorter durations are also possible dependent on the location and type of infection
- Despite clear indications of bacteria to be analysed and high technology solutions, testing still returns negative results despite healthcare workers judgements that patient is infected: the location of sample collection influences the output:

  i) Up to 69% of patients with sepsis, do not have a bloodstream infection
  ii) Pneumonia focused approaches suggest taking deep alveolar swabs

Examples of the diversity, complexity and difference in approaches by healthcare providers guidelines for empiric antibiotics and sepsis.

Southern Health and Social care trust (Ireland)	http://www.southernguidelines.hscni.net/?wpfb_dl=844
Greater Glasgow and Clyde NHS (Scotland)	https://www.cem.scot.nhs.uk/adult/antibiotguid.pdf
Public Health Ontario (Canada)	https://www.publichealthontario.ca/-/media/documents/A/2016/asp-empiric-prescribing-guidelines.pdf?la=en
Nebraska Medicine (U.S.A.)	https://www.unmc.edu/intmed/divisions/id/asp/clinical-pathways/docs/sepsis-antibiotics-2019.pdf

Microbiology, Antibiotics and Antibiotic resistance

Bacteria detected and their frequency (%) in culture positive infected patients

Gram-positive		Gram-negative	
Overall*	46.8	Overall*	62.2
Staph. Aureus	20.5	*Pseudomonas sp.*	19.9
MRSA	10.2	*E. Coli*	16.0
Enterococcus	10.9	*Klebsiella sp.*	12.7
Staph. epidermis	10.8	*Acinetobacter. sp*	8.8
Strepto. pneumoniae	4.1	*Enterobacter*	7.0
other	6.4	other	17.0

In some cases, polymicrobial infection of simultaneous gram-positive and gram-negative bacteria is seen: Complete detail of bacteriology in references:* ***Sepsis: bacterial mechanisms of injury*

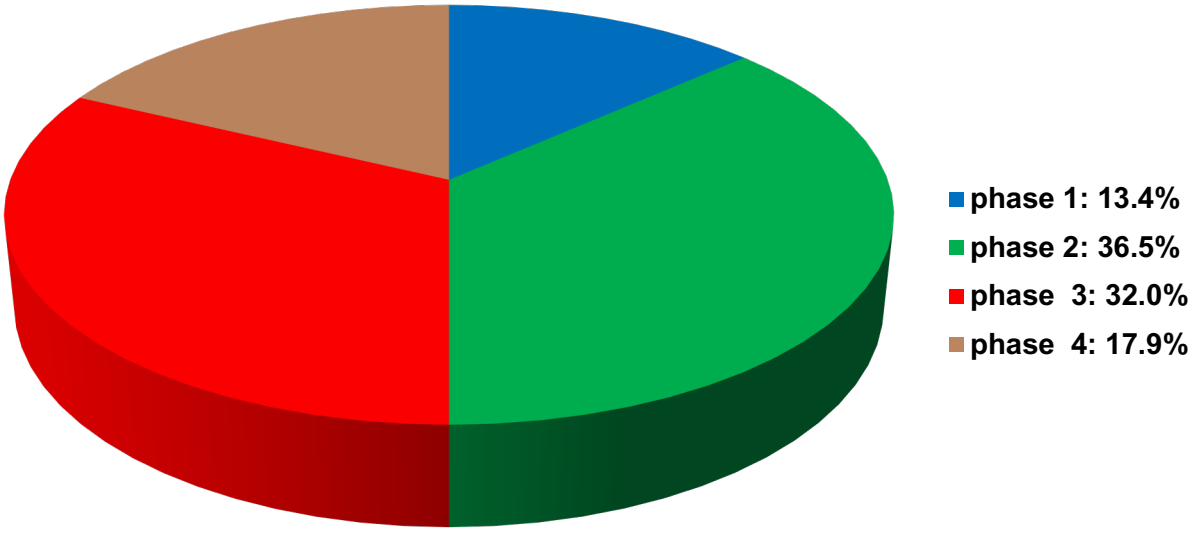
Summary table: Locations of sepsis, frequency, bacteria, and empiric antibiotics*

Site of infection	Case frequency (%)	Bacteria reported	Empiric antibiotic(s) examples
Respiratory (Pneumonia)	39 - 50	Klebsiella sp S. pneumoniae	Gram negative: Cefepime +/- tobramycin Gram positive: Vancomycin
Bacteremia	20.5	S. aureus Streptococcus sp. Enterococcus Pseudomonas. sp	Gram negative: Cefepime +/- tobramycin Gram positive: Vancomycin
Genitourinary (UTI, endometriosis, chorioamnitis)	14 - 20	Klebsiella sp E. coli Proteus mirabilis Enterococcus	Gram negative: Ceftazidime/Ceftriaxone Gram positive: Aminopenicillin
Abdominal (pancreatitis, intra-abdominal abscess)	8 - 15	E. coli, Bacteroides fragilis, (ESBL increasing in frequency)	Primary Peritonitis: Piperacillin/tazobactam or Cefepime (typically only gram negative bacteria) Secondary and Tertiary Peritonitis (Polymicrobial): Piperacillin/tazobactam or Cefepime and Metrondiazole +/- Gentamicin (for Gram+ bacteria)
Device-related (indwelling catheter)	1.1	S. aureus Pseudomonas Enterococcus	Gram negative: Cefepime +/- tobramycin Gram positive: Vancomycin
Wound/soft tissue (burn, wound, cellulitis)	8 - 10	Pseudomonas sp. S. pyogenes S. aureus Klebsiella sp	Gram negative: Ceftazidime/Ceftriaxone Gram positive: Vancomycin
Central Nervous System	0.6	S. pneumoniae N. meningitides	Gram negative: Ceftazidime/Ceftriaxone Gram positive: Vancomycin
Endocarditis	0.7	S. aureus Streptococcus Enterococcus	Gram negative: Cefepime +/- gentamicin Gram positive: Vancomycin

**possible combinations are significantly more extensive than the examples indicated here and are prescribed based upon practitioner or healthcare institution/insurance guidelines: this includes further subdivision depending on if the infection was community vs hospital acquired*

Clinical trial design

Ongoing clinical trials for sepsis = 134 (17 are focusing on antibiotics)



Clinical trial characteristics for Antibiotic Trials

Phase 1

CT cost $ 56 000

Median Patient No. 28
Median Duration: 0.5 (months)

Phase 2

CT cost $ 520 000

Median Patient No. 82
Median Duration: 1 (months)

Phase 3

CT cost $ 1 928 000

Median Patient No. 382
Median Duration: 0.5 (months)

Standards of care and market values (SAM and SOM)

- **Treatment Cost (TC)** represents the precise treatment regimen (annual or recommended duration if < 1year) multiplied by the price of the intervention(s) sourced from published prices from the marketplace geography and are indicated in $US equivalent values.
- The **market size** of the intervention, the **Serviceable Available Market (SAM)** value, are annual values and calculated as a function of the patient population eligible for that particular treatment for all possible locations of infection multiplied by the TC.
- **Forecasted SOM values** are calculated assuming the final product has a **14-year marketplace lifespan with a 21% SAM penetration**, which are then used in development risk calculations below; following the Health Economics caveat that **the innovative solution will be better than that standard of care (comparator product) but sold at the same price**
- A detailed list of antibiotics, with types and mechanisms can be found at: orthobullets.com

Vancomycin (Glycopeptide)

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	337.0	323.2	950.2
North America	576.4	487.9	1434.4
Latin America	469.3	1559.0	4583.6
Asia	286.6	4715.5	13863.6
Africa & ME	286.6	3988.9	11727.6

Cefepime (4th gen cephalosporin)

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	100.8	101.8	299.3
North America	546	486.8	1431.3
Latin America	630	2204.5	6481.4
Asia	96.6	1674.0	4921.7
Africa & ME	96.6	1416.1	4163.4

Tobramycin (aminoglycoside)

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	102.9	85.1	250.2
North America	352.8	257.6	757.3
Latin America	395.4	1133.1	3331.5
Asia	14.4	204.4	601.0
Africa & ME	14.4	172.9	508.4

Ceftazidime (3rd gen cephalosporin)

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	378	134.7	396.2
North America	420	132.1	388.5
Latin America	268.8	331.9	976.0
Asia	173.8	1063.5	3126.7
Africa & ME	173.8	899.6	2645.0

Aminopenicillin (3rd gen penicillin)

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	3.2	0.7	2.2
North America	9.9	2.0	6.0
Latin America	5.0	4.0	11.9
Asia	2.9	11.7	34.5
Africa & ME	2.9	9.9	29.2

Metrondiazole (Nitroimidazole)

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	29.8	5.2	15.3
North America	26.2	4.0	11.9
Latin America	8.0	4.8	14.4
Asia	0.3	0.9	2.8
Africa & ME	0.3	0.8	2.4

Development risk

Using SOM values to estimate development risk, even with the ideal environment of a homogenized and integrated global marketplace defined by common regulatory and reimbursement requirements that would enable a validated solution to penetrate the complete TAM:

To reach a balance of zero following innovation investment, integrating in indication specific parameters, required lifetime threshold SOMs for antibiotics are:

987 $Mn for Repositioning **2685 $Mn for De Novo**

Integration of local socioeconomic realities into pricing

Below we report the development risk assessments as a function of the calculated outputs of TC and patient populations for de novo or repositioning of antibiotics for sepsis. However, there is a significant caveat.

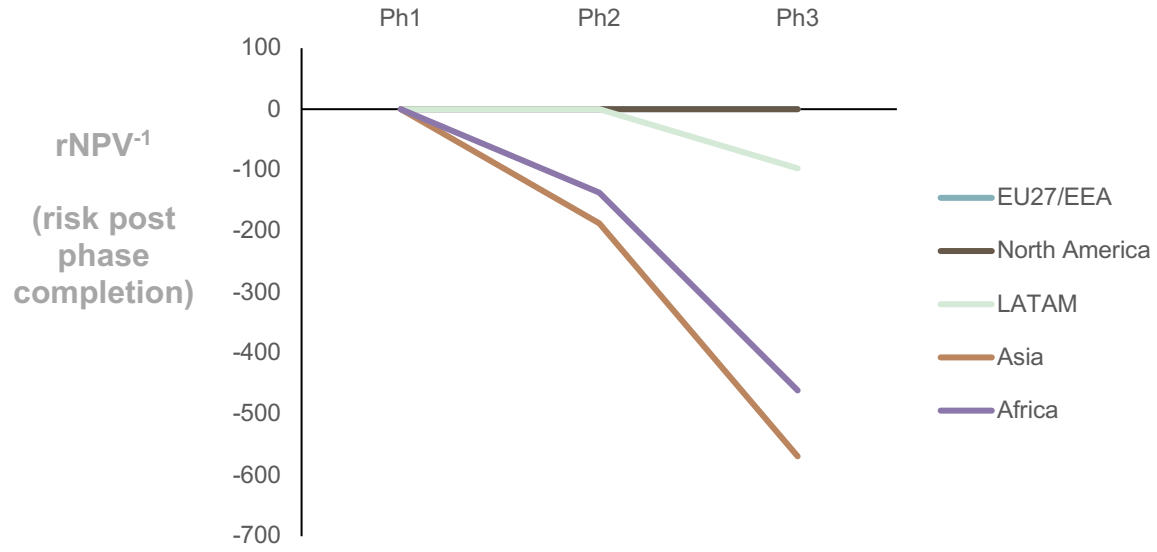
While Latin America and the Caribbean, Africa and the Middle East, and Asia present SOM values above the threshold, the treatment cost prices, which for Africa & ME and Asia are already at generic pricing, are very high compared to the average income of the patients, and any reimbursement entity or agency.

These prices, therefore correspond to what the wealthier members of these societies can afford: however epidemiology and demographic analysis reveals it is the poorest members of society that suffer the most and therefore need the most.

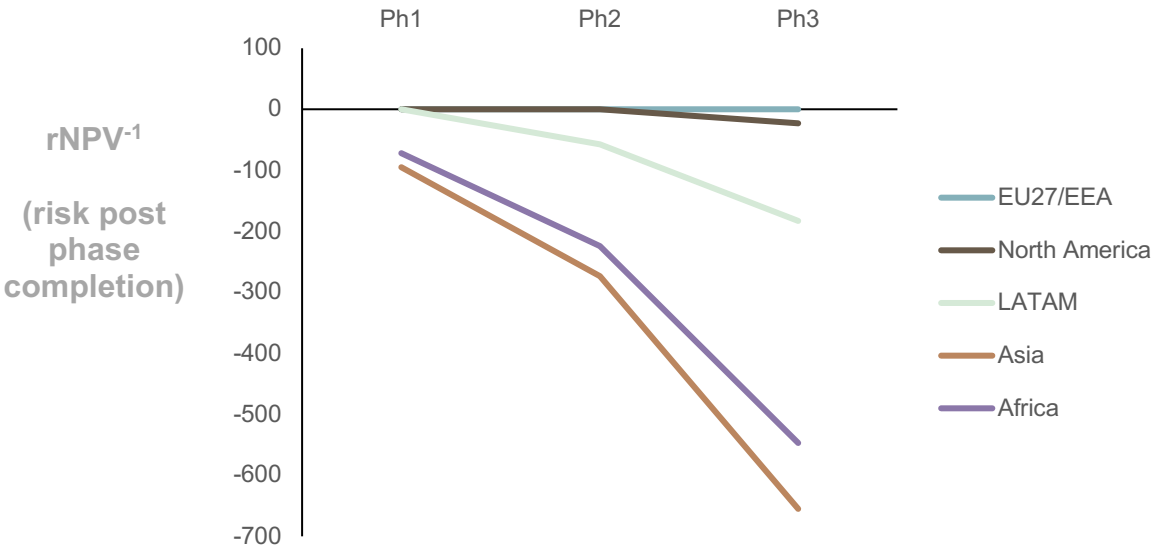
To be able to reach these populations, it will mean decreasing prices by a factor of 2 to 10: the result is that SOM values then drop beneath the threshold that would encourage an innovator to launch a programme on antibiotic development. This is discussed more comprehensively in Antibiotic Innovation, later in this document.

Glycopeptides (Vancomycin)

De Novo development risk:

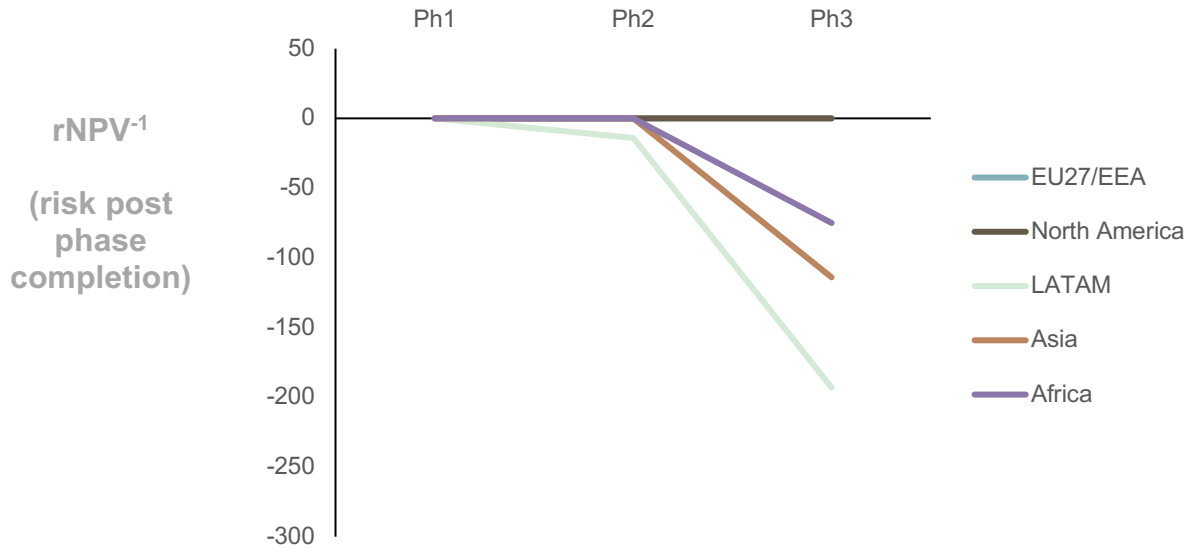


Repositioning development risk:

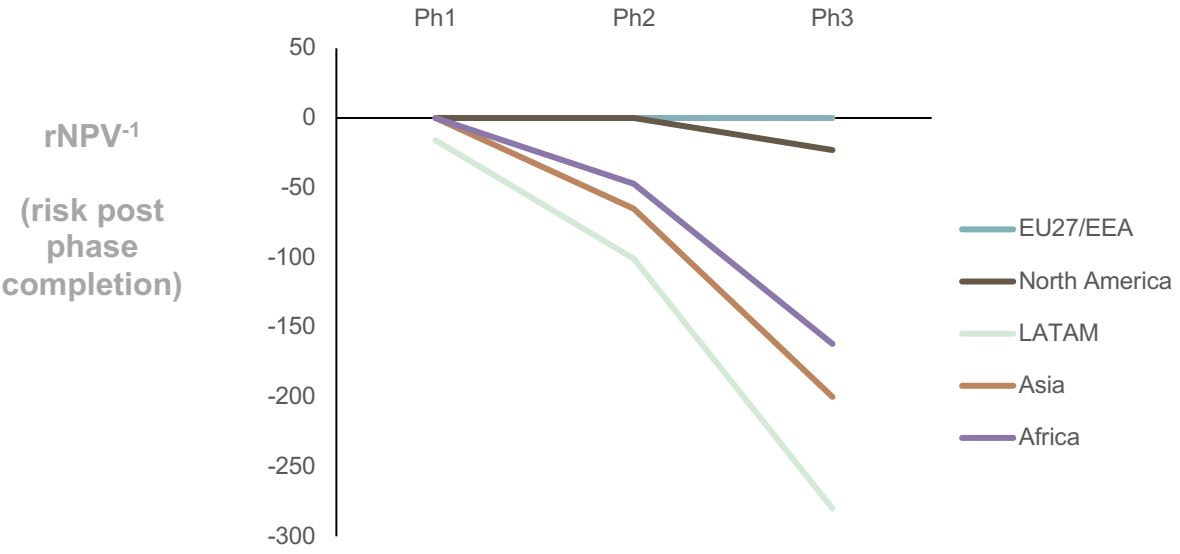


Cephalosporins – 4th gen (Cefepime)

De Novo development risk:

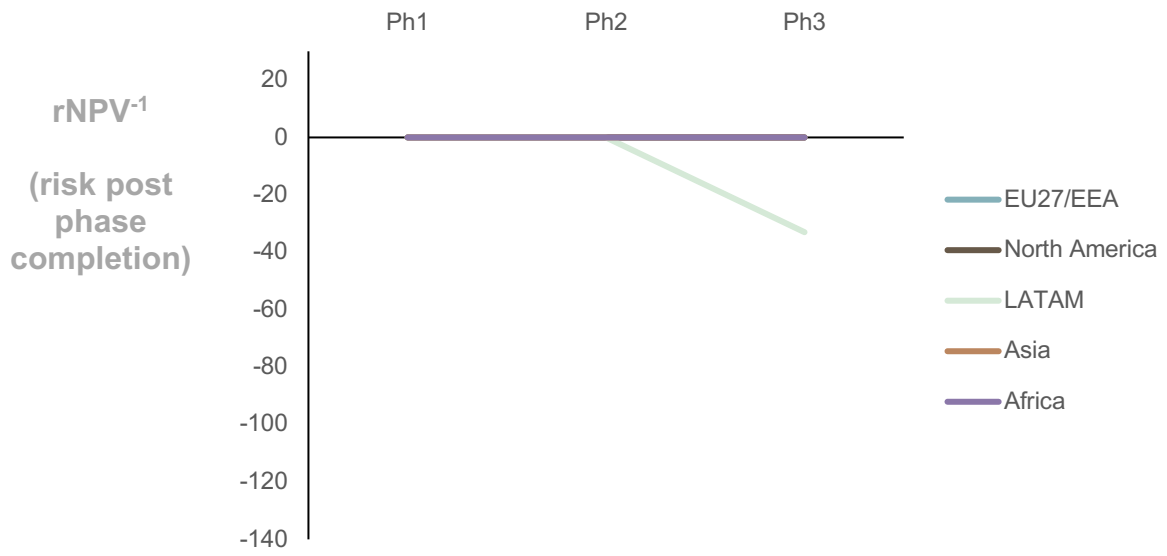


Repositioning development risk:

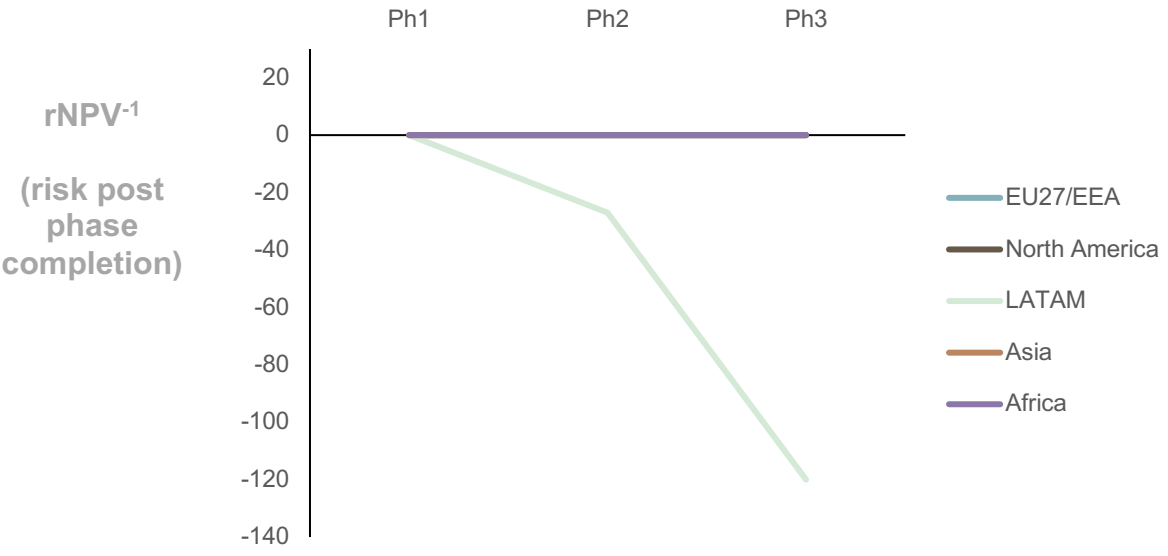


Aminoglycoside (Tobramycin)

De Novo development risk:

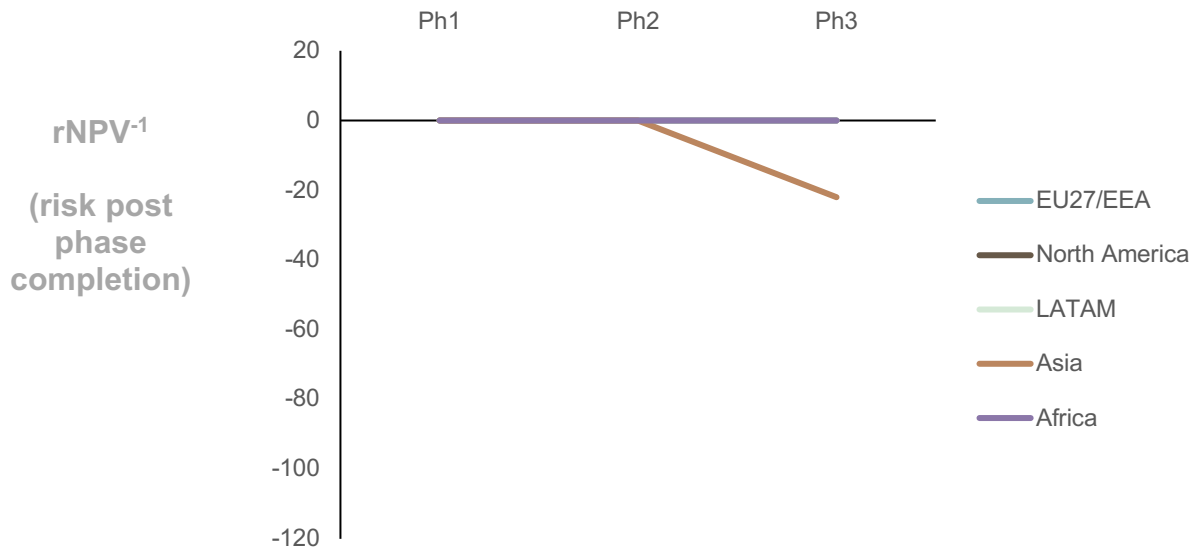


Repositioning development risk:

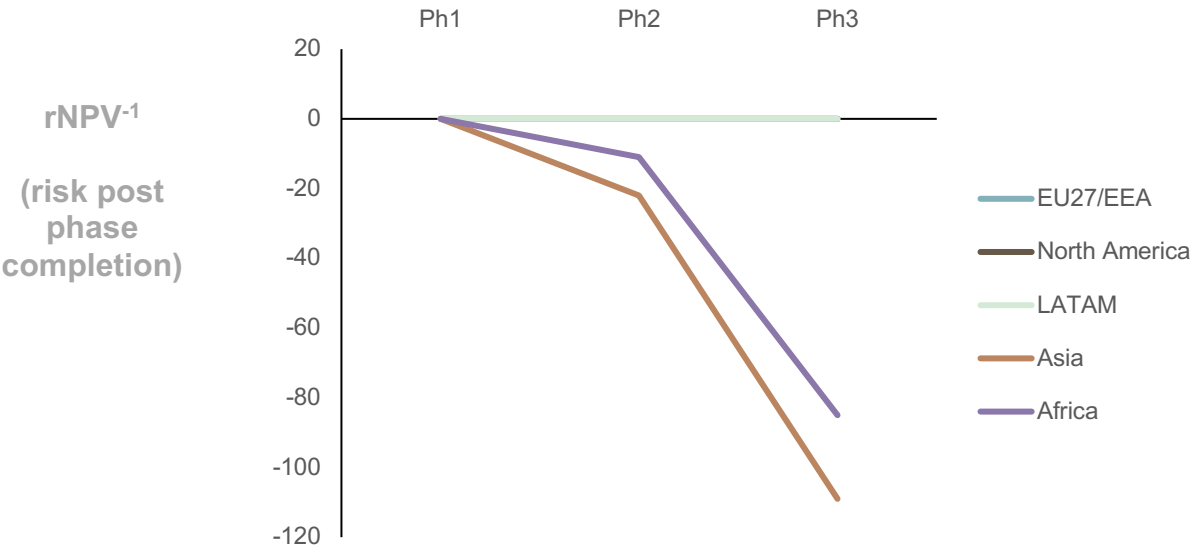


Cephalosporins – 3rd gen (Ceftazidime)

De Novo development risk:



Repositioning development risk:



Aminopenicillin (3rd gen penicillin)

De Novo development risk: No solution reached threshold to generate a ROI for de novo development

Repositioning development risk: No solution reached threshold to generate a ROI for repositioning development

Metrondiazole (Nitroimidazole)

De Novo development risk: No solution reached threshold to generate a ROI for de novo development

Repositioning development risk: No solution reached threshold to generate a ROI for repositioning development

Development Risk: model parameters

Development risk assessment was calculated using rNPV methods with the following most optimistic conditions:

De Novo and Repositioning risk measurement conditions

i) Product characteristics

- The new innovation will be superior to the existing standard of care, but will be priced equivalently (best case scenario)
- That the innovative product is a disruptive new 'best-in-class', compared to the standard of care
- That over its lifetime, the product, will achieve an overall 21% Serviceable Obtainable Market, equally over the studied geographic space, and that all citizens have equal access to the product
- The percent of the target population eligible for the intervention, based upon existing treatment regimens within the 'indication and intervention class' are used to create the market uptake

ii) Valuation characteristics

- Disease Indication and phase specific clinical success rates are used
- Cost of capital risk rates are used
- Disease specific clinical trial metrics are used
- HEOR (Health Economics and Outcome Research) clinical evidence multiple requirements is used
- SOMs are based upon local pricing structures
- For '***De Novo***' Full value chain costs, from experimental development up to first scaled up manufacturing prior to market release are used
- For '***Repositioning***' Full value chain costs, from the end of phase 1, up to first scaled up manufacturing prior to market release are used
- Risk is presented as $rNPV^{-1}$

(During development risk going down does not necessarily mean value going up due to long term aggregate market influencers)

Antibiotics: a unique development risk?

- Historically broad acting antibiotics were the more logical business wise as they enable a return on investment (ROI) based upon standardised business **operations** and models. i.e. **large volume sales to cover the cost of development and enable innovation sustainability**
- Narrow acting antibiotics, were parked or abandoned for precisely the inverse rationale: they generated no ROI
- Within healthcare, this approach was amplified, as precise microbe identification prior to antimicrobial prescription was not a prerequisite before antibiotic prescription
- The outcome was inappropriately prescribed antibiotics, that while maybe killing the targeted bacteria eventually catalysed both targeted and non-targeted bacteria to develop or acquire resistance: resulting in a broader or more sustained range of pathological impact

Antibiotic resistance: a species aiming to survive

Bacteria develop resistance through either:

Natural resistance: the mechanism is always turned on, or it is turned on in response to the antibiotic

Acquired resistance: bacteria mutate own DNA to develop resistance or through horizontal gene transfer

Mechanisms of resistance include:

- Drug inactivation
- Drug target modification
- Drug removal through efflux
- Reduction of drug uptake

- Prescription of broad acting antibiotics and inappropriate prescription overall is seen as a very bad idea and is now stopping…. **narrow acting antibiotics are now a preference**
- Pathology by pathology, at present, and still ongoing for many diseases, the use and rationale for **prescription of antibiotics is being re-evaluated by practicing specialists and their associations**, as a function of evidence-based acquisition and long-term benefit assessment…. The result for the innovator is that one from day to the next their pipeline can stop before it actually starts.
- **Precise identification of the causative bacteria** is considered one of the first steps in optimizing care: this can be either a benefit or a hindrance. If the strain of bacteria is observed in many diseases, but not exclusively then the potential to generate revenue without creating resistance is possible… if it is not, then it runs of the risk of being a **bacterial rare disease equivalent**
- The microbiota representing the balance of beneficial and detrimental bacteria that exist in any given biological space is being better understood and how **creating a dominant bacterial imbalance can create more problems than it solves**
- The prevailing recommendations are that **alternative approaches should be prioritised** and that antibiotic prescription should be restricted to only those circumstances in which complete and precise evidence suggests it is the optimal approach, but this is disease dependent.
- Within the most critical healthcare settings, the tertiary or hospital setting, the prevalence of antibiotic resistant bacteria is a significant issue, while **globally >700,000 die annually because of antimicrobial resistance**, speculated to increase to 10 million annually by 2050
- Cumulatively existing antibiotics are therefore becoming sparsely used, newly developed antibiotics are kept on the shelf as emergency backup, while the innovators are encouraged to create new ones to bolster the pharmacopeia knowing they will not generate income… this risk profile creates **innovation resistance**

Antibiotic Innovation: reset and redesign

The data presented in this briefing is most optimistic model possible.

Comprehensive analysis of the innovation ecosystem, integrating in the requirements of all stakeholders suggests a significant and potentially complete rearrangement in the business model used, maybe necessary.

Simply put, incremental changes to an historical approach (that previously worked, but should not be continued) will not resolve the problem: and any changes will not work unless each key stakeholder is integrated into the strategic plan, that has a directly implementable and measurable action.

Based on the analysis there are 2 clear areas for highly relevant and globally impacting innovation, and healthcare workers have the critical role:

1) Education, guidance and granular best practice development:

Professional associations of healthcare workers in selected geographies have made significant and welcome strides in creating new guidelines based upon **clinical evidence** to reduce and/or restrict antibiotic usage.

This is a first and monumental step and task.

It is unclear how widely spread or harmonised these guidelines are across nations, but a broader application and uptake will be essential.

Create professional and education guidelines and solutions that correspond to and link between each sector of healthcare practice and location (primary, secondary, tertiary and quaternary).

Make sure this information is multilingual, culturally sensitive and is applicable to the user. Specifically do not make it exclusively internet or smart phone/tablet based (you may need to send a memory stick): in many locations (LMIC, geographically disperse, unbalanced and non integrated healthcare systems) there is not the bandwidth or infrastructure to stream a teaching video, while someone who earns around the equivalent of $3000/yr is not going to spend $800 on a smart device.

The information should be tailored to versions that correspond to primary, secondary, tertiary and quaternary care, paramedic/ambulance staff capacity and activity infrastructure and practice.

Inversely, at the highest possible granularity, the healthcare workers by sector and location should create local versions of the patient journey, edited to reflect the realities on the ground. This should include healthcare infrastructure, available diagnostic and patient care/management solution, types of causative bacterial agent, AMR levels and types and available budget.

A cyclic care and innovation management solution, in which everyone shares best practice, applies it as best as possible, updates the solution as a function of local outputs and tailored to local possible implementable actions: a low cost low tech solution identified and confirmed in a LMIC location can have

just as much impact in a developed country with a geographically disperse population or a healthcare system looking for the optimal cost-effectiveness.

It also creates an innovation wish list that innovators can reflect on and generate solutions for. Innovation here can be every component of the infrastructure:

- supply chain,
- staffing,
- physical infrastructure,
- resourcing and reusing physical assets of all types (if the guideline recommends a course of action that cannot be applied in a certain location, to higher (or lower) tech testing and diagnosis solutions
- Healthcare coverage and patient accessibility

e.g. a point of care sputum and blood test, using low tech with low cost that can be used in every possible setting, so that when the patient is stratified this can be done both at the clinical and microbiological level before they go to the hospital (at the primary care/quaternary care location or in the ambulance on the way to the hospital).

At the hospital (and in some cases these have been developed and launched based upon high tech formats) rapid confirmation of this information with higher specificity, would be highly beneficial.

2) Antibiotic development

Segueing on from point 1, the essential role of the healthcare workers has critical relevance to the development of new antibiotics: if healthcare workers do not prescribe the clinically validated and reimbursement agency approved solution, then it generates no revenue, and lack of usage typically results in the removal of the intervention from the pharmacopeia.

Why does this happen? The answer is the detailed guidelines that have been generated: prevailing needs, available solutions and evidence. While the horizon is a nice place to look, healthcare workers do not have that luxury. Their decisions related to a patient's welfare are not based on future potential solutions, but on the philosophy that the solutions to hand maybe the best they ever will have.

A suitably similar and comparable paradigm is that for the treatments of leukemia and lymphoma: solutions in that field are based upon highly granularized treatment protocols that progress and change with the disease and the patient. The solutions are complex, almost always a combination of different drugs, and if one does not work, another solution is integrated in. Outputs are recorded in clinical reports that become part of a larger evidence based solution.

Returning to antibiotics, the guidelines for treatments of bacterial disease function on the same level of complexity, and all recommendations are based upon evidence. When the evidence is weak, it is clearly indicated. When one solution does not work, there is another suggestion, until they can do no more.

In that context, any newly developed antibiotic will have to undergo the equivalent stringent evaluation criteria: substituting one antibiotic for a newer version, within a complex algorithm, accounting for patient

stratification, that only summarises the patient's complexity without evidence on longer term recurrence, refraction or relapse related events is unlikely to be recommended for usage by the healthcare workers.

The evidence requirements for this change to occur are going to be significant: generating 5000 new antibiotics, whoever or however it is paid for, will not change this. Innovating is essential, but it is only an innovation if it is used.

From an innovators perspective, there is still value in this sector, but only if the patients can be accessed as a function of their precise healthcare environment: how the value is created will require a paradigm shift in later phase clinical validation and a globalised strategy: in some cases there is space for development and validation in established drug development cultures and then application in geographies where the need is greatest, providing the solution can be provided effectively.

The sensation, though is that the innovators themselves are not completely understood by the policy makers: large industry abandoned antibiotics because it did not correspond to their business model. Narrow acting solutions were stopped, broader acting antibiotics were prioritised, and when they stopped generating revenue so did the motivation. Providing further financial incentives, along with R&D tax credits and non-dilutable funding sources that are used by them is unlikely to invigorate the pipeline. This has indeed been the case, with smaller companies then taking up the challenge, assuming even greater risk than the larger incumbents.

Several solutions have been suggested and indeed rolled out, to try to compensate for this and stimulate innovation in antibiotic development, such as 'De-linkage' or a 'Netflix subscription' based approach. The financing and economic models suggested and publicised need to be presented in a clear and high granularity that integrates in the specifics of how antibiotics are prescribed and used, and how they are developed and validated to be able to better understand the ramifications and applicability.

From the perspective of a small company, that many large companies use as a source for new innovations, and that have been the driving force for new antibiotics, these new financial mechanisms will not be sufficient. The new models are based upon the product getting to market, the company being given a payment and then receive payments based upon sales.

For this model to be valid the governments or insurance companies will need to give the small companies a payment of approximately $3.5 Billion for each solution generated: this $3.5 Billion will be used to cover the $2.7 Billion needed to get the product to market and a further $800 million to ensure pipeline growth and development (otherwise the company closes). Are governments or large companies willing to do this, on the basis that obtaining an ROI to enable enterprise sustainability is critical, but also very rare in antibiotics?

Given that the problem is global, and like the recent pandemic, infectious agent spread can be global and rapid, it maybe a better idea that a worldwide body creates a universal company and clearing house for antibiotics (UCCHA).

The 'de-linkage' or 'Netflix' model will need to be adapted slightly: every antibiotic that is developed by any entity will be licensed by UCCHA at phase 2a/2b, **ONLY** if the clinical evidence generated is valid and a select panel of healthcare workers (all types) have approved it and can see its potential impact. Phase 2a/2b trials will need to be reconfigured to be more comprehensive and detailed to create as much relevant data as possible. For the investors in these companies, unique tax breaks and credits, as well as value protection will need to be developed.

The successful innovating company will be paid for the costs (minus previous public contributions) of its development to that point, plus $100 million for sustainability. UCCHA will then continue the validation of the antibiotic as a function of the species of bacteria and most prevalent population location, coordinated by the healthcare workers, and paid for by government contributions.

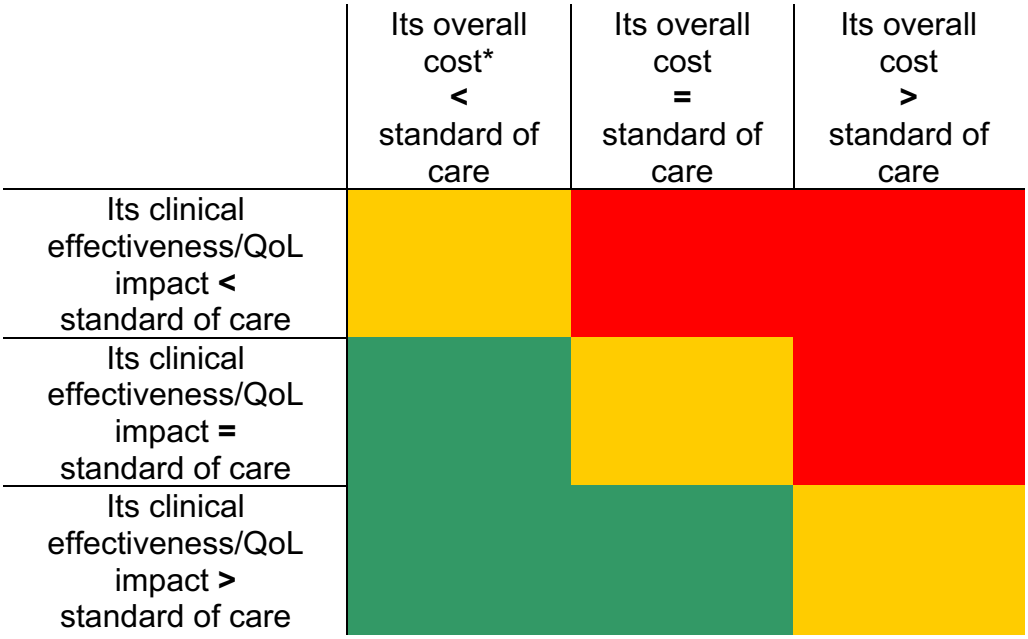
Once validated and launched onto the marketplace, its manufacture will be exclusively generic: this will prevent me too equivalents, unless they are next generation improvements, protect the innovation scheme, and enable the widest possible application as drug price will be as low as necessary.

This model preserves the competitive nature of innovation that is critical for its continued relevance and success, satisfies investment and aggregate risk, surpasses any political based market policy changes, enables healthcare workers and protects patients: for UCCHA the broader its portfolio the more it can use higher revenue generating solutions to offset the lower ones, at no detriment to the patient.

Revenue distribution should be simple: 10% of the sales revenue goes to the original innovator, the rest goes to UCCHA to keep funding later stage studies and enable repaying those innovators that present solutions at phase 2a/2b.

To go full circle, if combined with better patient care, management and diagnostic innovations, there should be no reason why the model will not optimise itself and become sustainable.

Health Economics and Outcomes: how will your solution compare to the Standard-of-Care?



- If your solution has the characteristics of the cross-references in **red**, it is highly unlikely any agency or insurance company will agree to the purchase of your product
- If your solution has the characteristics of the cross-references in **amber**, the agencies or insurance companies will perform an Incremental Cost Effectiveness Review (ICER) to determine if it is worth purchasing your product
- If your solution has the characteristics of the cross-references in **green**, it is highly likely that all agencies and insurance company will agree to the purchase of your product

**Cost: this does not mean the price of the intervention exclusively. This includes evidence indicated below, that also includes operational costs for healthcare facilities, capital expenditures, staff training, procedure changes and monitoring, long term impact on quality of life and associated healthcare costs.*

To arrive at a point of reimbursement, and a customer paying for it, agencies attach a significant amount of emphasis to patient reported outcomes (PROs) that reflects an impact on the Quality of Life (QoL); these are not clinical efficacy endpoints. These are based upon questionnaires presented to the patient during the trial and when approved during treatment, that scales the impact of the intervention as a function of what the patient tells the doctor.

Common key HEOR evidence requirements

The predominant process for HEOR value-for-money assessments by authorities and payers are so called 'health technology assessments. Each country and sometimes its subregions use HEOR and HTA with varying preferences to certain components of the evidence file. We would recommend that the reader also visit the links below for HTA in different geographies as an introduction to understanding these requirements. Typical information requirements are indicated below.

- Details of clinical trials and (if available) real world evidence for new product
- Clinical & economic systematic literature reviews (for new product and comparators and other required evidence)
- Comparative effectiveness vs. standard of care in clinical practice (often more than one comparator will be required)
- Pricing
- Budget impact analyses (financial consequences/change in expenditure of adopting a new intervention)
- Cost-effectiveness analyses (of the new product vs. its comparators that is country dependent), i.e. cost-utility analyses (e.g. Euro or Dollar per quality adjusted life year (QALY)). In these countries the cost-effectiveness is then measured vs. an established cost-effectiveness threshold. However, cost-effectiveness is not the only decision criterion in these countries.
- Other countries (typically those with more decentralised healthcare systems), e.g. Germany, France, Switzerland, Italy, Spain, etc., assess the added benefit of the new technology vs. its comparators followed by a pricing negotiation or reference pricing (depending on the added benefit).

Characteristics of HEOR requirements for Bacterial Sepsis

For bacterial sepsis QoL specific questionnaires have not been generated: assessments have been performed using generic types that include.

QOL-IT	Quality of life measurement for intensive care patients
QOL-SP	Quality of life measurement for intensive care patients
SF-36	RAND Medical Outcomes Study Short Form 36
EuroQOL EQ-5D	EuroQOL Group non-disease specific QoL instrument
WHOQOL-BREF	World Health Organization Quality of Life abbreviated version

Innovators need to carefully consider the patient outcome benefit from multiple perspectives to ensure their innovation is addressing all stakeholder needs. We would recommend reviewing these questionnaires and the outcomes that can be reported from the them. These should then be used to address how to integrate them throughout the innovation development plan to address later stage needs, and increase the value of their solution.

Recommended reading

Subject matter	Type	Author	Link
Patient support, education and advocacy	website	Global sepsis alliance	https://www.global-sepsis-alliance.org
Patient support, education and advocacy	website	Sepsis alliance	https://www.sepsis.org/about/global-sepsis-alliance/
Epidemiology of severe sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3916382/
Bacterial sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/books/NBK537054/
Sepsis: bacterial mechanisms of injury	Peer reviewed publication	Scientific and medical specialists	https://sjtrem.biomedcentral.com/articles/10.1186/s13049-019-0596-4
Diagnosis of bacterial sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.tandfonline.com/doi/full/10.1080/14737159.2019.1660644
Global epidemiology of sepsis	Peer reviewed publication	(Rudd K. E. et al, 2020) Scientific and medical specialists	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32989-7/fulltext
Viral sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6170629/
Global report on sepsis	report	WHO	https://apps.who.int/iris/bitstream/handle/10665/334216/9789240010789-eng.pdf
Global antibiotic resistance	report	GLASS/WHO	https://apps.who.int/iris/bitstream/handle/10665/332081/9789240005587-eng.pdf?ua=1
Characterisation of pathogenic sepsis and patient profiles	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6350122/
SOFA score sheet	report	Scientific and medical specialists	https://www.atsu.edu/faculty/chamberlain/website/lectures/lecture/sepsis2007.htm
Enhancing recovery from sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5839473/
Antibiotic treatment approaches for sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7139065/
Sepsis recurrence and hospital admissions	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5600690/
Pathogenesis of sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6862039/
Molecular diagnostics in sepsis management	Peer reviewed publication	Scientific and medical specialists	https://www.clinicalmicrobiologyandinfection.com/action/showPdf?pii=S1198-743X%2818%2930221-0

Empiric antibiotics in sepsis	Peer reviewed publication	(Strich et al 2020) Scientific and medical specialists	https://academic.oup.com/jid/article/222/Supplement_2/S119/5874155
Sepsis management	ACCP Online book	Scientific and medical specialists	https://www.accp.com/docs/bookstore/CCSAP/cc2019b1_sample.pdf
Health economics			
HEOR in sepsis	Peer reviewed publication	Scientific and medical specialists	https://ccforum.biomedcentral.com/articles/10.1186/cc2812
HEOR in sepsis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6772145/pdf/pone.0222450.pdf
HTA systems in Europe	website	EUPATI	https://eupati.eu/national-platforms/
EU HTA core model	guidelines	EUnetHTA	https://www.eunethta.eu/hta-core-model/
Evolving HTA approaches in EU countries	Peer reviewed publication	Scientific and medical specialists	https://link.springer.com/article/10.1007/s10198-019-01037-2
Medtech position paper on HTA for IVD	report	Medtech europe	https://www.medtecheurope.org/wp-content/uploads/2017/07/HTA-for-IVDs-in-the-Context-of-Market-Access-update-June-2017_0.pdf
About ICER	website	ICER	https://icer-review.org/about/
About CADTH	website	CADTH	https://www.cadth.ca
HTA for medicare & medicaid	website	AHRQ	https://www.ahrq.gov/research/findings/ta/index.html
HTA background in the USA	White paper	Scientific and medical specialists	https://healthpolicy.usc.edu/wp-content/uploads/2020/02/Health-Technology-Assessment-for-the-U.S.-Healthcare-System_Background-Paper.pdf
HTA in North America	presentation	Scientific and medical specialists	http://globalmedicines.org/wordpress/wp-content/uploads/2014/01/Garrison-HTA-US-CAN-July-5-2011-FINAL-7-5.pdf?1478792404
HTA implementation in Latin American countries	Peer reviewed publication	Scientific and medical specialists	https://www.sciencedirect.com/science/article/pii/S2212109917300171
Health authority list of Latin America	website	ISPOR	https://tools.ispor.org/htaroadmaps/HealthAuthorityLatinA.asp
HTA in Latin America	Peer reviewed publication series	Scientific and medical specialists	https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/health-technology-assessment-for-decision-making-in-latin-america-good-practice-principles/91A5ED0CAAF60052C0311FD3920EC42D
Addressing HTA challenges in Asia	Peer reviewed publication	Scientific and medical specialists	https://www.valuehealthregionalissues.com/article/S2212-1099(19)30087-1/fulltext

HTA Asia network	website	HTAsiaLink	https://htasialink2020.com
HTA in Asia	Peer reviewed publication series	Scientific and medical specialists	https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/hta-flourishing-in-asia/C783395A99500AF786B34B07B8A0322D
HTA development in Asia	Peer reviewed publication	Scientific and medical specialists	https://www.sciencedirect.com/science/article/pii/S2212109919305783
HTA in sub-saharan Africa 2020	Peer reviewed publication	Scientific and medical specialists	https://f1000research.com/articles/9-364
HTA in South Africa	website	Scientific and medical specialists	https://www.heroza.org
HTA in Africa	website	AFHEA	https://afhea.org/en/

In addition, for those wishing to delve a little deeper on their own time, reliable information can be found through

WHO
(epidemiology and demographics, forecasted changes)

Indication specific patient associations and charities
(pipelines, epidemiology and demographics, forecasted changes)

Indication specific Professional Associations
(treatment regimens, patient care and management pathways, epidemiology)

Pubmed
(epidemiology, demographics, background info, treatment protocols, updates)

Clinical trials gov
(ongoing pipelines in late stage development)

National and regional databases (typically in local language)
(pricing, regulations and reimbursement approaches and requirements)

Drugbank
(detailed information on drugs on the marketplace, manufacturers, producers)

EMA/FDA
(patient stratification and eligibility)

Company annual reports
(information on sales revenue by geography)

Cochrane library
(clinical trials, evidence)

Your next step

If you are motivated to design new solutions and products that will provide a better Standard of Care, Aestimo is able to provide tailored strategic insights, support and/or advice.

These solutions can provide **higher granularity information** on:

- Reimbursed interventions and solutions (all products in all classes: SOM, forecasted SAM and development risk)
- Solutions in development
- Disease subtypes; prevalence, evidence requirements, clinical trial design, measurements and outcomes
- Repositioning strategies: international growth, additional indications, new indications
- Country specific regulation and evidence requirements
- Feasibility assessments: stakeholders, opportunities, partners, non-dilutive funding, product launches

And support the company to develop the evidence and engage with reimbursement authorities and payers.

To talk to us about your needs and plans, please contact Jonathan at jdando@aestimo.ie to schedule a webconference.

Aestimo Innovator's Briefings (AIB)

Bring together

- Marketplace specific standards of care (health products) for each class of intervention used within the indication
- Standard of care specific treatment regimens (dose and duration)
- Marketplace specific prices of standards of care
- Indication specific prevalence and incidence
- Eligible patient populations for each intervention and treatment
- Clinical trial logistic requirements
- Indication specific clinical trial success rates, durations and patient numbers
- Modeled optimal and realistic valuations based upon Serviceable Obtainable Market within a market place for each intervention class
- HEOR evidence requirements
- Development risk and opportunity calculations for *de novo* generation or repositioning of innovations, using full value chain economic costing.

These briefings link together all the key components of the value chain (concept to genericisation) in healthcare intervention development to enable any innovator to assess opportunity and risk for their idea, intellectual property, investment or intervention pipeline.

They also provide logistic and strategic insights that enable the innovator to design global innovation development and launch plans, by understanding what commercialisation action should be taken, when it should be done and where it should be made.

Annex: epidemiology data extracted from

Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, Angus DC, West TE. The global burden of sepsis: barriers and potential solutions. Crit Care. 2018 Sep 23;22(1):232. doi: 10.1186/s13054-018-2157-z. PMID: 30243300; PMCID: PMC6151187.

	Underlying infection		Underlying non-communicable disease		Underlying injury	
Location	**Incident sepsis cases**	**Sepsis ASIR per 100,000 population**	**Incident sepsis cases**	**Sepsis ASIR per 100,000 population**	**Incident sepsis cases**	**Sepsis ASIR per 100,000 population**
Armenia	5,663	205.3	4,819	131.8	295	9.2
Algeria	49,813	124.1	50,238	131.3	6,509	16.2
Afghanistan	180,876	424.5	97,683	436.3	14,540	48.9
Albania	2,175	91.9	2,843	85	260	9.3
American Samoa	133	297.7	86	203	9	18
Andorra	114	88.2	78	63	6	6.4
Angola	302,615	1,002.20	78,613	362	7,198	29.1
Antigua and Barbuda	188	235.7	128	144.1	11	12.9
Argentina	120,419	252.9	64,573	133.4	6,589	14.3
Australia	28,863	85.2	24,084	65.6	2,304	8
Austria	5,841	44.4	10,962	69	961	7.9
Azerbaijan	34,544	417.7	16,224	196.1	1,057	10.8
Bahrain	893	108.9	831	101.8	145	10.9
Bangladesh	780,190	546.3	347,180	259.7	20,352	14.2
Barbados	1,084	368.1	551	151.9	34	10.3
Belarus	9,332	93.2	14,835	108.4	1,866	16.7
Belgium	24,762	116.1	14,687	69.5	1,504	9.5
Belize	937	272.9	556	176.4	88	23.8
Benin	154,791	1,200.30	33,458	335.3	3,369	37.4
Bermuda	69	84.2	72	67.8	5	6.3

Bhutan	2,568	331.7	1,665	211	180	22.4
Bolivia	34,999	306.7	25,866	254.8	2,307	21
Bosnia and Herzegovina	1,694	50.6	5,534	105.1	341	8.7
Botswana	13,730	667.4	2,851	175.5	358	17.2
Brazil	550,051	290.2	292,452	141.4	36,629	17
Brunei	633	203	462	138.6	62	15
Bulgaria	7,445	101.7	13,005	108.1	874	11.2
Burkina Faso	403,201	1,512.70	60,971	341.5	6,809	38
Burundi	122,918	1,086.00	30,547	380.7	3,082	38.8
Cambodia	63,081	452.1	30,173	239.3	5,856	42.7
Cameroon	319,809	1,133.80	85,022	394.1	7,001	32.8
canada	54,760	102.1	40,133	72.3	4,023	9.5
Cape Verde	1,484	302.5	736	152	68	13.1
Central African Republic	75,749	1,673.70	19,728	557.3	6,038	134.1
Chad	317,470	1,535.20	81,962	623.3	5,378	40.1
Chile China	28,432 1,241,273	146.7 106.1	21,210 1,488,253	103.4 94.6	2,070 202,295	10.7 14.1
Colombia	104,732	227.8	53,999	107.8	6,021	11.9
Comoros Congo Brazzaville	3,474 45,663	547.1 1,032.50	1,452 12,134	262.3 335.8	147 1,233	25.8 29.4
Costa Rica Côte d'Ivoire	5,012 261,580	112.5 994.4	4,842 82,283	105.8 387	638 6,496	13.2 34
Croatia	4,690	79.6	6,501	83.1	600	9.8
Cuba Cyprus	18,912 1,301	144.1 76.3	15,137 1,174	93.8 67.5	1,731 122	11.9 8.5
Czech Republic	15,028	92.4	14,346	75.6	1,362	10
Denmark	10,141	95.8	8,365	85.9	493	6.2
Djibouti	5,637	546.9	3,012	327.4	215	25.9
Dominica	253	464.5	184	265.1	13	18.2
Dominican Republic	49,491	492.6	19,947	199.4	2,421	23.2
DR Congo	1,097,977	1,250.90	235,819	378.7	27,968	36.6

Ecuador	36,285	233.6	25,321	165.5	3,472	21.1
Egypt	336,817	365.2	108,071	165.1	22,712	24.2
El Salvador Equatorial Guinea	13,892 14,638	243.1 1,116.90	9,176 2,920	159.1 293.4	1,134 220	18.5 19.6
Eritrea	45,608	918.6	21,057	479.2	1,734	41.4
Estonia	1,388	78.2	1,740	75	180	11.6
Ethiopia	740,224	707.1	257,349	320.2	20,819	28.3
Federated States of Micronesia	204	245.1	204	284.6	21	23.3
Fiji	2,551	325	2,164	296.2	139	16.4
Finland	4,443	46.7	7,455	68.8	683	8.6
France	87,728	81.8	80,706	64	8,474	8.7
Gabon	11,452	727	3,593	263.6	389	25.9
Georgia	4,960	137	7,014	139.1	730	18.3
Germany	136,622	87.4	133,680	81.4	8,676	7
Ghana	291,711	983.1	64,539	260.5	7,335	31
Greece	12,340	61.4	14,607	70.3	1,076	8.5
Greenland	72	138.2	77	138.9	13	23.1
Grenada	281	232.6	244	183.8	19	15
Guam	392	237.9	235	140.3	25	14.9
Guatemala	79,558	476.9	30,169	213.4	3,430	21.4
Guinea	153,988	1,166.40	53,035	532.7	,311	34.7
Guinea-Bissau	16,402	918.2	6,434	437.3	539	39.8
Guyana	2,217	323.4	1,856	277.8	193	27.5
Haiti	73,722	590	37,455	399.1	4,187	39.3
Honduras	19,772	226.1	15,229	201.9	1,460	16.9
Hungary	8,663	65.4	16,639	97.6	1,273	9.3
Iceland	350	74.6	267	52	30	7.5
India	8,027,453	703	2,898,369	254.7	415,492	34.6
Indonesia	1,092,211	533.7	508,216	245.7	35,136	15.5
Iran	76,301	110.9	75,779	116.6	17,097	21.6
Iraq	83,711	61.5	43,625	115.3	103,821	218.8

Ireland	5,520	84.4	4,393	67.3	290	5.3
iribati	403	425.7	384	471.5	23	21.9
Israel	12,641	112.8	7,691	68.9	698	**7.3**
Italy	61,977	62.2	82,876	61.1	5,288	5.7
Jamaica	4,809	206.5	5,340	204.4	318	11.2
Japan	295,847	91.3	163,064	46.3	11,120	6
jordan	18,145	179.8	10,300	129.7	1,359	12.9
Kazakhstan	28,942	165	24,139	145.6	3,615	19.7
Kenya	466,278	1,029.70	118,497	326.1	9,518	27.2
Kuwait	2,821	101.5	1,714	58.1	401	10.1
Kyrgyzstan	13,360	202.7	10,301	182	859	13.7
Laos	37,295	538.4	17,021	300.7	1,650	25.8
Latvia	2,635	101.9	3,565	102.1	386	16.4
Lebanon	11,418	142.7	7,039	101.9	2,611	29.6
Lesotho	19,063	1,066.00	5,272	370	865	47.9
Liberia	53,516	1,123.80	15,903	405.6	810	23
Libya	8,638	143	6,680	130.9	7,480	106.1
Lithuania	4,196	117.2	5,024	99.5	627	17.5
Luxembourg	665	79.6	639	68.8	59	7.9
Madagascar	294,840	992.8	95,193	459.6	5,288	27.2
Malawi	159,345	918.8	41,878	305.6	3,345	26.4
Malaysia	114,424	443.5	29,779	116.5	4,950	16.4
Maldives	779	218.2	336	93	32	8.1
Mali	458,818	1,684.30	101,115	494.5	8,562	40.3
Malta	748	104.8	565	83.2	36	6.3
Marshall Islands Mauritania	142 32,867	311.2 861.9	129 13,096	338.2 399.6	14 784	29.2 24.2
Mauritius	1,933	183.7	2,514	181.5	175	13.4
Mexico	256,767	217.5	201,946	173.5	24,871	19.8

Moldova	8,094	281.6	6,292	134.8	669	16.3
Mongolia	7,073	215.9	5,594	211.8	801	23.8
Montenegro	291	45.9	864	99.1	71	10.2
Morocco	64,529	205.5	55,395	178	6,101	17.6
Mozambique	314,111	1,076.20	76,694	361	7,686	36.4
Myanmar	235,342	516.7	140,886	312.1	12,327	25.3
Namibia	15,584	701.5	3,812	207.1	497	23.1
Nepal	120,259	474.6	65,300	266	6,742	26.7
Netherlands	35,208	135.2	21,970	74	1,529	6.1
New Zealand	5,088	85.1	4,583	69.3	469	9.8
Nicaragua	13,054	210.1	8,160	147.5	634	10.5
Niger	506,854	1,864.90	55,625	326.7	6,127	32.3
Nigeria	4,394,358	1,591.20	886,118	451	53,291	26.3
North Korea	36,475	192.1	48,230	190.5	5,048	20.2
North Macedonia	1,039	60.5	2,930	112.4	166	7.1
Northern Mariana Islands	79	196	55	127.1	6	13.1
Norway	9,480	99.9	5,512	61.6	509	7.3
Oceania	69,562	600.2	45,842	475.7	4,976	42
Oman	4,429	148.6	2,775	100.8	992	22.5
Pakistan	1,168,998	537	922,353	480.5	53,072	28.2
Palestine	6,295	138.6	3,899	120.7	853	17.1
Panama	11,196	306.5	5,186	135	489	12.6
Papua New Guinea	58,168	704.1	37,895	549.3	4,159	48.2
Paraguay	11,005	173.7	10,049	167.4	969	14.7
Peru	125,949	369.6	41,033	125	5,025	15.1
Philippines	560,710	595.5	184,905	221.3	17,580	17.8
Poland	41,790	80.4	53,365	89.6	5,323	11.3
Portugal	23,915	118.7	16,726	75.1	1,040	7.4
Puerto Rico	9,134	224.7	5,623	101.7	1,298	36.5
Qatar	1,188	91.4	930	94.6	425	16.3
Romania	29,071	148.6	33,446	108.7	2,764	12.6

Russia	273,831	177.4	262,312	128.2	37,343	23.2
Rwanda	96,455	789.2	22,786	247.3	2,728	29.4
Saint Lucia	332	216	298	167.3	27	14.3
Saint Vincent and the Grenadines	270	264.6	243	204.6	20	16.6
Samoa	352	195	260	181.7	26	14.9
São Tomé and Príncipe	729	434.9	389	265.9	32	19.9
Saudi Arabia	47,807	229.4	18,839	97.3	18,971	53.6
Senegal	100,944	700.1	40,601	344.6	3,088	26.9
Serbia	6,494	57.9	16,750	120	902	8.2
Seychelles	322	351.3	163	163.7	14	13.9
Sierra Leone	141,138	1,607.00	33,682	471.1	2,112	32.1
Singapore	9,551	152.3	2,265	35.9	226	3.7
Slovakia	6,572	96.7	7,149	93.6	741	11.6
Slovenia	1,951	58.1	2,617	65.8	332	11
Solomon Islands	2,144	430.4	1,105	280	189	38.1
Somalia	149,874	844.7	62,407	528	15,196	102.3
South Africa	338,483	650.6	81,024	172.9	13,559	24.5
South Korea	53,202	86.6	46,764	64.7	5,616	8.8
South Sudan	164,160	1,329.20	48,708	595.2	11,413	117.8
Southeast Asia	2,588,007	459.7	1,132,405	197.7	113,922	18.3
Spain	73,359	93.2	61,271	63.7	3,309	5.3
Sri Lanka	54,502	278.6	24,778	118.9	3,444	15.7
Sudan	311,972	688	89,505	240.8	14,102	33.7
Suriname	2,044	409.4	1,269	238.4	137	24.6
Swaziland (eSwatini)	9,530	910.4	1,983	277.4	384	37.4
Sweden	16,045	84.4	11,491	58.4	940	6.3
Switzerland	10,466	80.7	8,510	57.7	773	6.1
Syria	19,555	130.3	11,593	91.7	152,790	862.5
Taiwan (province of China)	59,227	184.4	26,568	79.2	2,832	10.3
Tajikistan	65,570	569.1	16,919	198.2	1,104	11.6
Tanzania	417,859	737.2	157,504	340	10,971	24.3

Thailand	230,771	365.3	82,168	102.1	12,580	17.5
The Bahamas	840	268	548	154.2	67	17.9
The Gambia	17,167	854.4	8,652	481.3	450	29
Timor-Leste	6,098	478.7	4,098	384.1	175	15
Togo	82,971	1,108.00	16,998	289.3	1,522	27.1
Tonga	293	312.9	200	241.5	15	15.9
Trinidad and Tobago	2,325	184.1	2,795	184.8	222	15.9
Tunisia	10,479	101.4	9,947	94.4	2,272	19.8
Turkey	96,692	138.7	80,942	109.2	18,921	24.4
Turkmenistan	14,246	281.9	7,649	177.6	573	11.4
Uganda	337,654	801.2	82,134	277	7,666	27.7
Ukraine	72,496	166.5	84,964	133.1	11,331	25.1
United Arab Emirates	5,170	156.8	4,705	133.7	2,541	31.5
United Kingdom	148,548	124.4	92,125	86	5,109	5.8
Uruguay	8,642	206.3	5,461	114	593	15.3
USA	597,370	142.3	440,454	100	45,184	12.7
Uzbekistan	98,090	313.8	40,434	167.4	4,039	12.6
Vanuatu	868	342.4	599	318.7	75	30.5
Venezuela	78,315	277.3	44,882	157.3	6,008	19.3
Vietnam	187,134	224.3	105,880	125.3	19,854	21.2
Virgin Islands	243	204.6	232	162.6	18	15
Yemen	197,690	533.1	89,362	326.7	51,832	157.9
Zambia	140,204	826.2	34,135	281.6	3,529	29.3
Zimbabwe	104,803	765	34,458	317.9	4,073	35.2