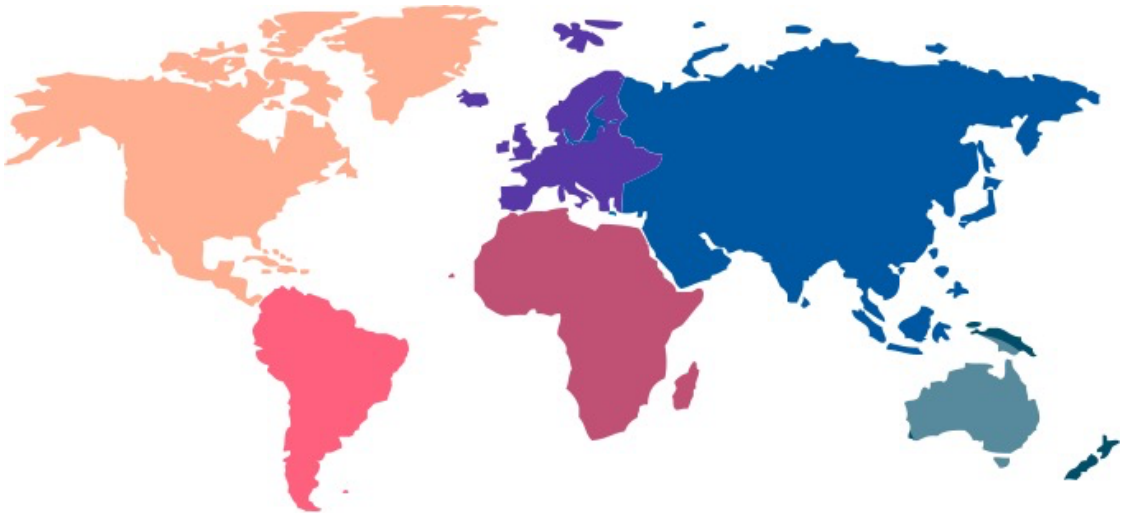
Aestimo

Innovator's Briefing

Antibiotics:

Lower Respiratory Tract Infections



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About LRTI

Epidemiology

(data extracted from GBD Lower Respiratory Infection Collaborators 2018, The Lancet)

Location	LRTI ASIR per 100,000 population	Incident LRTI cases	Incident bacterial pneumonia cases
EU27/EEA	4319	14,724,000	11,206,187
North America	3880	13,930,000	10,601,887
LATAM	3990	26,140,000	19,894,712
Asia	4710	171,370,000	130,426,811
Africa	3185	89,510,000	68,124,548

Lower Respiratory Tract Infections (LRTI)

- Leading infectious disease cause of death and 5th overall globally: it is the leading cause of death of children under 5 years of age
- Manifests as bronchitis, bronchiolitis, influenza, and pneumonia (inflammation of one or both lungs parenchyma)
- Involves acute infections of trachea, bronchi and lung parenchyma
- Risk factors include age, gender, socioeconomic status (lower income households have a higher incidence), lifestyle choices (alcohol consumption/smoking), pre-existing respiratory conditions (e.g. COPD, Asthma), medical treatments, immunosuppression, nutritional deficit, poor dental health
- Bacterial forms mainly manifest as bronchitis/bronchiolitis or pneumonia, for which antibiotics are prescribed almost exclusively for pneumonia forms
- Bacterial Pneumonia form exists in 4 infection location types: Community acquired (CAP), Hospital acquired (HAP), Ventilation/intubation acquired (VAP) and Health Care facility acquired (HCAP – this is being reviewed regarding a separate status, due to its similarity to CAP)
- Often presents with comorbidities and additional complications
- Caused by viruses, bacteria and fungi, with co-infection of more than one agent often observed
- Depending on form of pneumonia and geographic location different bacterial species have different prevalence, that dictate the antibiotic prescription

Differentiating factors of bacterial and viral pneumonia

Viral aetiology	<5 years or >65 years, observed seasonally or because of epidemic, slow disease onset, inflamed membranes in the nose with wheezing, no response to antibiotics, leukocyte counts <10million c/L, <20mg/ml CRP, <0.1 ug/L serum procalcitonin. X-ray imaging reveals bilateral, interstitial infiltrates
Bacterial aetiology	Adults, observed throughout year, rapid onset, high fever and rapid or irregular breathing, leukocyte counts >20million c/L, <20mg/ml CRP, >0.5 ug/L serum procalcitonin. X-ray imaging reveals lobar alveolar infiltrates

Confirmation of bacterial aetiology

- The figures obtained by GBD collaborators indicates a bacterial related aetiology of 76%. This is in contrast to other publications and analyses that have indicated a bacterial or bacterial+virological aetiology of 40% in Brazil, 15% in North America from the EPIC study, 21% in Europe, up to 50% in Africa and 90% in Asia (the remaining percent causes were due to viral infection exclusively).
- It is important to note that method of diagnosis and agent confirmation highly influence the confirmed diagnosis: it is known that <10% of blood tests from pneumonia patients reveal a disease indicator.
- Higher sensitivity data has been obtained using a combination of blood and urine antigen tests, standard culture tests, and culture tests from transthoracic lung aspirates.
- In general healthcare practice up to 44% of all types of pneumonia do not have the causative pathogen accurately identified.

Microbiology

Microbiological work up of patients by treatment location, outpatient (low severity), a non-ICU in-patient (mild severity) or ICU in-patient (high severity) reveals that M. pneumoniae is more prevalent in low severity cases, while S. pneumoniae is more prevalent in mild to high severity cases.

Summary of rates of bacterial species prevalence for CAP (%) by geographic region*:

	Europe	North America	LATAM	Asia	Africa
Staph. aureus	23	36.3	20.1	7	24
P. aeruginosa	20.8	19.7	28.2	9.1	5.5
Klebsiella sp.	10	8.5	12.1	15	19
E. coli	10	4.6	5.5	4.6	16
Acinetobacter sp.	5.6	4.8	13.3	2	-
Strep. pneumoniae	5.5	2.5	2.4	17	46
H. influenzae	5.4	2.5	1.3	7	0.8
Legionella sp.	*0.2*	*2.0*	-	*3*	*9*
M. pneumoniae	*4.8*	*8*	*11*	*8*	*9*
Chlamydophila sp.	*5.3*	*2.2*	*9*	*7*	*21*

**represents best possible data collected from 16 different peer reviewed publications. (- means data not available)*

Pneumonia severity, complications/comorbidities and patient stratification

A significant patient management issue with regard to bacterial pneumonia treatment are location of infection, pre-existing conditions and/or comorbidities and prior antibiotic exposure

Patients typically acquire pneumonia outside of a hospital (Community Acquired Pneumonia: CAP) or in the hospital (nosocomial or Hospital acquired pneumonia: in which Ventilator associated pneumonia is a further subset corresponding to patients who develop pneumonia within 48 hours of intubation: HAP/VAP)

CAP patients are then triage through an additional level of stratification dividing patients into treating as an 'outpatient', a 'non-critical' in-patient or a 'critical' in-patient, that also informs the antibiotic prescription (this is performed using the CURB-65 method, or the Pneumonia Severity Index method: both methods have weaknesses and neither has been reliable for identifying patients needing ICU. In this AIB we used the CURB-65 related methods due to extensive documentation related to antibiotic prescription protocols).

CURB-65: a protocol that scores severity based upon level of confusion, blood pressure thresholds, age, respiratory thresholds and blood urea thresholds. Each measurement point results in a 0 or 1 score, the cumulative sum of which indicates how to treat the patient. Score 0-1: outpatient. Score 2: inpatient non-ICU or closely monitored outpatient. Score 3-5: inpatient ICU.

Comorbidities in managing pneumonia, understandably have a significant impact and are closely evaluated and monitored. Pivotal comorbidities that are monitored and influences treatments are:

- Additional respiratory diseases: COPD, Cystic Fibrosis, Asthma
- Other infections: influenza, coronaviruses, HIV
- Cardiovascular diseases
- Neurological diseases
- Liver diseases
- Renal diseases
- Diabetes

Stages and histopathology of bacterial Pneumonia

Histopathologically, bacterial pneumonia is typically Bronchopneumonia (initiates in bronchi/bronchioles and then spreads locally into lower lobes) or Lobar pneumonia (inflammation of entire lobe)

stage	***description***
1. Congestion/consolidation	24 hours duration in which vascular swelling and intra-alveolar edema occurs: large bacterial infiltrate
2. red hepatization	Around 3 days duration occurring 3 days after consolidation, in which lungs take on liver-like firmness. The tissue is pink/red with associated early fibrosis (fibrin fibres)
3. gray hepatization	Around 6 days duration occurring 3 days after red hepatization. Tissue still has liver-like firmness with fibropurulent exudate and red blood cell disintegration
4. resolution/restoration	By 8 days after gray hepatization tissue infrastructure begins to repair including enzymes that degrade fibrous content

The Patient Journey

Patient manifests

- Severe cough +/- discoloured phlegm
- Breathlessness/wheezing
- High temperature and/or fever
- Dizziness
- Chest pain +/- tightness
- Skin changing colour (more blueish)

Patient diagnosis

- Blood tests to look for infection
- Sputum test
- Pulse oximetry
- Chest X-ray imaging (X-ray, CT)
- Pleural fluid culture (not always effective)
- Co-morbidity assessment/CURB-65 scoring
- Possible SMART-COP if need for ventilation suspected

Confirmation of bacterial infection, severity, risk and staging

Treatment

- Cough medicine, analgesics
- Antibiotics in an outpatient setting
- Antibiotics in an inpatient non-ICU setting
- Antibiotics in an inpatient ICU setting
- Antibiotics for HAP/VAP patients

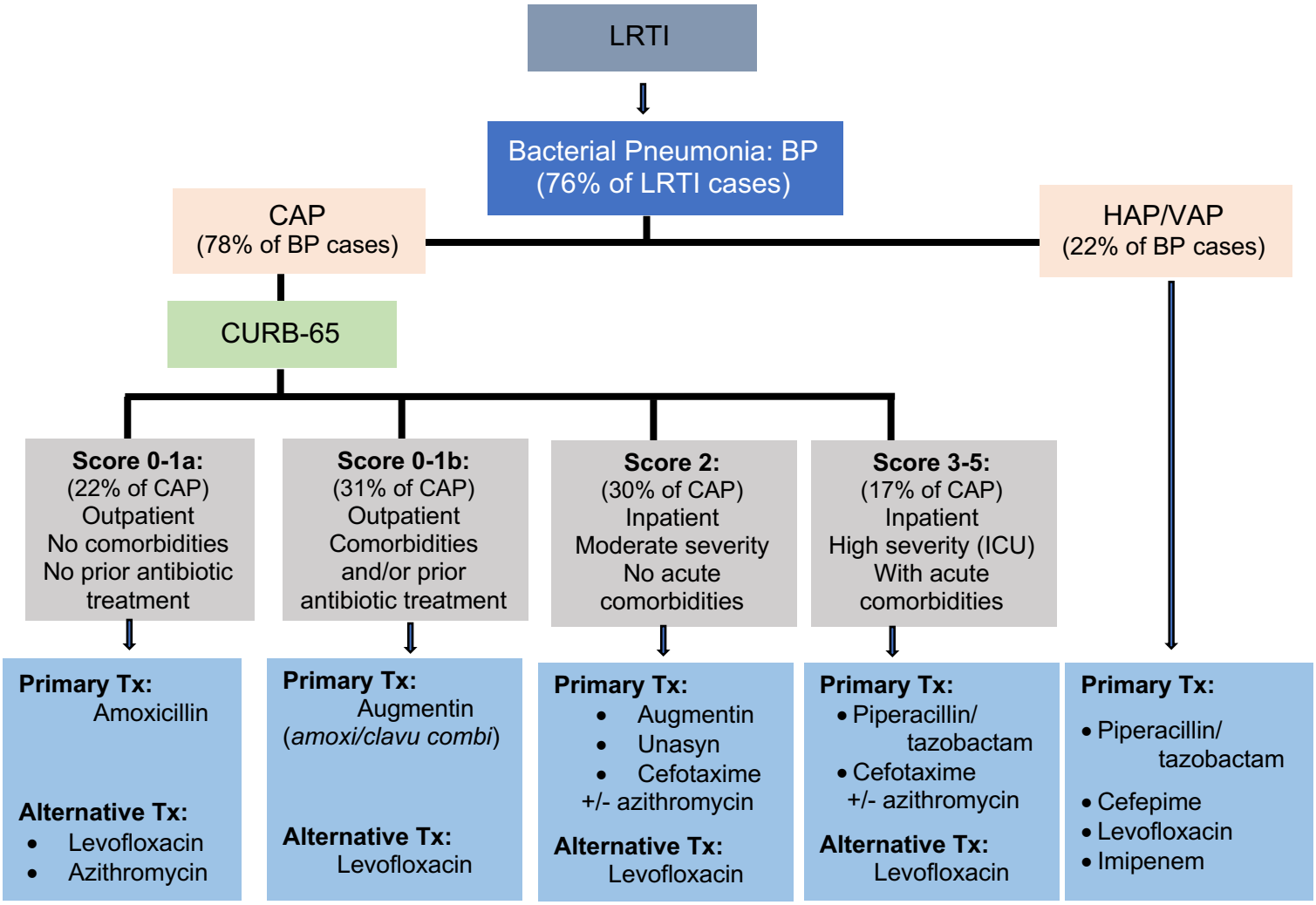
Follow up
patient care and management

- Can take more than 30 days for return to normalcy
- Given severity of disease follow up starts at a high frequency (weekly) decreasing to monthly
- 6 weeks post treatment imaging assessment recommended

Recurrence, refraction or relapse:

- Relapse defined as 2 or more episodes in a 6-month period
- Symptoms can persist in a high percentage of patients for longer than 50 days after antibiotic treatment cessation
- Up to 10% of patients can develop recurrent pneumonia within 5 years

Treatment approach*



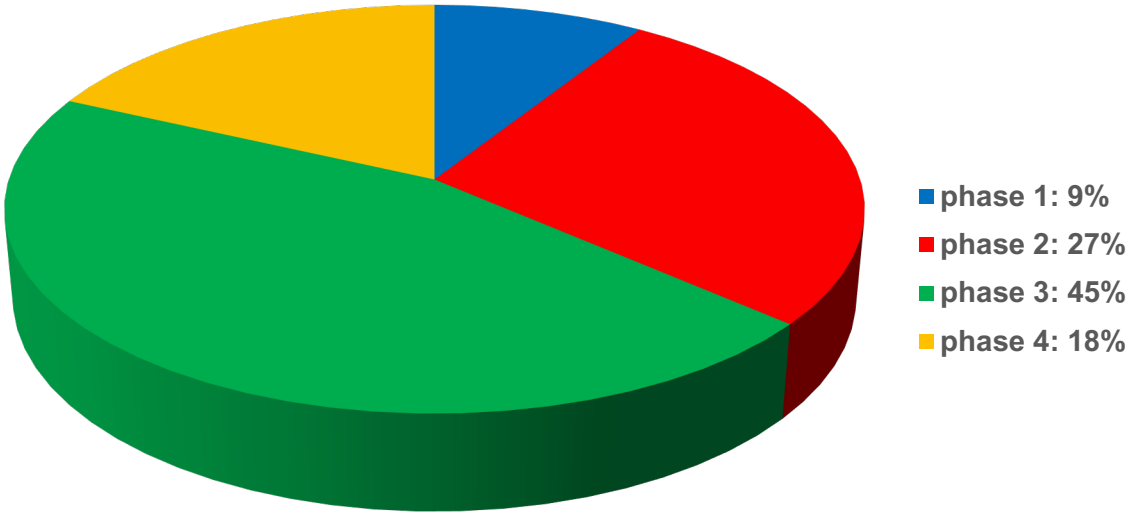
**these are not the complete list of antibiotic options, for each risk stratification + primary or alternative Tx several options exist: these can be generic or branded versions: pneumonia cases tend to be urgent and precise microbiology results are not always available, in each geography 'empiric' acting antibiotics are a typical first line approach. The precise prescription is based upon geography local data on typical micro-organisms presenting and local antibiotic resistant patterns*

Examples of approaches by healthcare providers for evidence based antibiotic treatment in CAP/HAP.

German Healthcare approach example	CAP	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5754574/
U.S.A. Thoracic Society/IDSA approach	CAP	https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST
U.S.A. IDSA approach	HAP/VAP	https://www.idsociety.org/practice-guideline/hap_vap/
Indian Chest Society	CAP	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6852216/

Clinical trial design

Ongoing clinical trials for bacterial pneumonia = 11 (5 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.

Antibiotic Treatment Costs (TC $US equivalent) for each risk stratification group and geography

Group	Treatment	EU	North America	LATAM	Asia	Africa
CAP 0-1a	amoxicillin	4.8	14.9	7.6	4.4	4.4
CAP 0-1a	levofloxacin	30.8	29.8	17.5	1.8	1.8
CAP 0-1a	azithromycin	18.0	31.5	4.5	0.9	0.9
CAP 0-1b	augmentin	252.0	138.6	63.0	63.0	63.0
CAP 0-1b	levofloxacin	30.8	29.8	17.5	1.8	1.8
CAP 2	augmentin	554.4	304.9	138.6	138.6	138.6
CAP 2	unasyn	283.5	567.0	567.0	97.0	97.0
CAP 2	cefotaxime	210.0	210.0	37.8	18.1	18.1
CAP 2	azithromycin	18.0	31.5	4.5	0.9	0.9
CAP 2	levofloxacin	30.8	29.8	17.5	1.8	1.8
CAP 3-5	Piperacillin/tazobactam	302.4	302.4	113.4	189.0	189.0
CAP 3-5	cefotaxime	280.0	280.0	50.4	24.1	24.1
CAP 3-5	azithromycin	18.0	31.5	4.5	0.9	0.9
CAP 3-5	levofloxacin	30.8	29.8	17.5	1.8	1.8
HAP/VAP	Piperacillin/tazobactam	302.4	302.4	113.4	189.0	189.0
HAP/VAP	cefepime	100.8	546.0	630.0	96.6	96.6
HAP/VAP	levofloxacin	23.1	22.3	13.1	1.3	1.3
HAP/VAP	imipenem	336.0	1008.0	854.0	378.0	378.0

- 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 classifications of infection multiplied by the TC.
- To **obtain the most optimistic values** for each treatment or alternative, 100% of the stratified population is modelled to take each possible standard of care and summed for each geography.
- **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 or drugbank

Amoxicillin (3rd gen penicillin)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	9.2	27.1
North America	27.1	79.7
Latin America	25.9	76.3
Asia	98.5	289.5
Africa & ME	51.4	151.2

Levofloxacin (3rd gen fluoroquinolone)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	326.1	958.9
North America	298.4	877.4
Latin America	328.9	966.9
Asia	220.4	648.0
Africa & ME	115.1	338.4

Azithromycin (advanced gen Macrolide)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	108.5	319.1
North America	179.7	528.4
Latin America	48.1	141.6
Asia	63.1	185.7
Africa & ME	32.9	97.0

Augmentin (3rd gen penicillin + β-lactamase inhibitor)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	2135.5	6278.5
North America	1110.4	3264.6
Latin America	596.3	1753.2
Asia	3909.5	11494.2
Africa & ME	2042.0	6003.6

Unasyn 3rd gen penicillin + β-lactamase inhibitor)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	742.0	2181.7
North America	1406.6	4135.5
Latin America	2639.5	7760.3
Asia	2960.4	8703.6
Africa & ME	1546.2	4546.0

Cefotaxime (3rd gen cephalosporin)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	966.7	2842.2
North America	914.6	2688.9
Latin America	308.9	908.2
Asia	969.2	2849.4
Africa & ME	506.2	1488.3

Piperacillin/tazobactam (4th gen ureidopencillin + β-lactamase inhibitor)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	1194.8	3512.9
North America	1130.4	3323.4
Latin America	795.4	2338.7
Asia	8691.8	25553.9
Africa & ME	4539.9	13347.3

Cefepime (4th gen cephalosporin)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	248.5	730.6
North America	1273.4	3744.0
Latin America	2757.4	8106.7
Asia	2783.3	8182.9
Africa & ME	1453.7	4274.1

Imipenem (Carbapenem)

	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	828.3	2435.3
North America	2351.0	6912.1
Latin America	3737.8	10989.1
Asia	10846.2	31888.1
Africa & ME	5665.2	16655.7

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 LRTI/BP. However, there is a significant caveat.

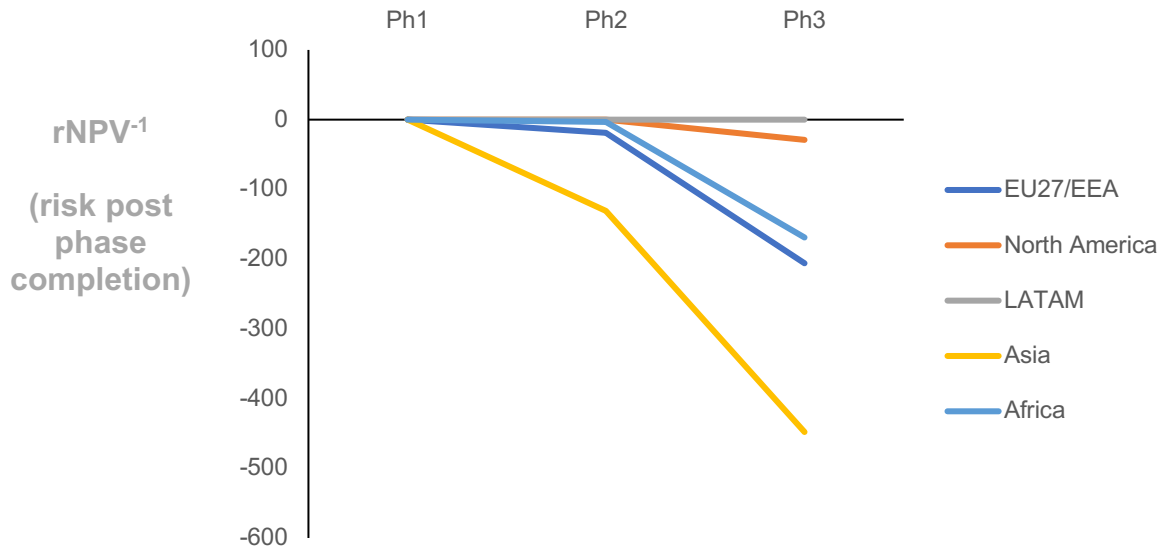
While Latin America and the Caribbean, Africa and the Middle East, and Asia present SOM values above the threshold, the treatment cost prices, which for Africa & ME and Asia are already at generic pricing, are very high compared to the average income of the patients, and any reimbursement entity or agency.

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.

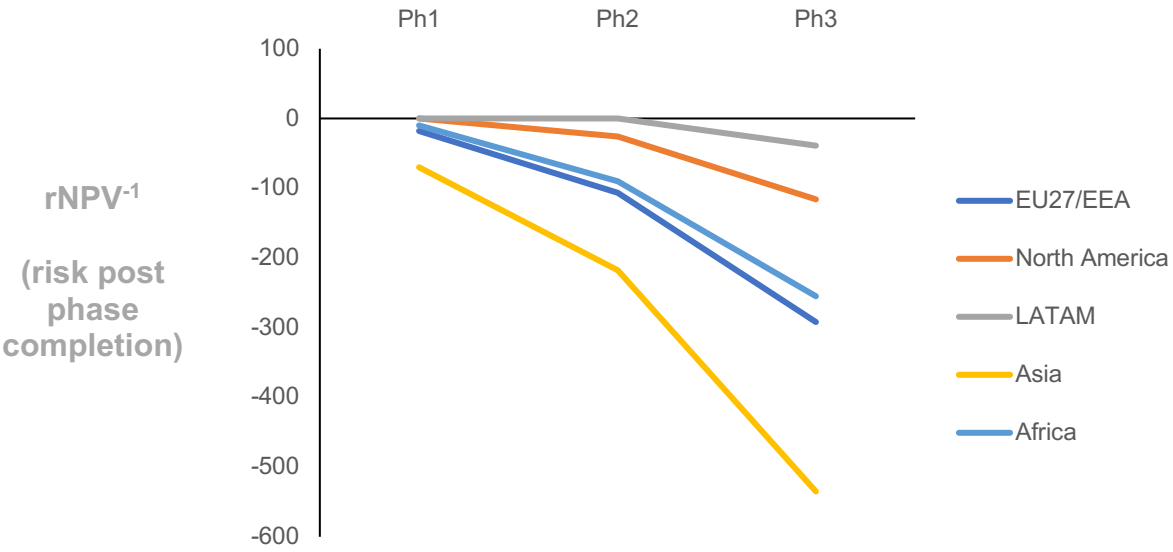
To be able to reach these populations, it will mean decreasing prices e.g. Piperacillin/tazobactam, Cefepime, Unasyn, Imipenem and Augmentin: the result is that SOM values then drop beneath the threshold that would encourage an innovator to launch a programme on antibiotic development. This is discussed more comprehensively in Antibiotic Innovation, later in this document.

Augmentin (3rd gen penicillin + β-lactamase inhibitor)

De Novo development risk:

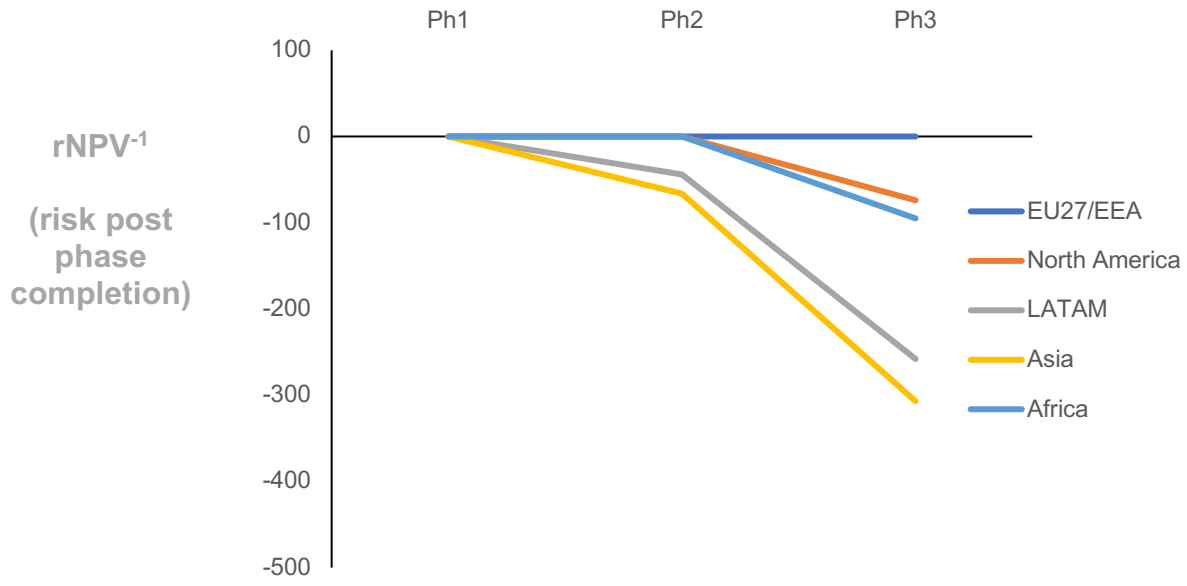


Repositioning development risk:

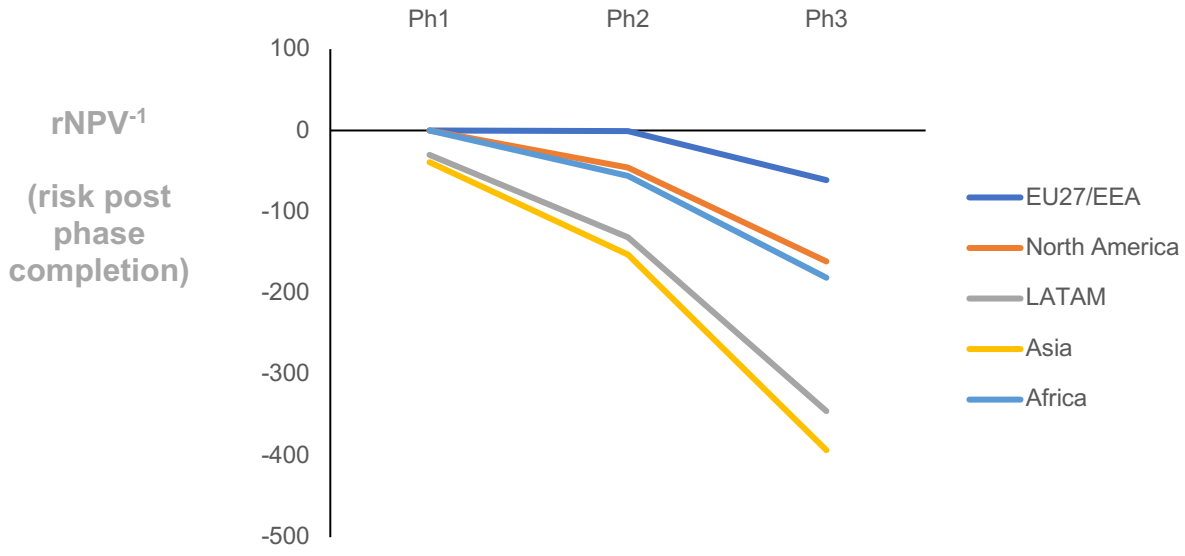


Unasyn 3rd gen penicillin + β-lactamase inhibitor)

De Novo development risk:

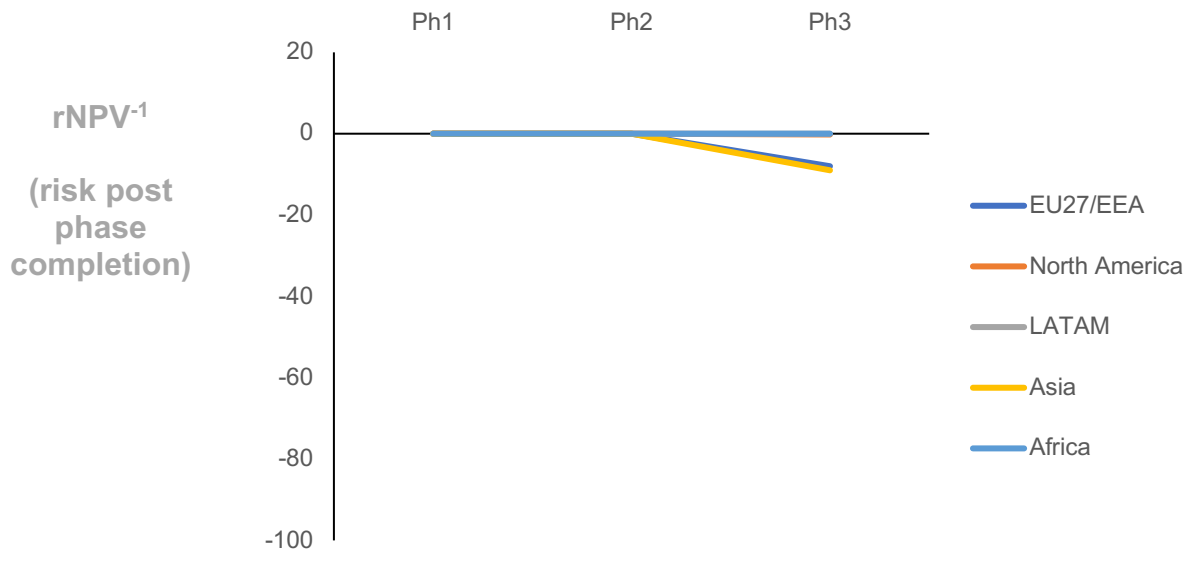


Repositioning development risk:

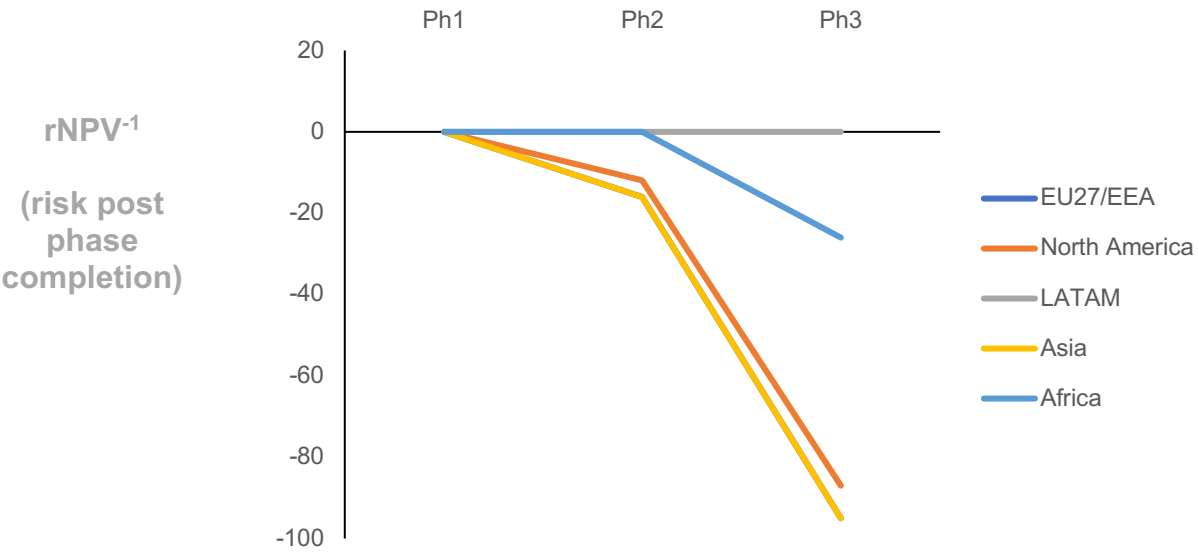


Cefotaxime (3rd gen cephalosporin)

De Novo development risk:

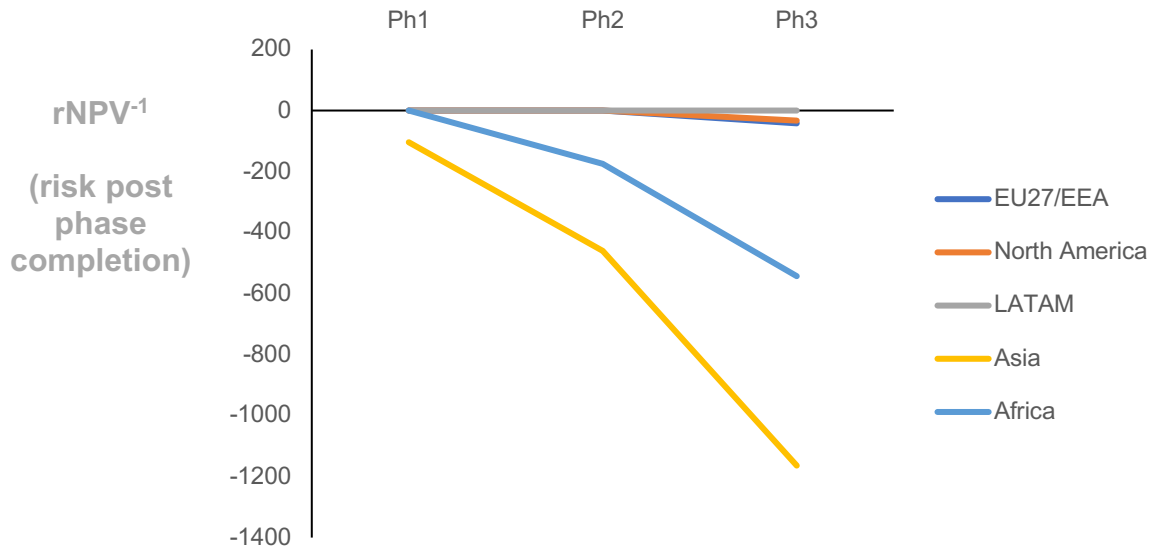


Repositioning development risk:



Piperacillin/tazobactam (4th gen ureidopencillin + β-lactamase inhibitor)

De Novo development risk:



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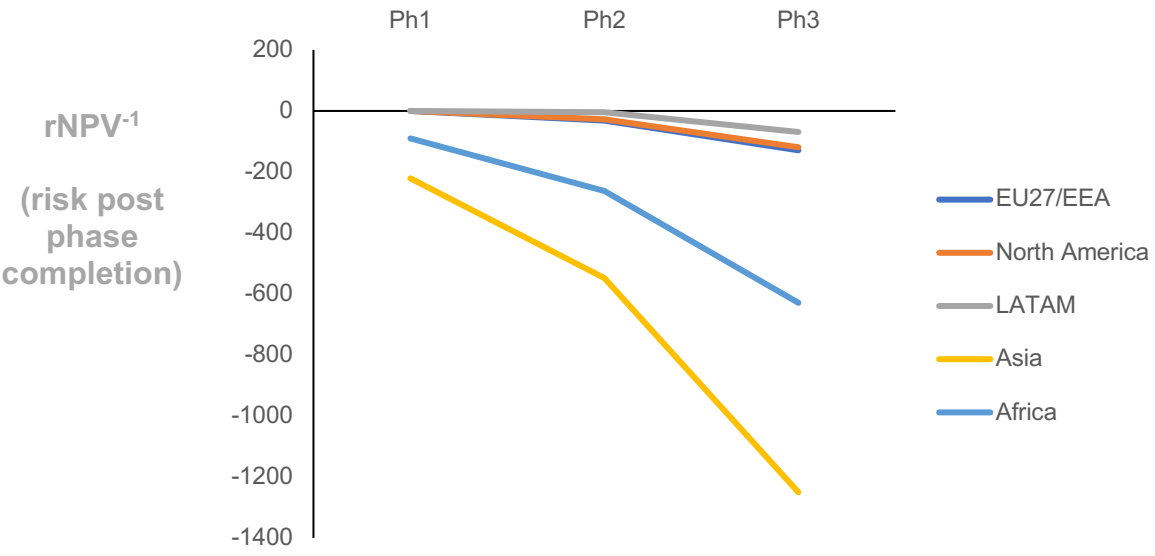
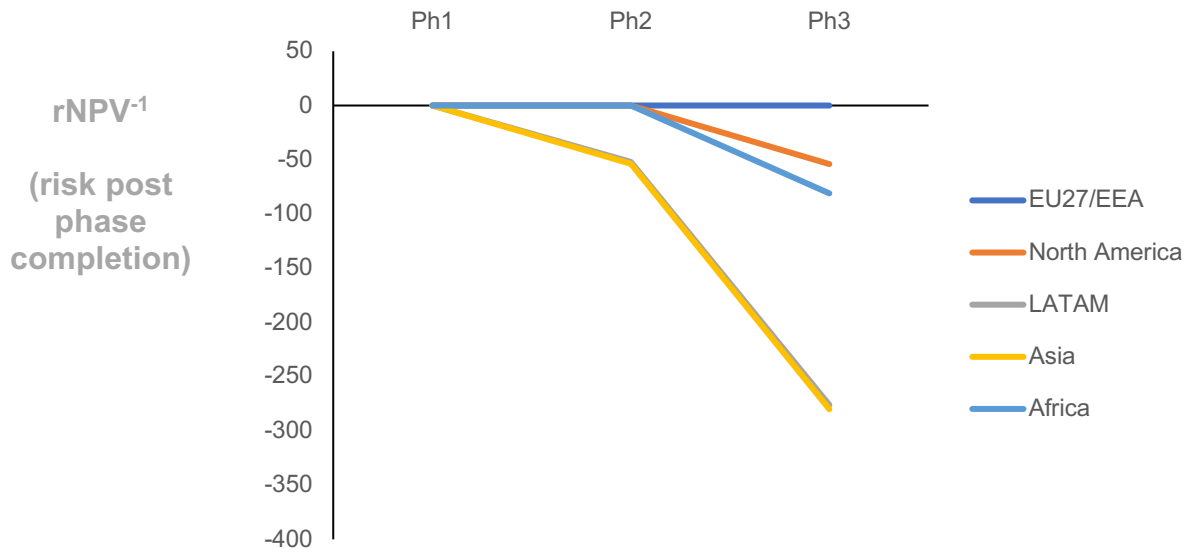
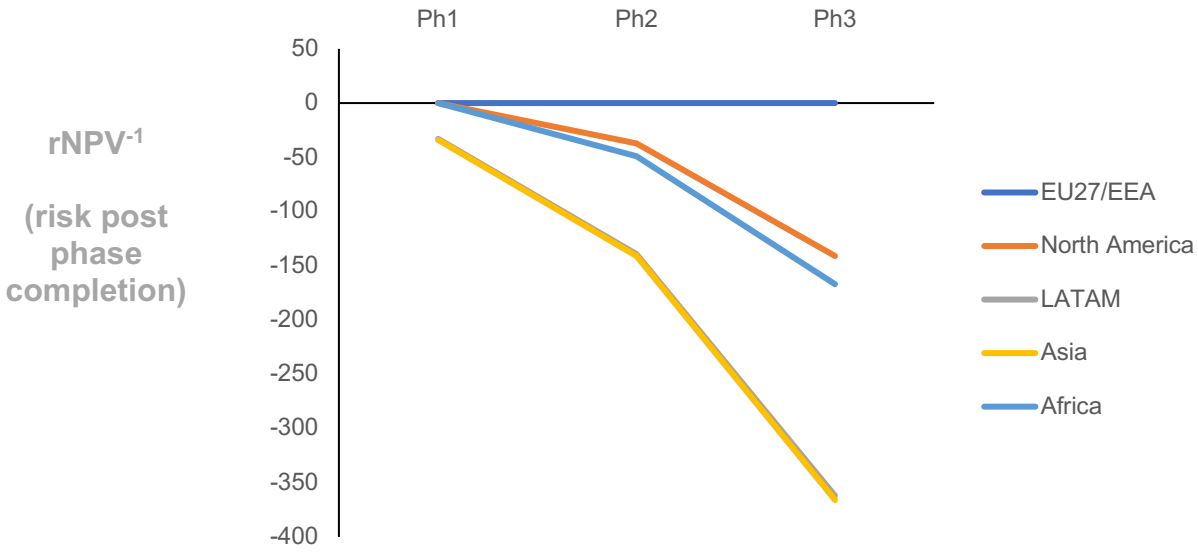


Cefepime (4th gen cephalosporin)

De Novo development risk:

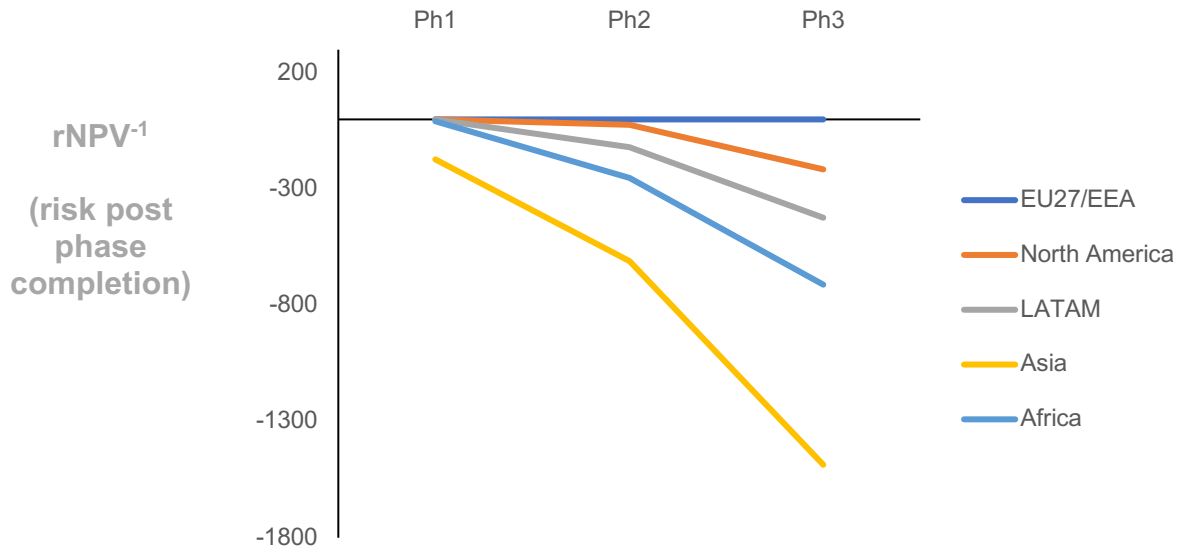


Repositioning development risk:

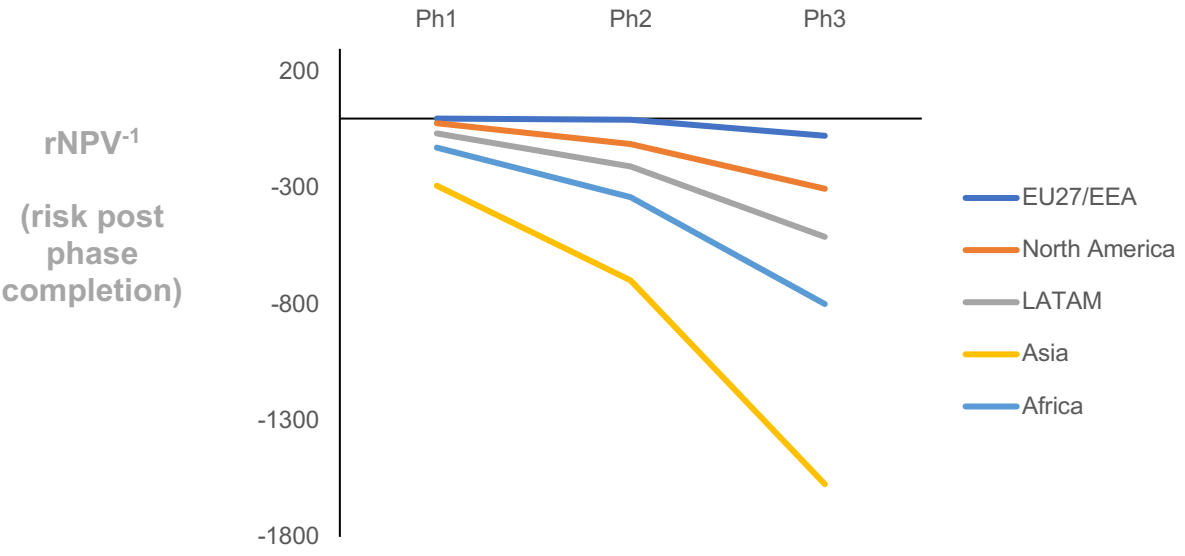


Imipenem (Carbapenem)

De Novo development risk:



Repositioning development risk:



Amoxicillin (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

Levofloxacin (3rd gen fluoroquinolones)

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

Azithromycin (Macrolide)

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/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 suggested development 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 isl likely creating 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.

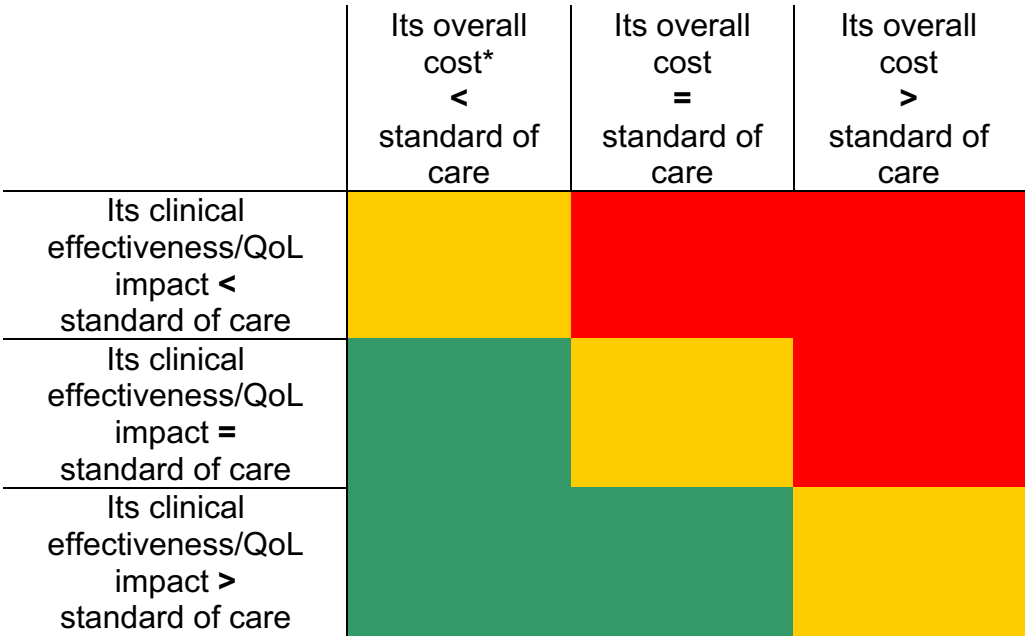
Once validated and launched onto the marketplace, its manufacture will be exclusively generic: this will prevent me too equivalents, unless they are next generation improvements, protect the innovation scheme, and enable the widest possible application as drug price will be as low as necessary.

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 Pneumonia

Pneumonia specific QoL questionnaires have been generated (*italicised*), but their usefulness has not been reliably confirmed: assessments also use lung function specific assessments as well as the use of generic types: examples include.

CAP-Sym	*Community acquired pneumonia Symptoms questionnaire*
CAP-BIQ	*Community acquired pneumonia burden of illness questionnaire*
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
LCQ	London Chest Questionnaire
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 addressed to see if and 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
Diagnosis and management of CAP- comprehensive clinical guideline (2014)	Guideline	UK National Institute of Health and Care Excellence	https://www.nice.org.uk/guidance/cg191/documents/pneumonia-guideline-consultation-full-guideline2
Diagnosis and management of CAP- comprehensive clinical guideline (2019)	Peer reviewed publication	Scientific/medical experts: approved by American Thoracic society and Infectious diseases society of America	https://www.atsjournals.org/doi/pdf/10.1164/rccm.201908-1581ST
LRTI epidemiology	Peer reviewed publication	GBD Lower respiratory collaborators: The Lancet (scientific and medical specialists)	https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30310-4/fulltext#supplementaryMaterial
Bacterial Pneumonia	Peer reviewed publication/ book	Scientific/medical experts	https://www.ncbi.nlm.nih.gov/books/NBK513321/
Pneumonia pathology	Peer reviewed publication/ book	Scientific/medical experts	https://www.ncbi.nlm.nih.gov/books/NBK526116/
Management of CAP in adults and antibiotic usage	Peer reviewed publication/ book	Scientific/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6852216/
CAP in sub-saharan africa	report	Scientific/medical experts	https://core.ac.uk/download/pdf/74363962.pdf
CAP in APAC region	Peer reviewed publication	Scientific/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7171710/
CAP in Europe	Peer reviewed publication	Scientific/medical experts	https://erj.ersjournals.com/content/20/36_suppl/20s
Bacterial aetiology of CAP in Asia	Peer reviewed publication	Scientific/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4023908/
Aetiology of LRTI in adults in primary care in Europe	Peer reviewed publication	Scientific/medical experts	https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(18)30152-6/abstract
Pathophysiology of pneumonia	Peer reviewed publication/ book	Scientific/medical experts	https://oxfordmedicine.com/view/10.1093/med/9780199600830.001.0001/med-9780199600830-chapter-115
CAP treatment protocols - De	Peer reviewed publication	Scientific/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5754574/
CAP treatment protocols - USA	Peer reviewed publication	Scientific/medical experts	https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST
HAP/VAP treatment protocols - USA	Peer reviewed publication	Scientific/medical experts	https://www.idsociety.org/practice-guideline/hap_vap/
CAP treatment protocols - India	Peer reviewed publication	Scientific/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6852216/

CURB-65 for CAP management	Peer reviewed publication	Scientific and medical specialists	https://europepmc.org/article/med/16928720
Use of CURB-65 for HAP patients	Peer reviewed publication	Scientific and medical specialists	http://www.ejcdt.eg.net/article.asp?issn=0422-7638;year=2019;volume=68;issue=2;spage=231;epage=235;aulast=Oktariani
Healthcare associated pneumonia	Peer reviewed publication	Scientific and medical specialists	https://onlinelibrary.wiley.com/doi/full/10.1111/resp.12132
Health economics			
HEOR in Lower Respiratory Tract Infections	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5970441/
HEOR in Lower Respiratory Tract Infections	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6561384/
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 standards of care 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.