Aestimo
Innovator's Briefing
Tuberculosis

AFRICA & MIDDLE EAST

www.aestimo.ie

About the disease

Epidemiology

Incidence

197 per
100 000 people

Annual cases in this geography

Latent: 2 704 633
Active: 540 926
MDR/RR: 210 961

TB infection process and phases Disease types		
Stage 1	Patient inhales TB bacillus, which then enter macrophages in the lung: macrophage either contains bacillus or it overwhelms the macrophage	Exposure
Stage 2	TB bacillus starts reproducing uncontrollably, that can last for up to three weeks	Exposure/latent
Stage 3	Bacillus stop growing: mass macrophage infiltration occurs and infection is controlled (occurs in 90% of patients): patients are asymptomatic and non-contagious, but bacillus is still present in a 'Ghon or Primary Complex' and can remain there for years	Latent
Stage 4	In 5-10% of patients after 12-24 months after initial infection, because the primary complex has not healed, and possibly due to additional risk factor impact, the bacillus reactivates and clinical manifestation of the disease occurs, with clear symptoms and patients highly contagious	Active
MDR/RR-TB and XDR-TB	WHO estimates put Drug Resistant TB at an incidence of 4.1% of new cases and 19% of previously treated active cases. The Multi Drug Resistant/Rifampicin Resistant TB is when the bacillus no longer responds to at least two medicines. This occurs in one of two ways; either directly infected with a MDR/RR-TB type (75% of DR patients) or existing infection develops into MDR/RR-TB (25% of DR patients). XDR represents a more severe manifestation in which the mycobacterium no longer responds to at least four medicines, including newer medications that are targeted towards MDR-TB.	Active

Key characteristics

Fundamentally: a disease caused by *Mycobacterium tuberculosis* that due to its mode of transmission (respiratory) typically demonstrates its major clinical manifestation in pulmonary tissue, however it has been demonstrated to also impact the:

- GI
- CNS
- Musculoskeletal
- Reproductive
- Hepatic
- Lymphoreticular systems.

Significant progress has been made to reduce its burden, but its impact is still very large, resulting in 1.4 million deaths annually, or long term pulmonary and CNS damage in survivors.

Similar to all infectious diseases, its capacity to progress represents a combination of changes it makes to itself and any opportunity to proliferate its host/permissive species offers

Millions of people are exposed to it, have been infected by it and in many cases fall into the latent infected patient category, that means progression to a clinical manifestation depends on the risk factors that a person is exposed to. Risk factors include:

- Socioeconomic status
- Nutritional deficit
- Immune dysfunction due to additional infections
- Ongoing treatments e.g. use of anti-TNFα antibodies
- Age
- Existing immunodeficiencies or immunity reduction e.g. stress or fatigue,
- Existing diseases: kidney disease, diabetes, oncology
- Environmental exposure,
- Lifestyle choices e.g. smoking,
- Additional infection such as HIV positive patients, in whom up to 35% have accelerated mortality due to the combination of viral and mycobacterium infection

The Patient Journey

Patient visits primary care physician/family doctor with following symptoms*:

- Fatigue and/or general malaise
- Fever/night sweats
- Persistent cough
- Neck swelling
- Appetite reduction

Patient referred to specialist centre:

- Medical history check & Physical examination
- Tuberculin skin test
- TB blood test
- Sputum smear/TB culture
- Potential chest X-Ray

**TB is difficult to confirm, even with these tests*

confirmation

Patient referred for treatment:

- If Latent: short course (3-4 months) of Antimycobacterials and Isoniazid
- If Active: long course (6-12 months) of Antimycobacterials and Isoniazid
- If drug resistant: long course (6-12 months) of Antimycobacterials, isoniazid and later generation drugs (Fluoroquinolones)

Follow up patient care and management

- Latent: Follow up every three months to assess any potential progression post treatment
- Active: Patients are monitored monthly for adverse effects, adherence and effect
- Drug resistant: every week if an outpatient, and then twice monthly when stable

Disease continuation/Recurrence:

Disease progression from latent to active to drug resistant as well as reactivation and reinfection means that for a significant proportion of patients the cycle of infection and pathological progression means recurrence is a constant reality

Standards-of-Care, Prices and Market size

- **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 multiplied by the TC.

Latent

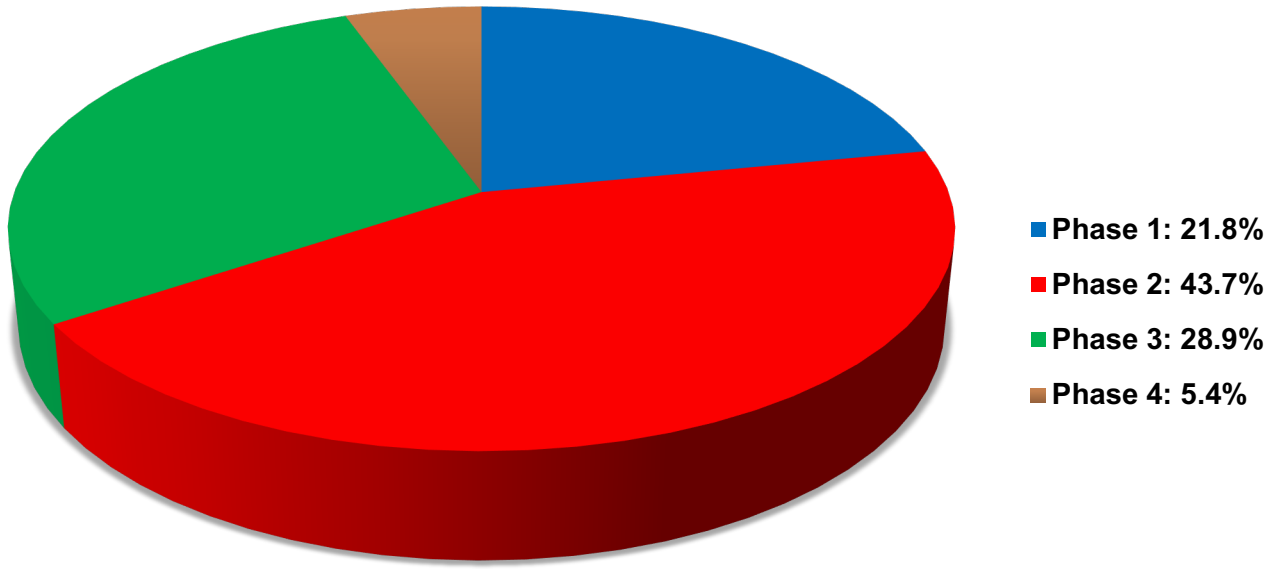
Treatment description	Example (s)	TC ($US)	SAM ($US Mn)
isonicotinic acid hydrazide + antimycobacterial	Isoniazid + rifapentine	84	227
antimycobacterial	rifampin	8.4	23

Active

Treatment description	Example (s)	TC ($US)	SAM ($US Mn)
isonicotinic acid hydrazide + antimycobacterial	Isoniazid + rifampin	12.6	6.8
isonicotinic acid hydrazide + antimycobacterials	Isoniazid + rifampin + ethambutol + pyrazinamide	4.5	2.4

Global Innovation Development

Number of clinical trials ongoing: 128 globally



Clinical trial characteristics

(Clinical trial 'CT' costs are presented as estimated maximums)

Phase 1	Phase 2	Phase 3
CT cost $ 840 000	CT cost $ 4 320 000	CT cost $ 85 302 000
Median Patient No. 42 Median Duration: 6 (months)	Median Patient No. 120 Median Duration: 6 (months)	Median Patient No. 677 Median Duration: 18 (months)

Marketplace Forecasting and Development Risk

To estimate risk for innovation development, **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 indication specific rNPV calculations; 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**

Type	Class	SOM ($US Mn)
Latent	isonicotinic acid hydrazide + antimycobacterial	670
Latent	antimycobacterial	67
Active	isonicotinic acid hydrazide + antimycobacterial	20.1
Active	isonicotinic acid hydrazide + antimycobacterials	7.1

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

- **2620 $Mn for Repositioning**
- **3840 $Mn for De Novo**

Modeling the creation of a new solution, in which reimbursement agencies will use the standard-of-care as the comparator (clinical benefit and cost benefit), aiming towards generating a higher patient benefit but with the same overall cost, we can estimate the development risk of that new solution. Risk is presented as $rNPV^{-1}$ in which the lower the value the lower the risk. Any risk value above 0, arguably carries too high a development risk with consequent ROI's of <1. More details on the model parameters are explained below.

De Novo development risk:

No intervention through de novo development generated a SOM value to enable a ROI

Repositioning development risk:

No intervention through repositioning generated a SOM value to enable a ROI

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

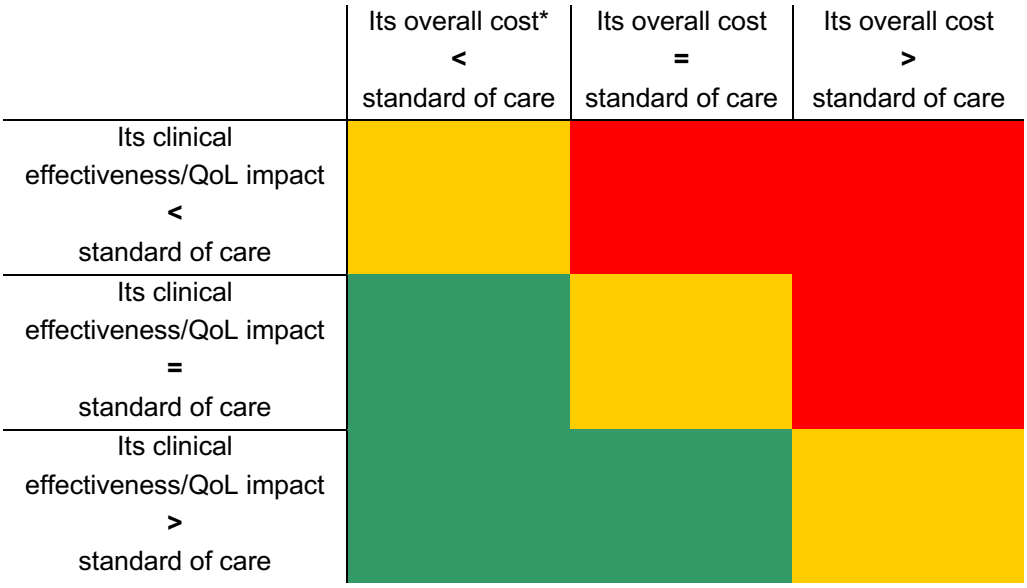
**detailed information on standards of care can be found at drugbank. go.drugbank.com (description, application, structure, DDI, development, manufacturer)*

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 (in this case imported from India)
- 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)

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

HEOR in Africa is a growing sector and perspective to healthcare solutions. This is linked to changes in the healthcare infrastructure itself to be able to provide sufficient quality health solutions to the population. Understandably, this will be a long journey.

There is clearly an impetus to develop better decision making in healthcare procurement, therefore we can anticipate that policy makers will be reviewing existing international processes and adapting them to their own locality. For the innovator, therefore, it would be logical to consider following the creation of HEOR data using standardized outputs and collect as much quality of life related information as possible during clinical trials following recognised approaches.

Recommended evidence that should be collected:

- 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
- Cost-effectiveness analyses (of the new product vs. its comparators), for life years saved and cost-utility analyses using local currency per quality adjusted life year (QALY).
- Budget impact analyses (financial consequences/change in expenditure of adopting a new intervention)

Characteristics of HEOR requirements for Tuberculosis

The HRQoL questionnaires used for assessing quality of life in sufferers of TB are:

SGRQ	St. George's respiratory questionnaire
FACIT-TB*	Functional Assessment of Chronic Illness Therapy – Tuberculosis
QLICD-PT*	Chinese Quality of Life Instruments for Chronic Diseases -pulmonary TB scale
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

(in addition to disease questionnaires, additional QoL questionnaires on depression and anxiety are also used).

**these questionnaires have not been internationally validated at present*

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 the outcomes that can be reported from the QoL questionnaires and address how to integrate them into the innovation development plan to address later stage needs, and increase the value of their solution.

Recommended reading

Subject matter	Type	Author	Link
About Tuberculosis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/books/NBK441916/
Drug resistant TB	website	WHO	https://www.who.int/activities/tackling-the-drug-resistant-tb-crisis
The challenge of latent TB infection	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5319563/
Latent TB epidemiology	Peer reviewed publication	Scientific and medical specialists	https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30307-X/fulltext
About TB	website	TBCAB: global TB community	https://www.tbonline.info/posts/2016/3/31/how-tb-infects-body-tubercle-1/
Global TB report	report	WHO	https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf?ua=1
Immune escape mechanisms of TB	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6359177/
TB and COVID19	Peer reviewed publication	Scientific and medical specialists	https://www.sciencedaily.com/releases/2020/06/200624103257.htm
Treatment strategies for MDR/RR-TB and XDR-TB	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/books/NBK247431/
Supporting new drug development	Association/ website	TB alliance	https://www.tballiance.org/about/mission
HEOR for Tuberculosis	Peer reviewed publication	Scientific and medical specialists	https://www.hsj.gr/medicine/health-status-and-quality-of-life-in-tuberculosis-systematic-review-of-study-design-instruments-measuring-properties-and-outcomes.php?aid=18409
HEOR for Tuberculosis	Peer reviewed publication	Scientific and medical specialists	https://www.sciencedirect.com/science/article/pii/S2405579419300622
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/

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.