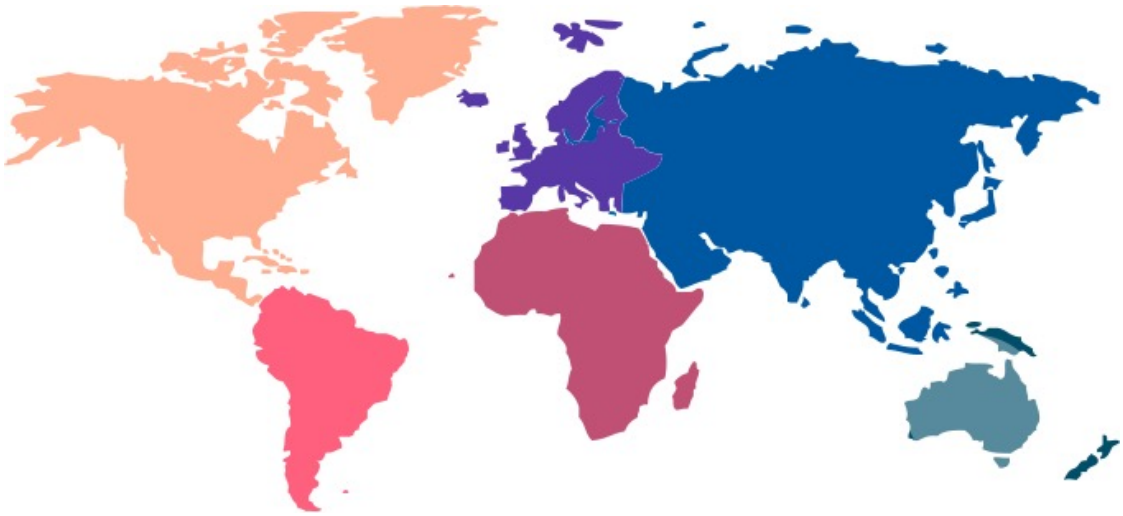
Aestimo

Innovator's Briefing

Antibiotics:

Periodontal and Periapical disease



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About the disease

Periodontal disease: Starts as gingivitis (sometimes classified separately to periodontal), a mild buildup of bacteria, only in the gums with no effect on teeth or connective tissue**,** that progresses to buildup in pockets between gums and teeth, with infection spreading to local bone.

Periapical or apical periodontitis: Most common type of dental abscess, caused by an infection of the root canal of the tooth due to a buildup of bacteria in the dental pulp as a result of tooth decay

Stages of infection: Odontogenic infections (of which Periodontal and Periapical disease represent 2 types) proceed through 4 stages

Stage 1 - Inoculation: lasts up to 3 days, resulting in tender tissue with mild soft swelling, precipitated mainly by aerobic gram-positive cocci bacteria

Stage 2 – Cellulitis: lasts up to 5 days, the infected tissue is more solid, that due to increased inflammatory infiltrate is also very sensitive. Bacterial infiltrate is both aerobic and anaerobic

Stage 3 - Abscess: lasts up to 10 days, swelling is reduced and is less tender, but anaerobic bacteria predominate, creating the liquid abscess (either in the gums or the pulp)

Stage 4 – Resolution: Abscess drains spontaneously or through medical intervention, with the host immune system eliminating the bacteria

Microbiology, Antibiotics and Antibiotic resistance

The oral cavity can host up to 700 species of bacteria (second only to the intestine), although each person typically has around 150 different active species here: post-partum the infants mouth is totally sterile, and through feeding, colonization occurs. Without teeth, within 12 months the mouth is invaded by aerobic bacteria of the *Streptococcus, Lactobacillus, Actinomyces, Veillonella* and *Neisseria* taxa.

Once the teeth start to emerge, this creates more surfaces for more types of bacteria to colonise within and on the oral tissues, as well as with each other, creating the oral microbiome, that is typically symbiotic. However if they enter a sterile environment, these same bacteria can create an infection.

Through the practice of good dental hygiene, each tooth can have up to 100,000 bacteria living on it; with poor dental hygiene this can be >1,000,000,000, meaning that in the instance of damage to the tooth, or opportunity to invade the gums, this high number of bacteria can increase the probability of tissue damage.

Not all bacteria are deleterious: the great majority do no apparent harm

Despite the large number of microbes in the oral cavity, only a few types have been linked to periodontal disease and apical periodontitis related tissue damage, examples include*:

Bacteria	Periodontal disease	Apical periodontitis	Antibiotic used	Antibiotic resistance reported
Treponema denticola	yes	detected	Tetracyclines, macrolides	yes
Porphyromonas gingivalis	yes	unknown	Tetracyclines, macrolides, penicillins, lincosamides, nitroimidazoles	yes
Tannerella forsythia	yes	unknown	Tetracyclines, penicillins, nitroimidazoles	yes
Fusobacterium nucleatum	unknown	yes	penicillins, nitroimidazoles +/- cephalosporin +/- lincomycin	yes
Enterococcus faecalis	unknown	yes	penicillins	yes
Streptococcus mutans	unknown	yes	Penicillins, lincomycins, cephalosporins, macrolides	yes

**Note that the complexity of known implicated bacterial is significantly greater than this list. See references*

The Patient Journey

Periodontal Disease

Patient manifests

- Halitosis
- Inflamed gums +/- bleeding
- Pain when masticating
- Loose and/or sensitive teeth
- Receding gums

Patient is assessed

- Medical history review
- Lifestyle assessment
- Dental assessment
- X-ray imaging
- Tooth-gum pocket depth measurement

Confirmation and staging

Treatment

- Lifestyle change
- Non antibiotic based antimicrobials
- Subgingival instrumentation
- Possible antibiotics

Follow up
patient care and management

- Ideally at 3 months to assess elimination

Some tests performed during original diagnosis maybe repeated

Periapical Disease

Patient manifests

- Dental sensitivity upon contact
- Most cases are asymptomatic
- Possible gum or teeth tenderness during chewing or alternative sources of pressure

Patient is assessed

- Medical history review
- Examination of tooth and surrounding tissue
- Dental assessment (tapping on tooth)
- X-ray imaging (X-ray or CT scan)

Confirmation and staging

Treatment

- Non antibiotic based antimicrobials
- Definitive Conservative Dental Treatment (pulpotomy, pulpectomy, non surgical canal treatment, incision+drainage)
- For acute apical periodontitis + systemic involvement, possible antibiotics

Follow up
patient care and management

- Ideally at 3 months to assess elimination

Some tests performed during original diagnosis maybe repeated

Recurrence, refraction or relapse:
Dependent on the stage at diagnosis and severity, but typically dental hygiene monitoring should be a routine procedure to assess for changes

Periodontal disease

A) Treatment approach

Evidence based treatment for the first three stages is focused by steps, as a function of the stage of the disease obtained through accurate diagnosis (Sanz et al, Treatment of stage I-III periodontitis: NB treatment of stage IV periodontitis is complex and not covered in this briefing):

Step 1: Behavioural change, adjuvant therapies and plaque/calculus removal
Step 2: cause treatment, subgingival instrumentation, chemical agents, antimicrobials
Step 3: if disease not responding to steps 1 & 2, these maybe repeated with possible surgery (flap, resective or regenerative)

Periodontitis stages, treatment and recommended use of antibiotics

stage	Description*	Treatment	Antibiotic usage recommendation	Type
1	mild	Behavioural change and Subgingival instrumentation	No	Not applicable
2	moderate	Behavioural change and Subgingival instrumentation	Possible local administrable form, but evidence could be better related to patient benefit	Ligosan, Arestin, Atridox (all tetracycline based)
3	Severe *(previously known as severe chronic)*	Behavioural change and Subgingival instrumentation	**Maybe: only when generalised type of disease in young adults**	Nitroimidazole, penicillin, macrolide types – systemic application, other types rarely
4	*Very severe*	*Complex multidisciplinary treatment*	*Maybe: generalised type of disease only*	*penicillin, macrolide based – systemic application*

**staging and grading of periodontitis (AAP updated guidelines on staging)*

B) Epidemiology

Epidemiology of stage 3 periodontitis and recommended treatment eligibility

	Prevalence per 100 people	Generalised type frequency	Young adult percentage (16-25)	Annual treatable population (million)
Europe	11	43%	10.1	2.13
North America	8		12.7	1.59
Latin America	17		16.2	7.7
Africa & ME	13		19.2	13.8
Asia	12		15	35

C) 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 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**

Macrolides (prescribed if allergic/hypersensitive to penicillin, approx. 14% of people)

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	5	1.5	4.4
North America	11	2.4	7.2
Latin America	5	5.4	15.8
Africa & ME	2	3.9	11.4
Asia	2	9.8	28.8
		Global Total	67.6

Penicillin

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	4	8.5	25.0
North America	4	6.3	18.7
Latin America	2.25	17.3	50.9
Africa & ME	2	27.6	81.1
Asia	2	70	205.8
		Global Total	381.5

Nitroimidazoles

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	22	46.8	137.8
North America	90	143.1	420.7
Latin America	6	46.2	135.8
Africa & ME	2	27.6	81.1
Asia	2	70	205.8
		Global Total	981.2

Periapical disease

Most common type of dental abscess, representing a buildup of bacteria in the dental pulp as a result of tooth decay

A) Treatment approach

Dental decay and degradation progress through 5 distinct stages

Stage 1: the enamel becomes demineralised by acid produced by bacteria (asymptomatic)
Stage 2: the enamel degrades further resulting in cavities (asymptomatic)
Stage 3: the tissue beneath the enamel, dentin, decays (asymptomatic/symptomatic)
Stage 4: the pulp becomes damaged (pulp = blood vessels, connective tissue and nerves) (symptomatic)
Stage 5: Abscess: bacterial penetration, infection and expansion (symptomatic)

These stages do not totally explain the pathogenesis and treatment approach. The table below is an adaptation and integration of the algorithm explaining the progression of an infected root canal to later stage disease (P. Abbott 2004) and the 2019 guidelines from the American Dental Association on the use of antibiotics in periapical disease.

What has been indicated as **phases**, is our way to present in an easily visible format the connection between the two: it **is not an official or peer reviewed and agreed definition**, while explanations, treatments and antibiotics + types are.

	Explanation	Treatment	Antibiotics	Type
Phase 1	Infected root canal	DCDT	No	Not applicable
Phase 2	Primary acute apical periodontitis arising because of Phase 1	DCDT	No	Not applicable
Phase 3	Primary **acute apical abscess** arising because of Phase 2	DCDT + antibiotics	**Yes, if pulp necrosis with systemic involvement (or if localised involvement and DCDT not available on day of diagnosis)**	Penicillin class
Phase 4	Chronic apical periodontitis arising because of Phase 1 or Phase 3 with no abscess	DCDT	No	Not applicable
Phase 5	Secondary acute apical periodontitis arising because of Phase 4 with no abscess	DCDT	No	Not applicable
Phase 6	Secondary **acute apical abscess** arising because of Phase 4	DCDT + antibiotics	**Yes, if pulp necrosis with systemic involvement (or if localised involvement and DCDT not available on day of diagnosis)**	Penicillin class
Phase 7*	*Intense inflammation Facial Cellulitis Periapical cyst or chronic apical abscess*	*surgery*	***Yes***	*Penicillin class*

**Very advanced stage of disease, that similar to late-stage periodontal disease necessitates a more comprehensive approach*

B) Epidemiology

Periapical or apical periodontitis is the most frequent dental manifestation, initiated by dental caries (tooth decay), in which the enamel of the tooth is damaged through trauma or acid created by bacteria on the teeth, that enables bacteria to enter.

Accurate epidemiology, region by region, is very difficult to obtain due to age related differences, dental treatment infrastructures, variation by type of teeth that are more prevalent for the disease and absence of centralised reporting.

However, the consensus from numerous peer reviewed articles is that periapical disease is one of the most frequent diseases on the planet: the most accurate epidemiological assessment indicates that 27% of 20-64 year olds, globally, have untreated dental caries, and of that patient population, approximately 13% present with an acute apical abscess of which around 50% have pulp necrosis.

Using these figures, we arrive at the following regional prevalence who would be eligible for antibiotic treatment:

	Annual treatable population (million)
Europe	63.9
North America	51.2
Latin America	94.0
Africa & ME	142.2
Asia	656.3

C) 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.
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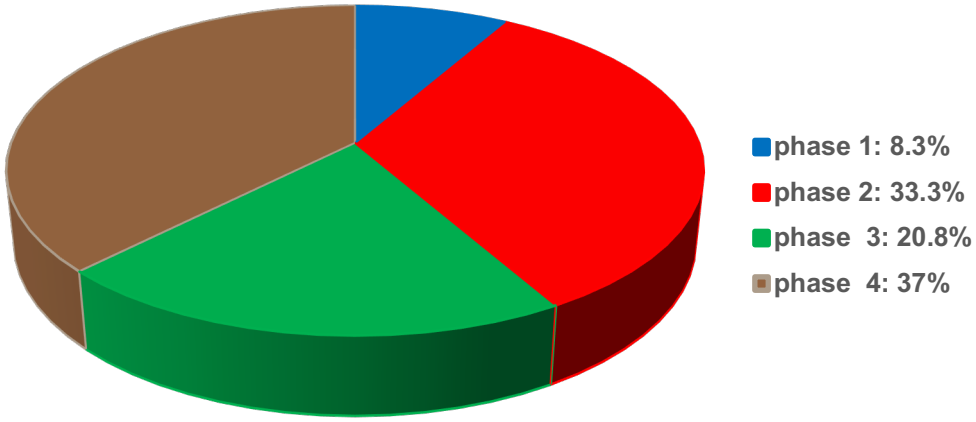
The antibiotic standard of care is to use penicillin types, approximately 500mg, 3 times a day for a maximum of 7 days.

	TC ($US)	Maximum SAM value ($US Mn)	SOM value ($US Mn)
Europe	6	766.6	1126.9
North America	6	613.8	902.4
Latin America	5	940.2	1382.1
Africa & ME	3	853.0	1253.9
Asia	3	3938.1	5789.0
		Global Total	10454.3

Clinical trial design

Clinical trial design and ongoing numbers: ongoing clinical trials for periodontitis and periapical disease n = 24 (6 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)

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 either Periodontal or Periapical disease are:

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

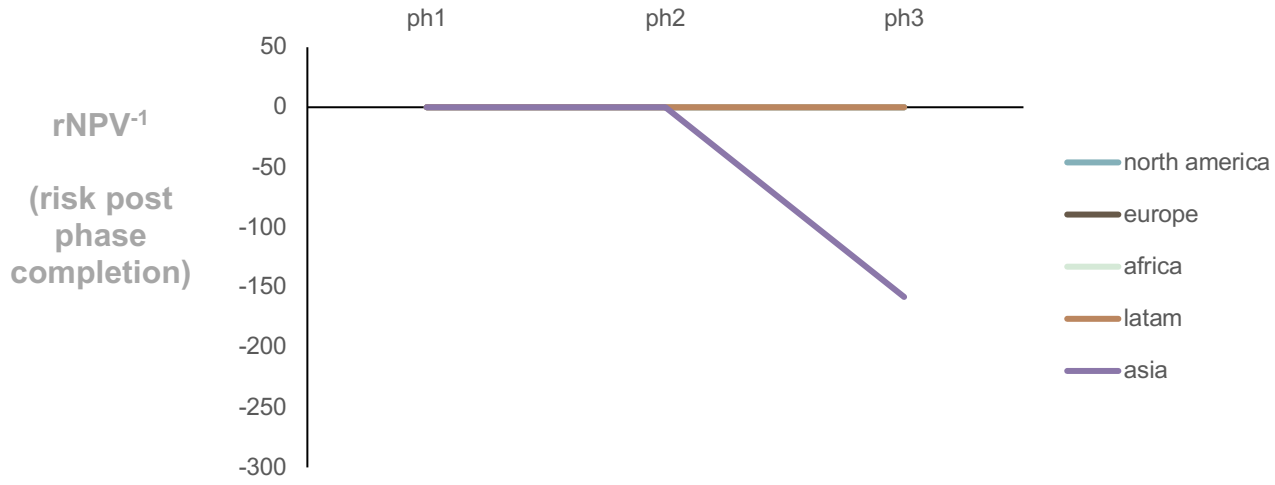
For Periodontal disease

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

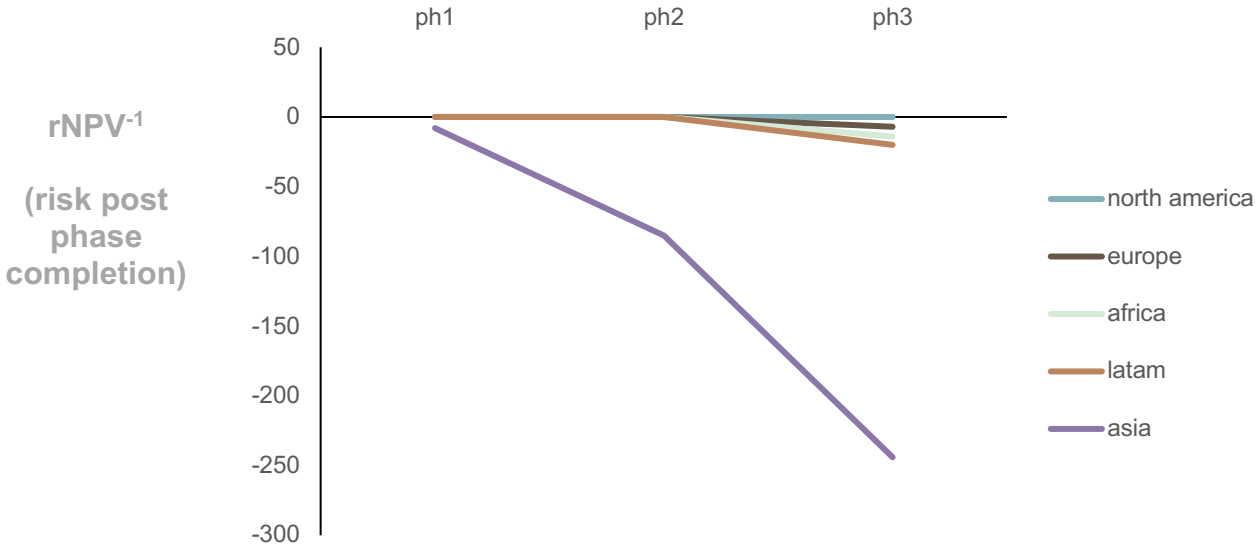
Repositioning development risk: No solution reached threshold to generate a ROI for repositioning development

For Periapical disease

De Novo development risk:



Repositioning development risk:



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.

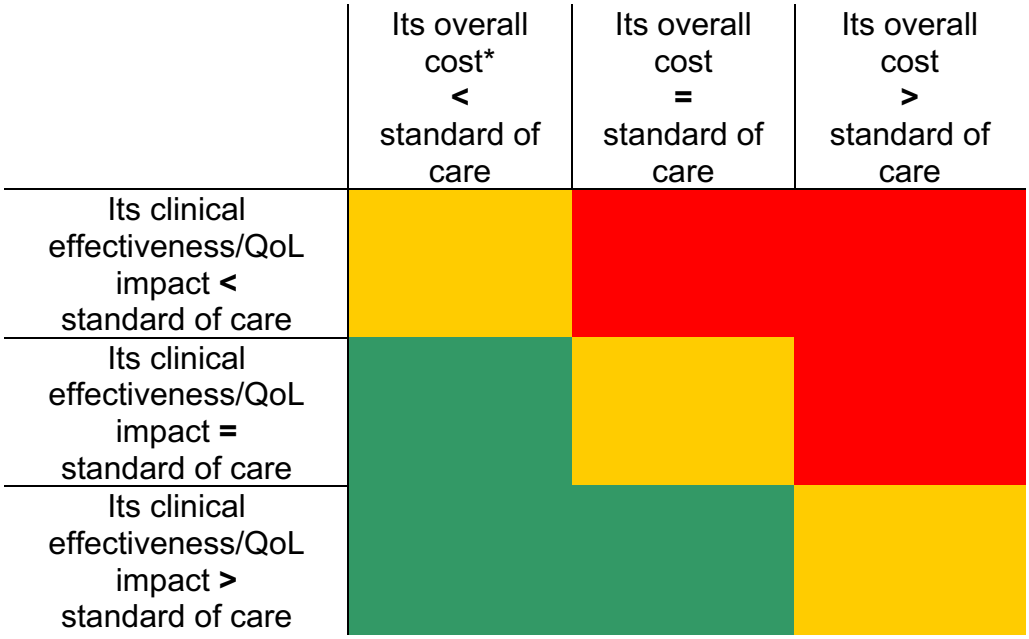
Once validated and launched onto the marketplace, its manufacture will be exclusively generic: this will prevent me too equivalents, unless they are next generation improvements, protect the innovation scheme, and enable the widest possible application as drug price will be as low as necessary.

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); <u>these are not clinical efficacy endpoints</u>. 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 Dental Health

For Dental Health QoL questionnaires have been generated as well as the use of generic types: examples include.

OHIP	Oral health Impact Profile
OHRQoL	Oral Health-Related Quality of Life
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
Disease overviews			
Dental infections	Online peer reviewed book	Scientist/medical experts	https://www.ncbi.nlm.nih.gov/books/NBK542165/
Dental Abscess	Online peer reviewed book	Scientist/medical experts	https://www.ncbi.nlm.nih.gov/books/NBK493149/
Periodontal disease	Online peer reviewed book	Scientist/medical experts	https://www.ncbi.nlm.nih.gov/books/NBK554590/
Global epidemiology of dental caries and severe periodontitis	Peer reviewed publication	Scientist/medical experts	https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/jcpe.12677
Oral Health Atlas	report	FDI world dental federation	https://www.fdiworlddental.org/sites/default/files/media/documents/complete_oh_atlas.pdf
Caries	website	MSD Manual	https://www.msdmanuals.com/professional/dental-disorders/common-dental-disorders/caries
Pulpitis	website	MSD Manual	https://www.msdmanuals.com/professional/dental-disorders/common-dental-disorders/pulpitis
Periodontitis	website	MSD Manual	https://www.msdmanuals.com/professional/dental-disorders/periodontal-disorders/periodontitis?query=periodontitis
Oral microbiota	Peer reviewed publication	Scientist/medical experts	https://www.sciencedirect.com/science/article/pii/S2213453018301642
Development of oral microbiota	Peer reviewed publication	Scientist/medical experts	https://www.nature.com/articles/s41598-019-46923-0
Oral microbiome fundamentals	Peer reviewed publication	Scientist/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6503789/
Association between periodontal pathogens and systemic disease	Peer reviewed publication	Scientist/medical experts	https://www.sciencedirect.com/science/article/pii/S2319417018302634
Antibiotic prescription by dentists	Peer reviewed publication	Scientist/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2909496/
Periapical disease			
Pathogens in acute apical abscess vs asymptomatic apical periodontitis	Peer reviewed publication	Scientist/medical experts	https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC5749828&blobtype=pdf

Diagnosis of pulpal and periapical diseases	report	Revise dental	https://revisedental.com/lesson/diagnosis-of-pulpal-and-periapical-diseases/?print=pdf
Microbia populations in the apical root system	Peer reviewed publication	Scientist/medical experts	https://www.nature.com/articles/s41598-020-67828-3
Microbiology/ treatment of acute apical abscess	Peer reviewed publication	Scientist/medical experts	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3623375/
ADA guidelines on antibiotic usage in pulpal- periapical disease	Peer reviewed publication	Scientist/medical experts	https://jada.ada.org/article/S0002-8177(19)30617-8/pdf
Periodontal disease			
Periodontal factsheet	website	American Academy of Periodontology	https://www.perio.org/newsroom/periodontal-disease-fact-sheet
Staging and grading periodontitis	website	American Academy of Periodontology	https://www.perio.org/sites/default/files/files/Staging%20and%20Grading%20Periodontitis.pdf
Treatment of stage I – III periodontitis	Peer reviewed publication	***Sanz et al***: Scientist/medical experts from European Federation of Periodontology	https://onlinelibrary.wiley.com/doi/full/10.1111/jcpe.13290
Periodontal pathogens from healthy adults	Peer reviewed publication	Scientist/medical experts	https://www.nature.com/articles/s41598-019-41882-y
Health economics			
HEOR in dental disease	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4606631/
HEOR in dental disease	Peer reviewed publication	Scientific and medical specialists	https://www.karger.com/Article/FullText/500855
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.