Global solutions for a global problem: Using diagnostics to prevent AMR

"We need a step change in the diagnostic technology available... all antibiotic prescriptions will need to be informed by up-to-date surveillance information and a rapid diagnostic test .... This will open the door to investment and innovation, by showing clever developers that if they build rapid tests they will find a market for them."

-- Tackling Drug-Resistant Infections Globally: Final Report & Recommendations (Review on Antimicrobial Resistance, 2016)

"...this is an issue of crucial importance for the entire human race – for people in developed and less developed countries alike. We must ensure that existing antibiotics remain effective, and that they are used only when medically necessary ...."

-- Statement by Federal Chancellor Angela Merkel at the 68th session of the WHO World Health Assembly in Geneva on 18 May 2015

"We face huge gaps in our ability to monitor the [AMR] situation in many countries. As this is a global crisis, we need to close these gaps. We need new diagnostics as well as replacement antimicrobials ..... We need to find the business models and incentives to stimulate the relevant R&D."

-- Margaret Chan, Director-General, WHO, addressing the EU Ministerial Conference on AMR, 10 February 2016

Geneva, October 2017
FOR EXTERNAL REVIEW

FIND
Because diagnosis matters

Abbreviations

AMR	Anti-microbial resistance
ARLG	Antibacterial Resistance Leadership Group
BARDA	United States Biomedical Advanced Research and Development Authority
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CDC	United States Centers for Disease Control and Prevention
DNA	Deoxyribonucleic acid
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FIND	Foundation for Innovative New Diagnostics
GAMRIF	Global Antimicrobial Resistance Research Innovation Fund
GARD-P	Global Antibiotic Research and Development Partnership
GLASS	Global Antimicrobial Resistance Surveillance System
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMIC	Low- and middle-income countries
LRTI	Lower respiratory tract infection
MDR-TB	Multi-drug resistant tuberculosis
MRSA	*Methicillin-resistant Staphylococcus aureus*
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
R&D	Research and development
ReAct	Action on Antibiotic Resistance
ReSeq	Relational Sequencing data platform
SDG	United Nations Sustainable Development Goal
STI	Sexually transmitted infection
TB	Tuberculosis
TTP	Target Product Profile
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
UTI	Urinary tract infection
WEF	World Economic Forum
WHA	World Health Assembly
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

1. Executive Summary

The inappropriate use of antibiotics and other medicines is fuelling the emergence of antimicrobial resistance (AMR) globally, and is reducing the effectiveness of the few treatment options we have left to treat severe bacterial illnesses. Currently, 700,000 deaths annually are due to drug-resistant strains of common bacterial infections, HIV and malaria and it is estimated that by 2050, 10 million deaths will be caused by AMR each year. Addressing the spread of AMR is essential to achieve United Nations Sustainable Development Goals (SDGs) like good health and well-being (SDG 3) and has been a key priority for the global health community and political stakeholders. Diagnostics have a critical role across the entire Global Action Plan on AMR and as the 'first prescription' have proven their ability to save 'the global good', patient health and economic resources.

FIND's AMR strategy is focused on halting and preventing AMR by 1) optimizing use of antimicrobials, 2) preserving new drugs and 3) empowering surveillance efforts.

- Optimizing use of antimicrobials:
    - The overuse of antibiotics is often linked to their use in non-bacterial infections, e.g., in patients presenting with acute fever, lower respiratory tract infections, urinary tract infections, sexually transmitted infections or diarrhoea.
    - Diagnosis enables the selection of the most appropriate therapy and reduce the inappropriate use of antibiotics.
- Preserving new drugs:
    - Stewardship of current and new antibiotics is critical to ensure they retain their efficacy for as long as possible, especially for critically needed antibiotics against gram-negative bacteria like *N. gonorrhoea*.
    - Early introduction of a gating diagnostic will ensure that these drugs are used in the most appropriate cases, shielding them from rapid overuse and early emergence of resistance.
- Empowering surveillance efforts:
    - Connected surveillance tools to track and map the emergence of resistance form the basis of national surveillance programs, and enable control measures and improved treatment strategies.
    - Screening and isolation of infected patients helps prevent the spread of resistant pathogens in community and hospital settings.

Eight priority drivers of AMR were identified for diagnostic interventions based on a broad needs assessment. In line with the WHO Framework to Combat AMR, FIND will develop integrated responses to the main barriers that are affecting the ability of diagnostic solutions to achieve impact:

- Development of "fit-for-purpose" diagnostics: Develop prioritized diagnostics strategies with WHO, create supporting services, e.g., virtual bio-repositories and steward the R&D pipeline for prioritized needs.
- Evidence for policies and guidance on use: Provide evidence on new tests for WHO-prioritized needs, expand ReSeq TB database to AMR as the basis for sequencing-based surveillance and develop decision aid packages combining algorithms, software and simple diagnostics.

- Country introduction and scaled access: Understand markets and motivators for behaviour change, apply connectivity learnings to AMR for patient management and surveillance and define and implement replicable diagnostic service delivery models, incl. financing and procurement mechanisms.

Given the global dynamics of AMR and its rapid spread across borders, the challenge needs to also be addressed in LMICs which carry the highest AMR burden in order to achieve sustainable results. FIND will ensure that diagnostic solutions and policies also address the needs of LMICs, and that access is guaranteed for vulnerable populations most at risk for contracting infections.

To date, FIND's work in AMR has focused on tuberculosis, malaria and fever; notably the development, evaluation and introduction of rapid molecular and sequencing-based solutions for drug susceptibility testing and point of care triaging tools. In the short-term, FIND plans to expand this successful existing portfolio in order to address priority needs:

- Triaging tools for community-acquired infections (expanding intervention): Building on an existing work focused on triaging for fever, evaluate the utility of simple triaging tools (e.g., UTI dipsticks, electronic health algorithms), redesign or adapt them for LMIC needs and develop models for uptake to optimize the use of antimicrobials.
- Virtual specimen bank and sequencing database (expanding intervention): FIND has seen success in its work to combat drug-resistant TB by developing a virtual strain bank with isolates and DNA from MDR-TB and pre-XDR-TB patients and by launching a relational sequencing data platform (ReSeq TB) to discover, grade, and track key bacterial drug resistance mutations. FIND plans to expand these applications to other disease areas creating an international resource for available specimens and genomic information on resistant pathogens to empower assay developers and surveillance programs.
- Companion diagnostics for new antibiotics targeting drug-resistant gonorrhoea (new intervention): FIND aims to support the development of better rapid gonorrhoea diagnostics and resistance testing to enable a definitive diagnosis prior to treating patients with new antibiotics that are currently in development. These tests will ensure that only patients with gonorrhoea or ideally drug resistant gonorrhoea receive the new treatment, thereby preventing overuse and early emergence of resistance.
- Data utilization for clinical decision-making and surveillance (expanding intervention): Establish connectivity for AMR diagnostics and decision aid tools, thereby extending the reach of national surveillance programs to include routine hospital and community data.

FIND is known to work as a bridge between experts in technology development, policy and clinical care and has active collaborations with more than 200 partners. Within AMR, FIND will work closely with WHO to support the development of TPPs, provide input on policy recommendations and guidelines and inform global surveillance efforts. In addition, FIND will collaborate with existing and new partners to support an integrated response to AMR. FIND will advocate for the creation of an AMR Diagnostics Use Accelerator to establish a smooth pathway to uptake in LMICs for AMR diagnostics, and create a pull mechanism for R&D investment. Results and impact of the different interventions will be monitored through robust and standardized processes, and results widely disseminated through partnering networks and other channels.

FIND will require a funding commitment of ~$72M to drive the work during the next 6 years:

- Phase 1 (2018-19): $17M to confirm market understanding on the impact of diagnostic solutions in AMR, publish landscapes and market analyses, set up virtual specimen/strain banks, work on end-to-end connectivity solution, build R&D portfolio for 2 priority TPPs, and demonstrate impact of at least 3 triaging tools through multi-centre studies.
- Phase 2 (2020-21): $30M to expand R&D portfolios and add 2 priorities, demonstrate impact of 4 emerging diagnostic solutions, define and implement at least 2 replicable models across 3-5 countries for diagnostics service delivery and expand the ReSeq sequencing database to standardize resistance profiles for pathogens beyond TB.
- Phase 3 (2022-23): $25M to mature R&D portfolios and deliver 3 new diagnostic solutions while intensifying activities and in country demonstrations to drive policy change, to ensure uptake and adoption of game-changing diagnostic solutions; inform growth into Phase 4 to support the global needs in AMR.

2. AMR challenges and opportunities: Global and local

The inappropriate use of antibiotics and other medicines is fuelling the emergence of antimicrobial resistance (AMR) globally, and is reducing the effectiveness of the few treatment options we have left to treat severe bacterial illnesses. Currently, 700,000 deaths annually are due to drug-resistant strains of common bacterial infections, HIV and malaria and it is estimated that by 2050, 10 million deaths will be caused by AMR each year, with a loss of over 100 trillion USD in economic output. In 2015 alone there were almost 500,000 new cases of multi-drug resistant tuberculosis reported. A major cause of neonatal deaths worldwide, sepsis is often caused by resistant bacteria.

Addressing the spread of AMR is essential to achieve the United Nations Sustainable Development Goals (SDGs). In addition to Good health and well-being (SDG 3), AMR also threatens sustainable food production (SDG 2), clean water (SDG 6) and economic improvement (SDG 1 and 8).

AMR is indiscriminate; however, the most vulnerable populations are most at risk for contracting life threatening infections. In particular, people living in LMICs are hugely affected by high rates of AMR as indiscriminate use of antibiotics – a major driver in the development of AMR – to treat infections that are not bacterial in nature is common, and doctors often rely on empirical treatment, even for 2nd and 3rd line antibiotics, due to a lack of accessible and usable diagnostics.

In the absence of appropriate diagnostics we have seen a 40% increase in the global consumption of antibiotics in a single decade. There is a clear observed correlation between antibiotic overuse and resistance. In LMICs, most children with fever and a negative malaria test are estimated to receive antibiotics (e.g. 60-95% in a study carried in Tanzania), while only a very small share of them would actually need them, as the majority of these cases are self-limited viral illnesses.

The issue of how to fight AMR has been on the global public health agenda for some time, and a Global Action Plan has been developed by the tripartite collaboration between WHO, FAO and OIE in 2015. Recently there has also been increasing political momentum with a number of organizations like the G20, WEF or OECD acknowledging the threat of AMR and need for a coordinated plan to reduce this threat. At the same time there has been as a growing recognition of the benefits that diagnostics can bring to many of the identified core action areas.

3. Diagnostics: a critical component of AMR solutions

Diagnosis means protection, both of our drug arsenal and of patients under threat from resistant pathogens. Diagnostics as the 'first prescription' have proven their ability to save antibiotics, health and money. A number of studies show that antibiotic use can be dramatically cut through the use of a simple diagnostic and there is increasing evidence that limiting overuse of antibiotics can have positive impact on individual patient outcomes[1,2,3,4,5,6,7]. Diagnostics have been shown to reduce the time to pathogen identification and to optimal and effective antimicrobial treatment and active surveillance testing can lead to significant cost savings[8,9,10]. For a number of action areas that have been identified in the Global Action Plan on AMR, diagnostics will be critical for public health and patient impact (Figure 1).

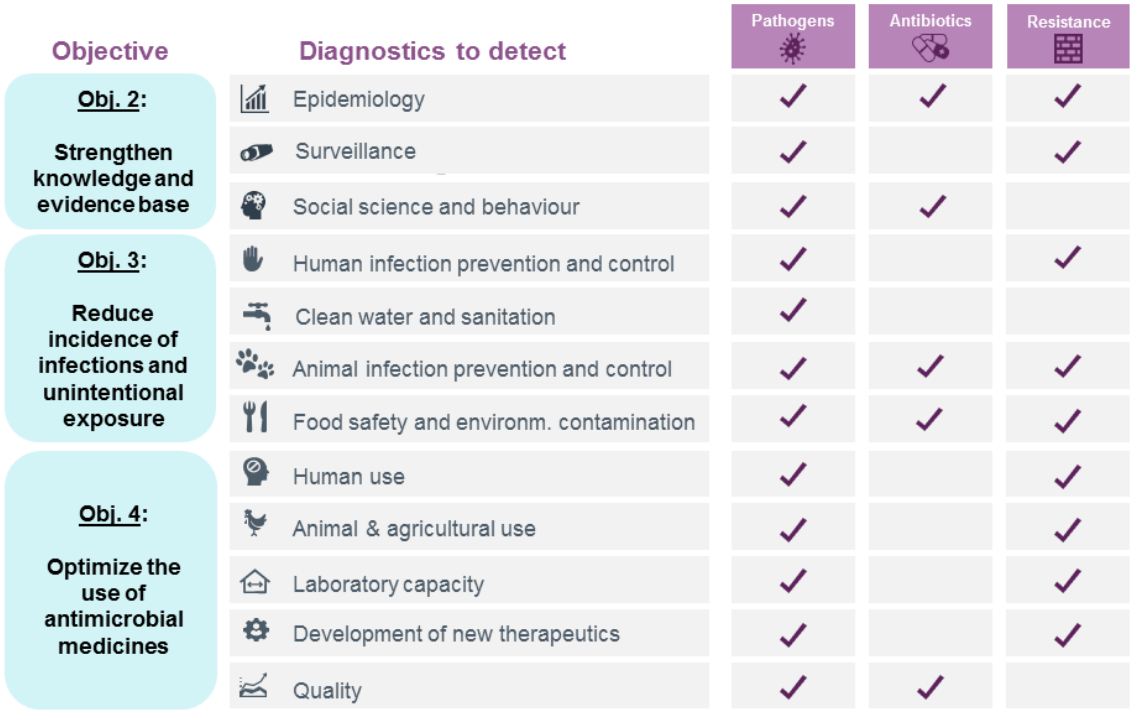

Figure 1: The role of diagnostics across the Global Action Plan on AMR

1 "Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial", August 2016

2 "Modelling the Impact and Cost-Effectiveness of Biomarker Tests as Compared with Pathogen-Specific Diagnostics in the Management of Undifferentiated Fever in Remote Tropical Settings", PLOS ONE, March 30, 2016

3 Lowe, Christopher F., et al. "Targeted Antimicrobial Stewardship Intervention for Inpatients with Viral respiratory tract infections." *Open Forum Infectious Diseases*. Vol. 3. No. suppl_1. Oxford University Press, 2016.

4 "White paper on rapid diagnostic technologies to tackle antimicrobial resistance", Health First Europe, 2017

5 Tonkin-Crine et al., Cochrane Review

6 "Recurrent Urinary Tract Infections in Children", Conway et al, 2007

7 Brismar, BO et al. "Comparative effects of clarithromycin and erythromycin on the normal intestinal microflora." *Scan. journal infect dis* 23.5 (1991); Buffie CG, et al. "Profound alterations of intestinal microbiota following a single dose of clindamycin." *Infect immun* 80.1 (2012); Sekirov, Inna, et al. "Antibiotic-induced perturbations of the intestinal microbiota alter host susceptibility to enteric infection." *Infect immun* 76.10 (2008); Teo, Shu Mei, et al. "The infant naso-pharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development." *Cell host* 17.5 (2015); Boursi, Ben, et al. "The effect of past antibiotic exposure on diabetes risk." *Eur J Endocrin* 172.6 (2015).

8 Banerjee et al., Clin Infect Dis 2015;61:1071

9 "Clinical Impact and Provider Acceptability of Real-Time Antimicrobial Stewardship Decision Support for Rapid Diagnostics in Children With Positive Blood Culture Results", Messacar et al., 2016

10 Peterson et al. J Clin Microbiol 2016

4. FIND's strategy in AMR

Acknowledging the critical role of diagnostics in achieving impact in AMR, FIND has developed a holistic strategy to address the global threat of AMR (Figure 2).

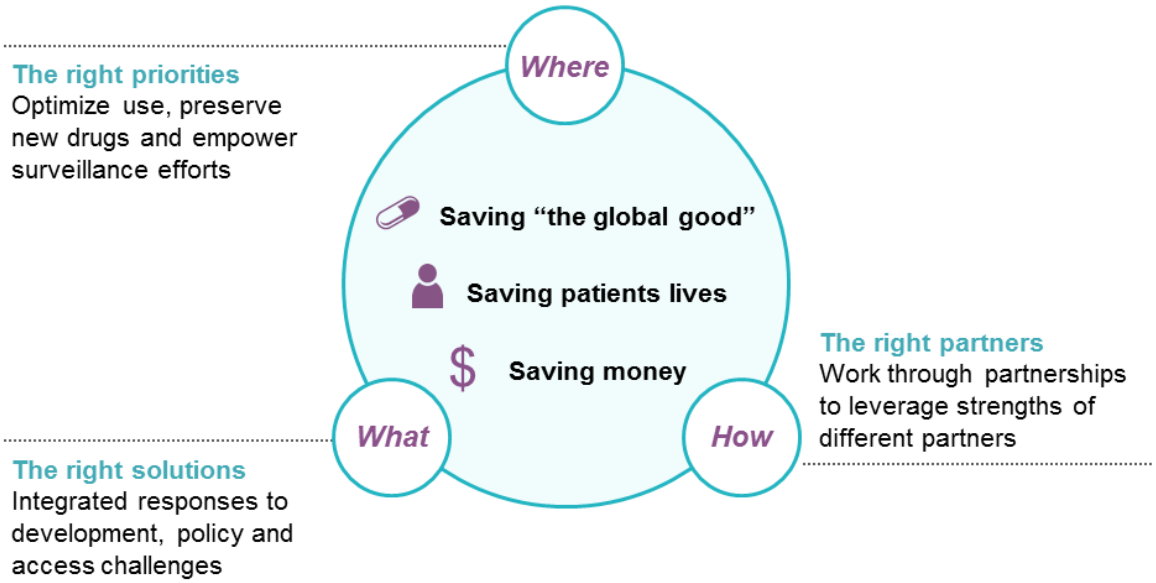

Figure 2: FIND's strategy to achieve diagnostics impact in AMR

FIND's AMR strategy is focused on halting and preventing AMR by 1) optimizing use of antimicrobials, 2) preserving new drugs and 3) empowering surveillance efforts.

Optimizing use of antimicrobials

The overuse of antibiotics is often linked to their use in non-bacterial infections, predominantly when patients present with generalized symptoms such as acute fever, lower respiratory tract infections, urinary tract infections, sexually transmitted infections or diarrhoea. A study in the United States of America showed that two-thirds (27 million) of the 40 million people who are given antibiotics for respiratory issues annually receive them unnecessarily[11]. Diagnosis enables the rapid selection of the most appropriate therapy. It can also reduce the length of time a patient may be treated empirically either with ineffective or unnecessary antimicrobials. Rapid susceptibility diagnostics allows for prompt escalation or de-escalation of antibiotic therapy, and switches between 1st, 2nd and 3rd line treatment options. For example, the use of blood culture diagnostics is associated with improved times to optimal and effective antimicrobial therapies and decreased unnecessary antimicrobial use in children[12]. Given the large problems around antibiotic quality, national quality assurance programs that are equipped with the right diagnostic solutions can detect counterfeit or sub-standard antibiotics.

The public health benefit of reducing the inappropriate use of antibiotics is directly linked to reducing the selective pressure that drives the emergence of resistance.

11 Data extracted from: Shapiro D J, Hicks L A, Pavia A T, Hersh A L. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. Journal of Antimicrobial Chemotherapy 2013

12 "Clinical Impact and Provider Acceptability of Real-Time Antimicrobial Stewardship Decision Support for Rapid Diagnostics in Children With Positive Blood Culture Results", Messacar et al., 2016

Preserving new drugs

Stewardship of current and new antibiotics is critical to ensure they retain their efficacy for as long as possible, especially for critically needed antibiotics, e.g., against gram-negative bacteria like *N. gonorrhoea.* Resistance will naturally emerge to any new drug but the early introduction of a gating diagnostic will ensure that these drugs are used in the most appropriate cases, shielding them from rapid overuse and early emergence of resistance. This protection of new drugs should slow the emergence of resistance and preserve this global resource.

Empowering surveillance efforts

Connected surveillance tools to track and map emergence, geographical patterns and range across pathogens of resistance form the basis of national and global surveillance programs like the Global Antimicrobial Resistance Surveillance System (GLASS), and enable appropriate control measures at local, national and global levels, as well as improved treatment strategies. Screening and isolation of infected patients helps prevent the spread of resistant pathogens in community and hospital settings. Sharing of information on the emergence of resistance at the national, regional and global level helps to set guidelines and drive prioritization of both development and access activities.

5. Unmet needs for AMR diagnostics

FIND interviewed ~30 experts and stakeholders to help identify priority AMR needs outside of the vertical programmes for TB, malaria and HIV. FIND's patient pathway analysis showed that different diagnostic information is needed at different levels of the health system. Eight priority drivers of AMR were identified for diagnostic interventions (Figure 3) based on a broad needs assessment.

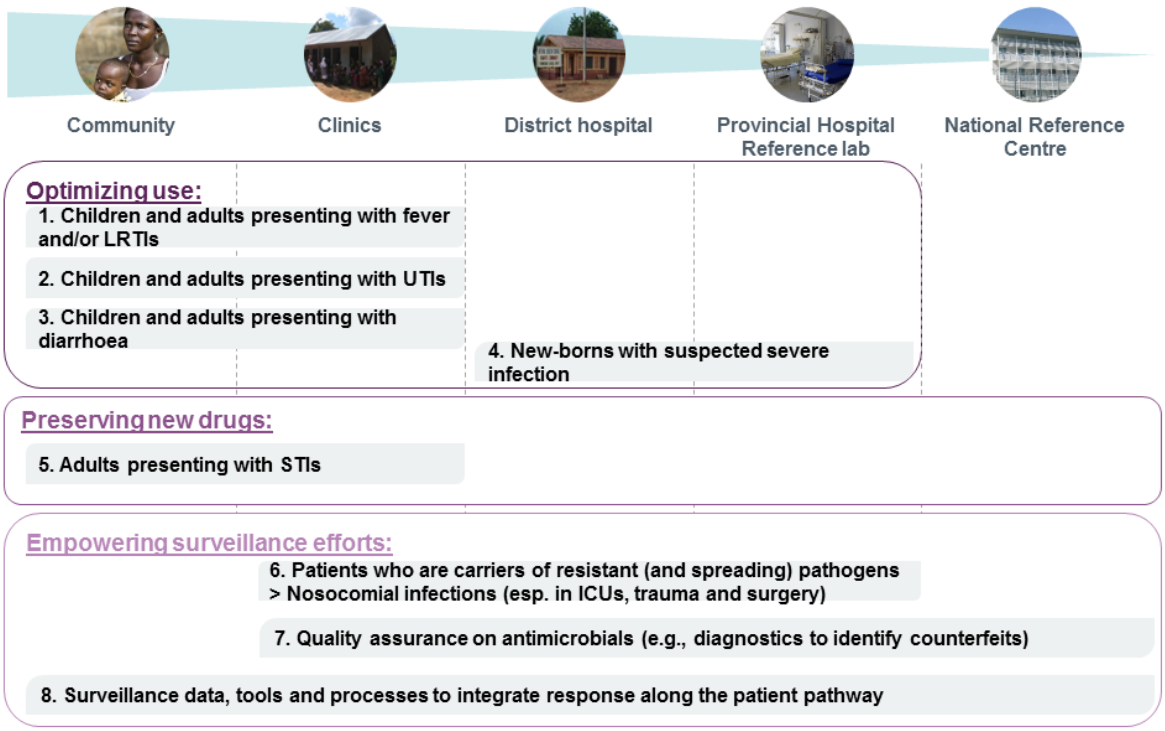

Figure 3: Priority scenarios where diagnostics interventions are needed

At the community level, antibiotic overuse is mostly in patients presenting with acute fever, lower respiratory tract infections (LRTIs), urinary tract infections (UTIs), sexually transmitted infections (STIs) or diarrhoea[13]. In this setting, the ability to triage out those patients who have a viral vs a bacterial infection and then to evaluate the severity of an infection, so that patients can be referred to a hospital quickly and when appropriate, is of key importance.

At the hospital level, it is critical to rapidly know what the causative agent of infection is, and if it is susceptible to 1st line treatment options or requires immediate escalation to 2nd or 3rd line treatments. This ensures that patients receive the most appropriate treatment as quickly as possible and stay on the shortest course of antibiotics required to have a positive outcome on their health. In addition, understanding the resistance profile of an infection early on can help prevent the spread of resistant pathogens in nosocomial settings. Extended-spectrum beta-lactamases-producing bacteria, MRSA, and carbapenem-resistance were amongst the most cited pathogens and resistance mechanisms that impact treatment decision in hospitals.

In summary, pathogen, resistance and susceptibility identification is needed at this level to ensure treatments are as targeted as possible, but current microbiology capacity in LMICs is poor and simpler, more rapid tools are needed.

Cross-cutting needs: Quality issues with antibiotics are a cross-cutting driver of resistance although the scale of the problem is not yet well understood. Quality assurance tests and systems need to be put in place to ensure drug quality. Diagnostic surveillance capacity is poor across LMICs, yet data for monitoring development and spread of resistant pathogens is the basis for treatment guidelines, national and global AMR strategies and efforts.

6. Solutions for diagnostic innovation and access

In line with the WHO Framework to Combat AMR, FIND will develop integrated responses to the main barriers that are affecting the ability of diagnostic solutions to achieve impact (Figure 4).

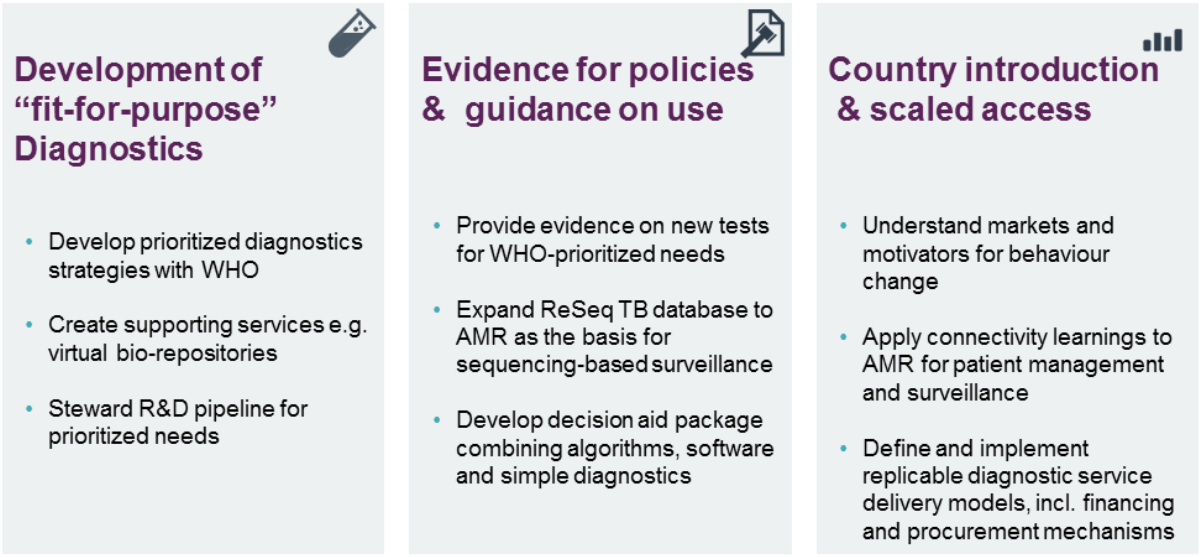

Figure 4: Solutions across the value chain to address barriers limiting access to and use of diagnostics

[13] A study conducted in Tanzania among acute febrile children shows that 70.5% of the children had a viral disease, 22.0% had a bacterial disease and 10.9% had a parasitic disease.

Given the global dynamics of AMR and its rapid spread across borders, the challenge needs to be addressed at a global scale, including LMICs which carry the highest AMR burden. New "fit-for-purpose" diagnostics are needed and even where diagnostic solutions may already exist, especially LMICs are faced with barriers to their use and uptake. Diagnostics may not be in use either because they are simply unavailable or too expensive for these markets. Some diagnostics may be available but have no data supporting their use in LMICs, which further hinders their uptake and appropriate market pricing. The low demand and resulting low industry investment is further complicated by the lack of a clear global health purchasing entity, like the Global Fund. AMR is a cross-cutting problem and as such does not belong within any of the traditional disease silos like malaria, HIV or TB. FIND will thus ensure that diagnostic solutions and policies also address the needs of LMICs, and that access is guaranteed for the most vulnerable populations most at risk for contracting infections.

While typical LMIC market dynamics hinder the access to available diagnostics there is also a larger problem at hand specifically for AMR diagnostics. In nearly all cases it is cheaper and simpler to treat a patient with antibiotics than to test a patient with a diagnostic. Antibiotics are generally unregulated and easily available. As patients are mostly responsible for their own health care costs it will be a challenge to convince them to pay for a diagnostic and treatment, especially when the diagnostic will likely be factors more costly than the drugs. Compounding this social complexity is the emotional aspect of providing an antibiotic. The doctor feels that they have provided good care and the patient in turn feels well cared for. This is particularly important for rural settings where patients don't have easy access to health care providers and a follow up visit might not be feasible even in the case of increasing severity.

Identified scenarios	Key needs	Diagnostics readiness	Impact: Antibiotic use	Impact: Lives saved	Role for FIND	R&D	Policy & Access
1. Fever and/or LRTIs	R&D: develop triaging tool for fever Pol. & Acc.: evaluate current diagnostics: e.g., CRP; Procalcetonin; CBC; molecular panels...	+++	++++	+++	+++	1	1
2. UTIs	Pol. & Acc.: evaluate urinary dipstick and define route-to-market	++++	++++	+	+++	3	1
3. Diarrhoea	Pol. & Acc.: evaluate rota/ adenovirus RDTs, multiplex molecular test	+**	+**	+**	+	3	3
4. New-borns with suspected severe infection	R&D: tbd Pol. & Acc.: evaluate procalcetonin; Blood culture; CBC; oximeters	+	++++	++++	++	2	2
5. STIs	R&D: improve gonorrhoea DST, new RDTs and multiplex molecular tests Pol. & Acc.: define route-to-market	++*	++*	++*	+++	1	2
6. Patients who are carriers of resistant pathogens	Pol. & Acc.: evaluate molecular screening of swabs or isolates	++	+++	++	++	3	1
7. Quality Diagnostics to identify counterfeits	R&D: tbd Pol. & Acc.: evaluate Minilab, CD3, Raman/NIR	+	+++	+++	++	2	2
8. Surveillance data, tools and processes	R&D: develop connectivity solutions Pol. & Acc.: integrate existing solutions into national surveillance	N/A	++++	++	+++	3	1

* Referring to overuse cause by drugs resistant gonorrhoea
** Referring to cases of viral infections to not receive antibiotic treatment

Figure 5: Preliminary prioritization of needs based on **e**xisting and relevant tools to address identified scenarios

7. Priority interventions for impact

To date, FIND's work in AMR has focused on TB, Malaria and Fever; notably the development, evaluation and introduction of rapid molecular and sequencing-based solutions for drug susceptibility testing and point of care triaging tools. In the short-term, FIND plans to expand this existing portfolio in order to address priority needs:

Triaging tools for community-acquired infections (expanding intervention)

One of the most promising solutions for triaging patients in the community that present with fever or other common symptoms like cough or diarrhoea, would be a test based on host biomarker detection to differentiate between bacterial and non-bacterial infections. Through an extensive, publicly available landscape analysis, FIND has identified a number of biomarkers for fever that could be used in rapid blood testing in low-and middle-income countries. In 2017, FIND has started a multi-centric study to evaluate the performances of potential new biomarkers to differentiate bacterial from non-bacterial febrile illnesses of outpatients from hospitals in 3 countries.

To prevent the use of unnecessary antibiotics, FIND plans to expand this triaging program to evaluate the utility of simple triaging tools (e.g. UTI dipsticks, electronic health algorithms), redesign or adapt them for LMIC needs and develop models for uptake to optimize the use of antimicrobials.

Virtual specimen bank and sequencing database (expanding intervention)

FIND has seen success in its work to combat drug-resistant TB by developing a virtual strain bank with isolates and DNA from MDR-TB and pre-XDR-TB patients and by launching a relational sequencing data platform (ReSeq TB) to discover, grade, and track key bacterial drug resistance mutations.

FIND plans to expand these applications to other disease areas creating an international resource for available specimens and genomic information on resistant pathogens (incl. ICUs, trauma and surgery). These tools will empower assay developers and surveillance programs.

Companion diagnostics for new antibiotics targeting drug-resistant gonorrhoea (new intervention)

FIND aims to support the development of better rapid gonorrhoea diagnostics and resistance testing to enable a definitive diagnosis prior to treating patients with new antibiotics that are currently in development. These tests will ensure that only patients with gonorrhoea or ideally drug resistant gonorrhoea receive the new treatment, thereby preventing overuse and early emergence of resistance. It is estimated, that introducing a point-of-care rapid test for gonorrhoea could significantly reduce the use of ceftriaxone and shorten the mean time to treatment by 2.3 days[14].

Data utilization for clinical decision-making and surveillance (expanding intervention)

Ensuring connectivity, i.e., linking diagnostic tests with communications technology, allows for better management of health data and maximizes the health impact of diagnostic tests. Connectivity solutions help strengthen the link between patient diagnosis and treatment. The real-time transmission of geo-tagged test results to national health information systems means that potential

[14] Turner K et al. Analysis of the potential impact of a point-of-care test to distinguish gonorrhea cases caused by antimicrobial-resistant and susceptible strains of *Neisseria gonorrhoeae*, 2016.

AMR cases can be addressed immediately, allowing for a rapid response. FIND plans to establish connectivity for AMR diagnostics and decision aid tools, thereby extending the reach of national surveillance programs to include routine hospital and community data. In addition, remote monitoring can improve supply chain management and forecasting and enhance diagnostic device quality assurance.

8. Operating model and impact

Several organizations and new mechanisms are aiming to address AMR through innovation, e.g., CARB-X, JPIAMR, NIH, BARDA, The Gates Foundation, and ARLG. However, diagnostics are usually a minor component of initiatives toward new treatments and there is currently no mechanism that supports interventions to drive uptake of existing and new diagnostics to combat AMR. FIND is known to work as a bridge between experts in technology development, policy and clinical care and has active collaborations with more than 200 partners.

Within AMR, FIND will work closely with WHO to support the development of TPPs, provide input on policy recommendations and guidelines and inform global surveillance efforts. In addition, FIND will collaborate with existing and new partners to support an integrated response to AMR (Figure 6). FIND will advocate for the creation of an AMR Diagnostics Use Accelerator to establish a smooth pathway to uptake in LMICs for AMR diagnostics, and create a pull mechanism for R&D investment (see appendix).

Figure 6: FIND's role in possible collaborations with key partners in the AMR response

Results and impact of the different interventions will be monitored through robust and standardized processes, and results widely disseminated through partnering networks and other channels

A step-change in diagnostic use is possible, as has been demonstrated for malaria and HIV where we have seen a rapid transformation of the diagnostics landscape in LMICs within a decade. Change for AMR will rely on strong partnerships and coordination. Funding for scalable and innovative interventions to overcome barriers and accelerate diagnostic impacts is critical.

In combination, our priority interventions will save the global goods by prolonging the life span of existing diagnostics, save health by ensuring better and timelier treatment and save money both by reducing the use of antibiotics and the health impact of antibiotic resistance.

9. Investment case

FIND recognizes the burden caused by drug resistant TB, HIV and malaria, and their role in contributing to the global AMR challenge. However, the focus of this investment case will specifically be on pathogens and syndromes not already addressed in existing programs.

FIND's AMR strategy will require a funding commitment of ~$72M to drive the work divided into 3 phases spanning the first 6 years, while expecting a 10 year program lifecycle (additional funding to be identified in the later phases). Phases have been structured where key deliverables must be completed to allow for next phase prioritization and maturation of the initiative. Support for the WHO's Essential Diagnostics List will be a priority during Phase 1 and Phase 2 to ensure alignment and clarity on priorities.

Phase 1: Launch AMR Strategy Years: 2018 - 2019 Funding Commitment: $17M
Phase 1 will focus on establishing the key partnerships and aligning on priorities in AMR beyond fever. Market understanding on the impact of diagnostics in AMR will be established and priority activities will be implemented across development, policy and access. An R&D portfolio will be built for at least two priority TPPs. Prioritized clinical scenarios, publication of landscapes and TPPs, and establishment of a virtual sample bank and a decision aid package combining algorithms, software and simple diagnostics will demonstrate early impact. Multi-centre studies will be conducted to demonstrate impact of at least three triaging tools. These demonstration and support for the WHO Essential Diagnostics List will inform priorities for Phase 2 as the work begins to expand.

Phase 2: Implement & Expand Years: 2020 - 2021 Funding Commitment: $30M
In Phase 2, the strategy will mature into established pipelines encompassing existing and emerging tools with investments into an expanded R&D portfolio adding two priorities. Demonstration studies for at least four emerging diagnostic tools will demonstrate impact. Focus on expanding the ReSeq database to standardize resistance profiles for pathogens beyond TB will support global development and surveillance efforts in the fight against AMR. At least two replicable service delivery models will be defined and implemented across 3-5 countries to ensure uptake of solutions. In-country champion networks will be established to facilitate change at the local and national levels and ensure a sustainable hand-off of projects once projects complete. Connectivity solutions will be linked to AMR to facilitate local-to-global communication, data sharing and response to AMR.

Phase 3: Continue at scale Years: 2022 - 2023 Funding Commitment: $25M
In Phase 3 will continue to mature R&D portfolios and deliver three new diagnostic solutions while intensifying activities and in-country demonstrations to drive policy change, to ensure uptake and adoption of game-changing diagnostics. The work started in Phase 1, and continued in Phase 2, around the establishment of a virtual sample bank will be matured to enable the development of emerging technologies. Definition and demonstration of additional replicable service delivery models in at least three countries will ensure impact of the developed solutions. New initiatives and opportunities will be clearly defined to inform how the strategy should evolve into Phase 4 to support the global needs in AMR.

10. Next steps

FIND has developed a high-level roadmap that considers priority activities that need to be undertaken in order to meet the Accelerator objectives (Figure 7). FIND's fever program, which includes some of the targeted activities is well underway, and broader TPP and landscaping work has started. Establishing and operationalizing partnerships will be amongst the initial priorities. Please reach out to catharina.boehme@finddx.org and cassandra.kelly@finddx.org if you are interested in partnering with us on this important program.

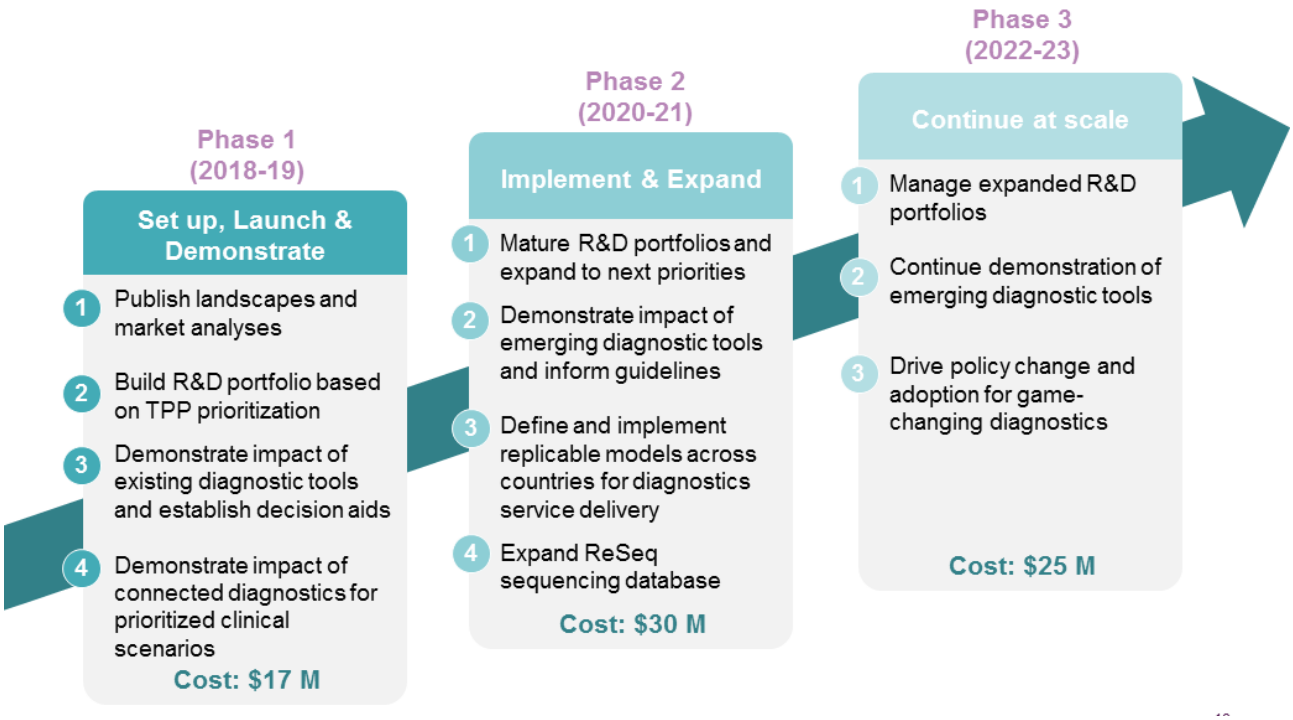

Figure 7: High level roadmap defining the key activities for the next years

11. Appendix: AMR Diagnostics Use Accelerator

The AMR response needs coordinated and effective efforts for developing and increasing access to diagnostics. Diagnostics play a key role in ensuring that people get the right medicines – thereby improving treatment outcomes, maintaining the effectiveness of drugs and protecting patients from the threat of emerging resistance. **The AMR Diagnostics Use Accelerator is an initiative considered by FIND and UNITAID with the aim to transform the way we use antimicrobials by ensuring the uptake of essential diagnostic solutions.**

The Accelerator will:

- Create market predictability, incentivizing product R&D
- Work with countries to demonstrate scalable and cost-effective interventions to address barriers in diagnostic service delivery for AMR in LMICs
- Shape policy and practices on use of antibiotics based on diagnostic information vs empiric therapy
- Address cross-cutting issues such as market and pricing interventions; procurement mechanisms; information, education and communication for behaviour change and civil society engagement; knowledge management

The aspirational goal of the Accelerator is to prevent the impact of AMR on people's lives and on the global economy by tackling key drivers of AMR in LMICs.

Key principles for the Accelerator would include:

- Scalability and focus on impact
- Lean partnership-based model that capitalizes on existing entities and their strengths, and is non-duplicative of existing mechanisms
- Fostering country co-ownership

The Accelerator will coordinate and work with stakeholders including industry, civil society, WHO, implementers and countries to align on priorities and potential interventions. Investments would be made through competitive bidding, and implementation of the selected projects managed in close collaboration with countries and partners. Results and impact will be monitored through robust and standardised processes, and results widely disseminated through partnering networks and other channels. Stakeholders will be convened to catalyse transitioning to scale-up of the highest impact interventions through large-scale global health agencies.