MSF Briefing Note

'The Review on Antimicrobial Resistance: Tackling Drug Resistant Infections Globally'

July 2016

OVERALL

This briefing note provides an analysis of the 'Review on Antimicrobial Resistance' commissioned by the government of the United Kingdom and the Welcome Trust and published by the AMR Review team in May 2016. Médecins Sans Frontières (MSF) also provides additional recommendations that governments and policymakers may wish to consider at upcoming inter-governmental discussions, including those to be held at the G7, G20 and the UN High Level Meeting on Antimicrobial Resistance in September.

Drug-resistant infections are a looming challenge for MSF's work. We see them in war-wounded people in Jordan, in new-borns in Niger, and in people in our burns units in Iraq. Our doctors have documented the presence of highly resistant bacteria such as ESBL, CRE and MRSA, in several of our projects and have recently started using last-line antibiotics such as polymyxin to treat multi-drug resistant gram negative bacteria.

The challenge of tackling growing levels of antimicrobial resistance, including that of drug resistant forms of TB, is immense. MSF therefore welcomes the AMR Review's recognition of the challenges caused by AMR and the broad cross-sectoral and global approach it takes in its nine recommended interventions as well as its useful contribution to quantifying the costs of governmental inaction.

Our analysis includes a range of considerations that could be taken into account to bolster certain recommended interventions. We also provide additional recommendations in the area of medical tool development, stewardship and access that we believe will more comprehensively safeguard access, are more efficient and will ensure that governments set priorities, in particular those that relate to the needs of neglected and most affected populations. This analysis is guided by our belief that the needs of patients should be at the centre of the response.

ANALYSIS

Our analysis comments upon the aspects of the various interventions where MSF has an appropriate mandate and possesses the relevant experience to respond, including on the proposed next steps and the costing estimates provided by the AMR Review.

Intervention 1: A massive, global public awareness campaign

The need for increased global public awareness about AMR is clear. The success of any proposed global interventions on combatting AMR hinges on their ability to reflect the public health needs and specificities of all countries, high income and developing countries alike. The current focus and heightened attention on AMR has happened through a somewhat 'top-down' approach led primarily by governments, philanthropies and academia. In addition AMR lacks the strong rooting in dedicated civil society organisations and patient advocacy groups due to its very nature of not being confined to one single disease nor one single sector. However, it is important to keep in mind that successful responses to health-related challenges over the last decades have tended to be built from the bottom-up. MSF agrees that awareness campaigns are an important element in a strategy aimed at informing

and changing patient's, doctor's and prescriber's behaviour, but awareness campaigns cannot substitute the positive role of a strong and engaged civil society. The current lack of ownership, engagement and awareness within broader civil society should be viewed as a critical deficiency.

Given these challenges, the success of the proposed global awareness campaign will depend on the uptake and ownership of the core messages by existing civil society organisations, community networks and structures such as, but not limited to, the global health community working towards achieving the Sustainable Development Goals, promoting universal health coverage, defending the human right to health and the global movement on access to affordable medicines, diagnostics and vaccines. It is imperative that compatibility with the existing work and advocacy of civil society and is sought from the beginning.

Moreover, given that measures needed to ensure rational use of antibiotics across all sectors will inevitably vary according to each country's context and patterns of antibiotic use, input from the existing national and/or regional civil society movements already engaged should inform how best to tailor messages and campaigns. This should be done alongside the input of the various governments in question.

Intervention 2: Improving sanitation and prevent spread of infection

MSF agrees that this is a critically important area for intervention. Infection prevention and control (IPC) needs to be the backbone of any discussion about AMR management.

It is worth considering duration of hospital stay and reducing unnecessary hospitalisation, as hospitalisation is associated with an increased risk of nosocomial (healthcare associated) infections (HAI) – especially bacterial infection. Prolonged hospitalisation increases the risk of nosocomial bacterial infections which are often more likely to be resistant infections. The data is limited and often of poor quality from the regions MSF works, but in general data from L/MIC report HAI rates that are 2-3 fold higher than HIC[1].

The availability and appropriate financing of health care facilities should also be considered alongside the promotion of hand washing and other IPC measures, since a lack of investment in health care infrastructure results in overcrowding which leads to poor Infection Prevention and Control practices.

Intervention 3: Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment

MSF cannot comment on agricultural antimicrobial use, notes but notes with great concern the emerging resistance to last-line antibiotic colistin, which is reported to have been driven by its use for veterinary purposes[2]. Strong stewardship principles that may be applied for human uses should also be translated into antibiotics use in animals. Otherwise any advances in preventing resistance generation and prolonging the life of antibiotics will not be achieved.

For manufacturing waste, MSF recommends that international standards are developed and enforced for the release of Active Pharmaceutical Ingredients (APIs) into the environment during the

[1] Health care associated infections, Fact sheet, WHO, available at: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf

[2] Liu et all., Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study; The Lancet, Volume 16, No. 2, p161–168, February 2016

manufacturing processes for both antibiotic API and finished antibiotic products. Entities such as the WHO Pre-qualification Programme, the European Directorate for the Quality of Medicines and Healthcare, the United States Pharmacopeial Convention, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme – which are all involved in manufacturing site assessments – could guide the development of these standards and inform national regulation on the same.

Intervention 4: Improve global surveillance of drug resistance in humans and animals

The call for global surveillance is both important and necessary to better inform global and national interventions. Harmonised surveillance methodologies and improved data on resistance patterns, use, prescription patterns, sales and access to antibiotics are needed to complete the picture. For resistance patterns in particular, appropriate diagnostic tools and platforms adapted to resource scarce settings need to be developed, in order to get all the necessary data, particularly national data on resistance patterns. There may be benefits of doing "spot" surveys in key areas as a starting point. There is also a need to work closely with WHO and other relevant UN agencies on developing capacity for surveillance.

Beyond the collection of data, the sharing of such data, how it may be applied, and who ultimately owns the data, are difficult questions that many research and medical organisations are currently grappling with. The system needs to allow for surveillance data to be shared openly and transparently, not only between the scientific, academic and research sectors, but also between governments and relevant UN agencies. Since the recent Ebola outbreak in West Africa, MSF has worked with others to develop practices for the sharing of both data and biological samples (via a bio-bank) to facilitate sharing and appropriate use of knowledge, while also seeking to put in place safeguards to discourage misappropriation of data and allowing contributions towards larger datasets and future research.

Intervention 5: Promote new, rapid diagnostics to cut unnecessary use of antibiotics

MSF agrees that there is a critical need to improve access to rapid point of care diagnostics. The recommendations of the AMR Review generally take their starting point in high income country contexts with already established and well-functioning health care systems and infrastructures. However, such recommendations may not always be appropriate or applicable in developing countries. In many countries for example, the basics of diagnosis and prescribing may not even be doctor-driven or driven by guidelines, and are performed in facilities with minimal infrastructure.

Creating and increasing a substantial, profitable market for diagnostics in high income countries through mandating that all prescription in these countries must be guided by testing technology by 2020, may lead to the development of diagnostic tests fit for use in these countries. However, in the absence of taking into account the suitability of a diagnostic in LMICs from the onset of the R&D process, it is likely that such a diagnostic test will not be suitable for use in these countries. This is due to the fact that technological and health care needs are likely to be quite different, and it is MSF's experience, that adaptation of such products does not happen automatically, and seldom happens in a satisfactory manner.

For LMICs, the Review does not address three inter-related challenges: how priority setting will occur taking into account the particular needs of LMICs, whether the diagnostics that emerge are suitable for LMICs, and whether they will be affordable.

While the report does recommend the use of target product profiles (TPPs) it does not address questions about who will be in charge of designing TPPs. MSF recommends that in order to ensure

that all needs are reflected, including being suited to conditions particular to LMICs, strong TPPs to guide the research and development process should be developed by the WHO in collaboration with its Member States. The TPPs should be aligned with the access norms set out in the follow up to the CEWG Report and agreed by all member states in resolutions WHA 66.22 and 69.23.

Affordability of diagnostics is another critical issue, for which additional measures, beyond those proposed in the Review, should be considered. First, TPPs should include affordability targets to ensure that subsequent diagnostic uptake is not undermined because empiric use of existing antibiotics on the market remains a cheaper option. Secondly, encouraging the development of open systems with an emphasis on interoperability will help ensure wide scale and use of the product as well as allowing competition to improve the product's affordability, with subsequent manufacturers designing adaptations to existing diagnostics that reduce costs.

Thirdly, the report proposes a 'Diagnostics Market Stimulus (DMS)' as a solution to address affordability barriers in LMIC by creating a fund to provide top-up payments to manufacturers for sales to LMICs. While top-up payments can mitigate costs for countries, experience has shown that they are often – despite their obvious 'economic value' – not available to all countries that would need it. Middle-income countries may have to self-finance uptake of such a diagnostic at higher prices. For example, Gavi, the Vaccines Alliance (Gavi), which is cited as a model for the DMS, is currently only present in 54 countries, and in the next five years a further 16 of those countries will 'graduate' from Gavi support and assistance. These countries will face steep increases in their vaccine expenses and may be unable to cope with both losing donor support and access to lowest global prices.[3] This endangers the sustainability of their national vaccination programmes. As a result, the uptake of new and expensive vaccines in MICs is falling behind that of LICs[4].

The report does also not consider the size of the market, which will hopefully be large, and how the DMS would have to change or adapt with increasing demand. The inclusion or exclusion of large, middle-income developing country markets will be of crucial importance in accurately designing such incentives.

In lieu of a stimulus, it would be better to design the diagnostic up front to cost far less to purchase and to consider offering other innovation rewards, such as prizes (milestone and market entry rewards) and targeted grants, to avoid having manufacturers recuperate their initial R&D investments through high prices and subsidies. Such prizes should be designed to reward open platforms and interoperability. Beyond the development process, potential implementation costs need to be considered, for example service and maintenance contracts and associated costs with diagnostic platforms that continue after the development and procurement of the test.[5] These additional costs, which are mostly unavoidable, also merit ensuring that a TPP for a diagnostic, and the incentive scheme, assure the lowest sustainable prices for the end product.

Intervention 6: Use vaccines more in humans and animals – and support alternative approaches

The interim review report from February 2016 titled "Vaccines and alternative approaches: reducing our dependence on antimicrobials on vaccination" included a welcome acknowledgement of key barriers to expand coverage of new and expensive vaccines, by stating that:

[3] A Fair Shot: bringing down barriers to affordable and adapted vaccines, 2nd Edition, MSF Access Campaign, January 2015, p. 14: http://www.msf.org.br/sites/default/files/msf_the_right_shot_report_2nded_2015.pdf

[4] Ibid.

[5] Beyond the Microscope: Addressing the critical need for better Tuberculosis diagnostics, MSF Access campaign, Issue Brief, 2013 http://www.msfaccess.org/sites/default/files/MSF_TB_Diagnostics_IssueBrief_2013.pdf

"The prohibitive prices of new vaccines for low and middle-income countries mean that vaccine coverage is often the lowest in places where the disease burden is highest ... there remain significant challenges associated with ensuring the sustainability and affordability of vaccines for the growing number of emerging economies which are 'graduating' from eligibility for development aid and GAVI support - key mechanisms for supporting access to vaccines in the developing world. Access to and uptake of vaccinations, such as those against rotaviruses and pneumococcal disease, by low and middle-income countries should be a priority for the international community." [6]

The lowest global price to vaccinate a child today is now 68 times more expensive than it was in 2001[7]. Prices of the newest vaccines need to be lower and access increased, first and foremost to avoid unnecessary death and suffering from vaccine-preventable diseases, which combined kills over 1 million children every year. The huge potential of the pneumococcal conjugate vaccine (PCV)[8] and the rotavirus vaccine to reduce the use of antibiotics only adds to the urgency of tackling the barriers that currently prevent their necessary roll out and scale up.

PCV alone accounts for about 45% of the total cost to vaccinate a child in the poorest countries[9]. The 77 countries that have not yet introduced PCV nationally (as of WHO's 2014 data), need to be supported to access affordable PCV alongside the countries that are losing donor support and access to Gavi-negotiated prices. In the case of PCV many countries are likely to be asked to pay at least 6 times more when phased out of Gavi support[10]. It would therefore have been good to have the same strong statement on the need to tackle affordability barriers reiterated in the final report.

The report rightly addresses the need to develop incentives to develop new vaccines relevant for tackling antimicrobial resistance. MSF cautions that the proposed incentives may not be the best approach to ensure widespread affordability and suitability for developing countries. The report does not address the importance of ensuring vaccines developed for use across all countries, are done in a manner that is suited to the needs of developing countries by for example ensuring thermo-stability, reducing the number of doses needed and adapting the vaccine's method of delivery. Moreover, the report proposes to emulate the recent experience of Gavi, through the advanced market commitment (AMC) for pneumococcal conjugate vaccines as a means to stimulate R&D and to promote access in LMICs, without considering its shortcomings.

The original AMC was in fact not a success in stimulating R&D and did not facilitate competition to encourage additional manufacturers to enter the market to sustainably reduce prices for all. While one of the four objectives of the AMC was to 'accelerate the development of vaccines that meet developing country needs', the evaluation from December 2015 concluded that:

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[6] Vaccines and Alternative Approaches: reducing our dependence on antibiotics, AMR Review, February 2016: http://amr-review.org/sites/default/files/Vaccines%20and%20alternatives_v4_LR.pdf; p.10 (accessed 16/6/2016)

[7] A Fair Shot: bringing down barriers to affordable and adapted vaccines, 2nd Edition, MSF Access Campaign, January 2015, p. 4.; http://www.msf.org.br/sites/default/files/msf_the_right_shot_report_2nded_2015.pdf

[8] Full PCV coverage is estimated to lead to a reduction of 11.4 million days reduction in antibiotic use (for <5yrs), or 47% reduction in antibiotic use. See more at: http://amr-review.org/sites/default/files/Vaccines%20and%20alternatives_v4_LR.pdf

[9] The 45% is based on the Gavi-AMC price, eg $7/dose (eg $21/child).

[10] A Fair Shot: bringing down barriers to affordable and adapted vaccines, 2nd Edition , January 2015, p. xx.; http://www.msf.org.br/sites/default/files/msf_the_right_shot_report_2nded_2015.pdf

"There is no evidence that any of the early-stage manufacturers successfully accelerated their product development timeline after the announcement [of the AMC]…the resulting lack of R&D outcomes makes clear the limitations of a pull mechanism to stimulate the development of an early-stage, technically complex product." [11]

Ultimately the focus of the AMC became to stimulate manufacturing and to improve affordability of PCV on behalf of Gavi-eligible countries. Yet even those aspects of the AMC, which could be incorporated into a R&D model, should be questioned as the AMC did not facilitate low-cost access for all LMICs.

The AMC was a 1.5 billion USD public and philanthropic subsidy which was only used to temporarily reduce prices for Gavi-eligible countries. Many other developing countries were left to pay higher prices, or to simply not introduce the vaccine due to lack of affordability. Moreover, the AMC did not sufficiently reduce the 'tail price' of the PCV to improve affordability even in the Gavi-eligible countries. In short, while the AMC may have increased uptake of PCV for Gavi-eligible countries, it was done at a significant cost without delivering long-term affordability and competition needed to encourage use of PCV worldwide.

For the proposed market entry rewards (MER) to incentivise the development new vaccines, they should be designed and targeted appropriately to ensure a clear public return for this public investment which ensures affordable prices for all countries, including safeguarding and accelerating the ability of subsequent manufacturers to rapidly enter the market in order increase competition and increase supply security.

Finally, it is a shame that the reports does not explore alternative methods of vaccine development, such as the one used for the Meningitis A vaccine (MenAfriVac). The MenAfriVac was developed by a product development partnership (PDP) that included WHO and PATH with the Serum Institute of India as manufacturing partner. The cost of research and development was separated from the final product price by paying for all the R&D through push funding over the duration of clinical development. The collaboration established two important benchmarks at the outset which were achieved - a specific affordability target of 0.50c per dose and approval for use in a controlled temperature chain (CTC).

Intervention 7: Improve the numbers, pay and recognition of people working in infectious disease

AMR is a complex issue and requires a certain level of expertise across several disciplines including infectious diseases, microbiology, pharmacy, laboratory work and infection prevention and control. There is clearly a need to capacity build in all these areas but a huge component will be to standardise training tools adapted to LMIC to ensure sustainability and promote evidence based practices.

Moreover, paying ID physicians more to rationalise the use of antibiotics in hospitals addresses one end of the problem. It does little to address the irrational prescribing practices outside of the hospital and the fact that in many contexts where MSF work, the management of patients involves lower level of health care professionals.

[11] The Advance Market Commitment Pilot for Pneumococcal Vaccines: Outcomes and Impact Evaluation, The Boston Consulting Group, December 2015: http://www.gavi.org/library/documents/gavi-documents/evaluations/pneumococcal-amc-outcomes-and-impact-evaluation/, p. 28 on R&D outcomes.

Intervention 8: Establish a Global Innovation Fund for early-stage and non-commercial research

The idea of a global innovation fund to address AMR is fundamentally a good one. MSF would like to understand how such a Fund relates to other efforts to stimulate R&D and access, both for AMR but also more broadly.

Firstly, clarification is needed on how such a Fund will relate to other R&D incentives and rewards that will be employed to develop new antibiotics (in particular those mentioned under Intervention 9). MSF believes that such funding, whether push or pull funding, should be aligned to ensure that public resources are invested in a coordinated fashion and that when developers receive sufficient incentives to develop new medical tools, they are not paid twice via high prices of the final product.

Secondly, MSF would like governments to consider how such a Fund should relate to other Funds which have emerged for R&D (which include AMR in their scope): the proposed voluntary pooled fund mechanism that could be hosted within WHO TDR, for example,[12] as well as the R&D Blueprint for Emergencies.

MSF supports the creation of a WHO Pooled R&D Fund given the oversight of all Member States and the principles that wound underpin such a fund, namely that R&D needs to be needs-driven, affordable, effective, efficient and a shared responsibility and that R&D costs must be de-linked from the end price of the product[13]. It is critical that such Funds do not compete with each other but that resources are raised and allocated among a range of developers to address public health needs in a manner that leads to improved public health outcomes.

Thirdly, MSF notes the recently adopted WHA Resolution 69.23[14] on the CEWG process and the efforts underway at the UN, via the UN Secretary General's High Level Panel on Access to Medicines[15], which seeks to lay out broader principles and even political approaches that governments could take forward to promote innovation and access to medicines, including medical tools to address AMR. Clarification on how the proposed Fund connects with the recommendations that come out of these processes would be needed.

At a minimum, it is critical that governments recognise the key role WHO should play in ensuring such a Fund sets priorities according to global public health needs and promotes policy coherence by implementing the agreed norms and principles set out in resolution WHA 66.22 and reaffirmed in May 2016 in resolution WHA69.23 to ensure all resulting products are adapted and available to populations in need.

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[12] Voluntary Fund hosted by WHO TDR (the Special Programme for Research and Training in Tropical Diseases) to address the persistent funding gaps for Type II, Type III and Type I diseases that address the needs of developing countries, including various forms of AMR.

[13] WHA66.22 Resolution on Follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, May 27, 2013.

[14] Resolution WHA69.23, Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, May 2016, available here: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_R23-en.pdf

[15] http://www.unsgaccessmeds.org/new-page/

Intervention 9: Better incentives to promote investment for new drugs and improving existing ones

MSF welcomes the report's recognition of the market failures of AMR, including the implicit recognition that the current innovation incentive mechanisms based on high prices and patent monopolies have failed to deliver innovation for AMR. MSF very much agrees there is a need to reform incentives for innovation so they better deliver for patients.

While the AMR review in regards to priority setting does recommend the use of TPPs and the proposes the criteria "most acute unmet medical need", it lacks further granularity on who is responsible for defining what an unmet need is and who will be tasked with setting priorities for AMR R&D globally. As previously stated MSF would recommend that TPPs and priority setting should independently be defined by the WHO and Member States and should ensure that the needs of all countries are considered and that affordable access is ensured.

The report proposes 2 billion USD for the Global Innovation Fund which is to fund both so-called 'blue sky' science and less 'cutting-edge' R&D which lacks a commercial imperative. By comparison the Market Entry Reward (MER) system is estimated to cost 16 billion USD over the coming decade. Given the current meagre state of the antibiotic pipeline with only very few compounds in all stages of development, MSF would emphasise that it is important to ensure that the allocation of funds is targeted towards where the scientific barriers and bottlenecks are the biggest. As such it is worth considering increasing the amount of funding available in grants to those involved in upstream early stage drug discovery and development. Moreover, clear criteria for awarding the MER should be designed to encourage R&D in truly novel classes of antibiotics, which match the TPPs.

MSF agrees that financing for innovation should be committed on a long term basis and be independent of political cycles. MSF also welcomes the involvement of the MPP and licensing agreements as pre-requisites for prize winners to offer licenses – for at least all low and middle income countries – as a means to facilitate generic competition and affordability. We enthusiastically support the proposal that 'strings be attached' to the allocation of MERs - this is vital to ensure that money is not misallocated. MSF would recommend that a multilateral body overseeing such a reward system is independent from organisations potentially applying for any award or prize, and would consider the WHO as the appropriate body to do this.

However, an area of clear concern for MSF is the redefinition of the concept of delinkage in the AMR review. Defining the concept, as the Review does, as de-linking profitability from volume of sales is to fundamentally alter its meaning and purpose. De-linkage was originally defined in the CEWG report as to de-link the cost of R&D from the end price of the product[16]. It is about separating the incentive to develop medicines from the promise of high prices earned through sales. While it is clear that no reliance on sales volume to recoup any R&D investments is desirable from a public health perspective in the case of antibiotics, it is concerning to see the definition of delinkage rewritten to use the Market Entry Rewards system as a way to only remove the link from sales volume - not the price of the product. Delinkage is presented as a tool to ensure stewardship, but not for ensuring affordable access.

This definition opens the door for segmenting markets and allows companies to charge high prices on top of the market entry rewards and the innovation fund subsidies already given in HIC markets and some MICs, which in the eye of the pharmaceutical industry are transforming into commercial markets. Such market segmentation may also skew investment priorities away from areas of "most acute unmet health need" towards the most profitable areas of antibiotics R&D.

[16] Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, WHO, April 2012 p. 45. http://www.who.int/phi/CEWG_Report_5_April_2012.pdf?ua=1

Regarding regulation, MSF notes that a current WHO-driven collaborative registration mechanism allows participating countries to collaborate with the WHO Prequalification Program to facilitate timely national registration of WHO Prequalified products. This can contribute to increased availability of WHO Prequalified antimicrobials. No mention of this helpful collaborative mechanism is made in the report, however, and MSF believes it is useful to lend it specific support.

MSF agrees with the idea of clinical trial networks and capacity building (this is already being attempted in the TB landscape via an initiative called RESIST TB). This would require good coordination and communication with clear oversight. There could be difficulties in getting private organisations/CROs to share their trial networks, but even a database of public sites and researchers could be a helpful start in taking this forward.

Tuberculosis - A cornerstone of the global AMR Challenge:

MSF is the largest NGO provider of treatment for drug resistant forms of tuberculosis (TB), treating over 2000 patients a year. The treatment for TB is an example of where the current system for drug R&D has failed. A curable disease is now the world's leading infectious disease killer and the numbers of people affected by these forms of TB are increasing year on year. In 2014 alone, 480.000 cases of MDR-TB were estimated to have occurred globally, but only about a quarter of these were actually detected. An estimated 190.000 people died in 2014 of MDR-TB.

It takes two years to treat an MDR-TB patient, including eight months of daily injections and a total of more than 14,600 pills - antibiotics - are needed. Many of the antibiotics used in today's combination treatment are very old and have toxic side effects such as deafness, psychosis and severe nausea. Moreover, the cure rate is dismally low at just 50% and the costs of treatment can be very high.

The ultimate goal in TB treatment is therefore the development of new combination of antibiotics to effectively, safely, quickly, affordably and simply treat all forms of TB. The change needed in the status quo for TB drug development is urgent. MSF therefore welcomes that the report clearly places the issues and global impacts of drug resistant forms of TB within the context of AMR, as well as the inclusion of the 3P project as a potential mechanism to address some of the specific issues that face TB drug and regimen development[17].

The 3P project consists of three mechanisms to facilitate the necessary R&D required for TB: Push, Pool and Pull. Each of these mechanisms have been used previously in other areas of medical R&D and by combining them and recalibrating them, it ensures that the right balance between reward for the innovator, access to scientific knowledge and collaboration can be found. Such well-targeted incentives aim to bring new researchers and developers to the problem, re-engage traditional investors in TB drug development, create a healthy drug development pipeline, and ensure that several drug candidates are developed in parallel as combination regimens.

The 3Ps project is an example of how full de-linkage can be implemented to result in affordable products that respond to the health needs outlined in target product and regimen profiles. Whilst ensuring collaboration, openness and access, the 3P project also considers how licensing agreements with generic manufacturers can incorporate condition to ensure sustainable access to the final products.

[17] 3P: PUSH.PULL.POOL. Better TB treatment. Faster. *Proposal to accelerate innovation and access to new treatment regimens for TB*: http://www.msfaccess.org/sites/default/files/TB_briefing_3P_ENG_2016_0.pdf

The 3P project is not just a concept, it has been costed and has the buy-in of all the major organisations[18] involved in TB from research to implementation with a clear governance structure. Early support and funding of this initiative would be a key step in addressing a key antimicrobial resistant infection.

What Global Action on AMR will cost:

The AMR Review estimates that the costs of proposed intervention will amount to 40 billion USD per decade, however this number only includes the investments needed to create the incentives outlined in the report. It does not take into consideration the financial burden that high product prices will impose on some countries afterwards. Given that the report relies primarily on HICs as the main profitable market, the actual costs for these countries are likely to be much higher.

The funding for the incentive mechanisms are proposed to be sought primarily through G20 countries, which leaves the question open on how the needs of developing countries will be met and who decides on setting research priorities and enforcing them. This will be important to address since it can be expected that G20 countries may wish to focus investments on their particular health needs.

The report provides little information on which data has been used to estimate cost of research and development and therefore calculate the appropriate size of the incentive for innovation. If incentives for innovation are created, especially with public funding as is suggested, MSF recommends that rules on appropriate transparency of research and development and manufacturing costs are included.

The 'Pay and Play' funding scheme by which a small fee is placed on pharmaceutical companies is an interesting idea, however its effectiveness would require rigorous assessment of the quality of the projects that companies would engage in, which could be very costly to implement. A tax on all pharmaceutical companies regardless of whether the company was engaged in AMR-relevant R&D could raise funds, but such a tax could simply be transferred to health care systems and patients through higher prices on other drugs and vaccines, especially at a time at which the power of the pharmaceutical industry to charge high prices is magnified through patent-backed monopolies.

Ultimately governments must consider whether the existing funding of the pharmaceutical industry by the public sector, philanthropies and patients, namely 40 percent of all R&D costs and a trillion dollar pharmaceutical market[19] is already sufficient to provide companies with the necessary funds to develop the drugs, diagnostics and vaccines needed to address AMR. Today pharmaceutical companies spend more on share buy backs and dividends than on R&D[20], and nine out of the ten largest drug companies spend more on marketing and advertising than on R&D[21].

The largest companies are also opting to spend significant sums of money on acquiring innovation, in lieu of investing in R&D. As examples have shown this may lead to companies not only failing to

[18] Including: TB Alliance, The Union, Stop TB Partnership, The Medicines Patent Pool, MSF, MRC SA, C-PATH and WHO.

[19] "Global pharma sales to reach $1.3 trillion", Reuters, August 2015: http://thomsonreuters.com/en/articles/2015/global-pharma-sales-reach-above-1-trillion.html

[20] Lives on the Edge, MSF Access Campaign, May 2016, p. 21; http://www.msfaccess.org/sites/default/files/MSF_assets/Innovation/Docs/R&D_report_LivesOnTheEdge_ENG_2016.pdf

[21] Ibid. p 14.

focus on developing new drugs, but often destroying the underlying value of the companies they are acquiring. For example, in December 2014, Merck spent 8.4 billion USD to acquire Cubist Pharmaceuticals, a drug developer that specialized in combatting methicillin-resistant staphylococcus aureus (MRSA). Less than three months later, Merck announced the closure of Cubist's early-stage research unit, laying off 120 staff. Three weeks later, Merck announced that it would spend an additional $10 billion buying back some of its own shares[22].

Finally MSF would agree with the critical, negative assessment by the AMR Review of the appropriateness of using incentive mechanisms such as the Priority review voucher and transferable periods of market exclusivity for the development of new antibiotics, vaccines and diagnostics.

Implementation and next steps:

The outline and description in the AMR Review of the global structures that need to be created are interesting and are in fact very similar to the recommendations made by the 'Consultative Working Expert Group on Research and Development: Financing and coordination' set up at the WHO in 2012. Given that it was set up to make recommendations on what is fundamentally the same issue as with R&D for tools to combat AMR: how to develop medical products for which there was no market – it is encouraging to see the similarities in recommendation for the global setup:

- the need for robust global priority setting and coordination mechanism
- and setting up of a global pooled fund with broad country participation.

The CEWG goes one step beyond and also recommends the establishment of global norms to ensure that resulting products are affordable, suitable and accessible.

So far countries have not collectively been ready to collaborate, coordinate and commit funds globally for medical R&D. However, the rising levels of AMR and the increasing problems of unaffordable medicines in low, middle and high income countries may bring the sense of urgency needed to make the global discussions on medical R&D to ensure affordable access and stewardship move forward.

Overall, governments should ensure that parallel discussions that seek to redress failures of the current system of pharmaceutical R&D, whether through the UN and WHO, or via the G7 or G20, are coherent with one another and seek to address the underlying flaws of the current system of drug development.

MSF would recommend however that instead of setting up a new "supra-national entity", that governments focus on strengthening WHO and that a specifically dedicated crosscutting AMR agency within the WHO, OIE and the FAO, with the WHO as lead agency, is set up to ensure that action taken will be done within the "One health" approach.

[22] O'Neill. Buy Back or Pay Forward? Project Syndicate: 2015 May [cited 8 July 2016]. Available from: https://www.project-syndicate.org/commentary/pharmaceutical-buybacks-research-by-jim-o-neill-2015-05

MSF RECOMMENDATIONS:

- Invest in building on and soliciting the input from civil society and community networks, which must sit at the heart of any broad-based effort to combat AMR.
- Ensure that priority setting is adequately addressed including through development of strong TPPs at the WHO, which include affordability targets and encourage open and interoperable systems. Funding committed in the area of R&D must be used to address global priorities - individual donor preferences and earmarked funding should be avoided.
- Ensure that affordable access is considered from outset of the R&D processes
- Increase access to affordable vaccines with strong potential for reducing the need to use antibiotics including through ensuring full price transparency, tackling affordability barriers and support bringing more manufacturers to market to increase competition for the relevant vaccines.
- Ensure that the AMR review works in line with other ongoing global processes relevant for AMR, to reduce duplication or contradictory recommendations
- Recommend the 3P project for TB as a rapidly implementable innovative mechanism for funding anti-infective R&D, which can commence while other proposed system MER and GIF are further developed.
- Continue to work within the "One Health" framework to ensure that human and animal antibiotics misuse and innovation market failure is dealt with together.