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MEETING REPORT

Antimicrobial Resistance (AMR) Research and Innovation:

Addressing Africa's Regional Priorities

Cape Town Lodge Hotel, Cape Town, South Africa / 1 September 2016

South African Medical Research Council (SAMRC)

Building a healthy nation through research and innovation

Global Antibiotic Research and Development Partnership (GARDP)

Developing new antibiotic treatments, promoting responsible use, and ensuring access for all

Antimicrobial Resistance (AMR) Research and Innovation: Addressing Africa's Regional Priorities
1 September 2016, Cape Town, South Africa

Meeting Report

This one day gathering of 45 participants from 11 African countries aimed at advancing a collective understanding of and potential to address the most pressing antimicrobial-resistance (AMR)-related medical needs, research and development gaps, and collaboration opportunities in South Africa and other sub-Saharan countries. It specifically aimed at ensuring that the realities in countries and in practice were brought forward through a participative programme, and that recommendations be made in three key areas (see under 'Priorities' in breakout sessions):

- Public health AMR priorities in Africa: surveillance, treatments, diagnostics
- Key elements of ensuring stewardship and sustainable access to new treatments
- Clinical research for antibiotic treatments in and for Africa: potential for regional collaboration and clinical trial networks

Opening remarks: Precious Matsoso, Director General, National Department of Health South Africa
Twenty years ago, there was no MDR-TB. AMR is now one of Africa's biggest problems in both humans and the agricultural sector. It is a serious and growing global health risk that needs to be prioritised at local and international levels. The development and implementation of a national AMR strategy is a major step towards dealing with this growing threat. A team has been put together in South Africa to provide guidance on how to address the AMR challenges facing Africa. It is important to find ways to change behaviours in terms of antimicrobial use, otherwise all the progress that has been made and that will be made will be wasted. Healthcare professionals require the right tools to do their jobs effectively and make informed decisions.

The UN General Assembly will be an important phase in addressing this problem at a global level. Health is indeed an important issue at this forum, where heads of state and global leaders will be asked to provide an appropriate global health policy response to AMR.

WHO Global Action Plan on AMR, What Does it Mean for Africa? Marc Sprenger, Director AMR Secretariat, WHO
Infectious diseases are still a very high burden in Africa compared to the rest of the world. There are many reasons why AMR is such a challenge in Africa. Some of these include weak health systems, vulnerability to infection because of malnutrition and HIV, and high burden of disease. Compounding this issue is the fact that antibiotics have become a substitute for good care, leading to a culture of over-prescription of antibiotics.

While data suggest that it is a major problem, AMR has yet to become a research priority in Africa due to competing priorities. A virtuous circle is required to address this: awareness needs to be increased, especially in the political arena, as should investment in research in order to generate better data to guide prescribing and advocacy, which in turn will lead to more responsible use of antibiotics and an overall improvement in the health systems.

South African Medical Research Council (SAMRC) Priority Areas of Research for AMR: Glenda Gray, President, SAMRC

The key challenges that Africa faces regarding AMR include the following:

- Health systems
- Lack of coordinated surveillance
- Disconnect between agriculture and human health
- Innovation (education, diagnostics and new drugs)

Currently, the SAMRC has a number of programmes that are looking into AMR, including diagnostics, host and bug genetics, and new drug development, for example, HIV resistance expanding into TB drug resistance, ART clinical research and pharmacovigilance. Going forward, the priorities for SAMRC projects will centre around funding community and hospital surveillance, linking surveillance activities, catalysing innovation in drug development, linking social science and health systems, and collaborating with the Agricultural Research Council.

Following the presentation, a number of suggestions and comments were made regarding the type of research projects on which to concentrate. The need to standardise methodologies across Africa was raised, and building on lessons learnt from the Ebola crisis was suggested. The influence from industry and the effect on the environment (in terms of agriculture) should be considered. The South African National Health Laboratory Services (NHLS) will be critical in ensuring consistency in any surveillance. Ultimately, investing in innovating vaccines will be of vital importance.

Global Antibiotic Research and Development Partnership, New Approaches to Delivering Innovations of Public Health Importance: Manica Balasegaram, Director, GARDP

GARDP, launched in May 2016, has the vision to develop new antibiotic treatments addressing AMR, and promote their responsible use for sustainable access in cooperation with public and private sectors. The guiding principles are that scientific relevance should guide choice and that R&D should focus on significant bacterial infections, with an emphasis on global needs. The development of antibiotics should be financed through a global funding mechanism and should experiment new models for conservation and access, and sustainable investment should be coordinated at country and international levels: the end result being that new antibiotics should be affordable for everyone and their access must be sustainable.

Criteria for projects are that they should address global health needs, fill gaps left by existing partners, have the potential for short-term fruition and to test access and conservation.
There are four potential pilot projects at this stage, two of which are disease or syndrome based (neonatal sepsis and STIs, including gonorrhoea) and two transversal drug discovery endeavours (including an antimicrobial memory recovery initiative and a drug combination platform) while others are in exploratory phase.

New treatments need to have sustainable access, but what does this mean? Sustainable access = innovation + access + conservation + stewardship and the solution will need to navigate a range of contexts. It will also depend on target product profiles (e.g. new vs. old drugs) clear guidelines; overlap with other aspects of healthcare; implication on laboratory capacity; and the need for advocacy. The approach will need to go beyond that of conventional product development partnerships (PDPs).

The practical steps that will be needed to achieve sustainable access include the following:

- Host incentive mechanism with some strings attached as significant resources will be needed
- Focus on Low- and Middle Income Countries (LMICs), segment market to ensure responsible licensing
- Support registration in priority countries
- Work with WHO to ensure policy change
- Ensure fair and sustainable pricing, especially if phase III supported for an NCE or expanding indication of use
- Support phase IV and implementation studies
- Promote a drug facility-type mechanism to ensure appropriate use, and support country scale-up with national plans
- Determine the focus – public or private sector
- Develop country-level strategies (identify key priority countries for initial implementation)
- Work with the ministries of health to update and disseminate guidelines
- Support laboratory capacity building
- Support health promotion and education by linking with local civil society groups

Break-out session introduction: Francis Ndowa, International Consultant, Zimbabwe
In general, there is a scarcity of data on AMR in Africa. *N. gonorrhoeae* is a clear example of this, but there are many other infections in the same situation such as Methicillin-resistant staphylococcus aureus (MRSA) infections. Laboratories seem equipped to conduct AMR studies at least for *N. gonorrhoeae*, but for many reasons it does not happen and critical sample sizes per individual country are not reached. Collaboration across and among neighbouring countries will be required. National Action Plans are unable to ensure that physicians, laboratory professionals, and patients are all on board when we say 'appropriate and responsible prescribing'. Policies and regulations that make sense and ensure stewardship and access at national level are needed.

Three break out groups were formed, chaired by Marc Mendelson, Mirfin Mpunda, and Monique Wasunna, respectively, with participants focusing on the following:

Group 1: Public health AMR priorities in Africa – surveillance, treatments, and diagnostics

- Surveillance:
  - What to survey and why?
  - Populations
  - Locations and periodicity
- Treatments
  - Standardisation
  - Use of antimicrobial agents
  - Availability
  - Procurement
- Diagnostics:
  - Priority of which infections and why
  - Interpretation

Priorities: The group **emphasised the need to prioritise research and development to address the ESKAPE pathogens** (*E. coli*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *E. cloacae*) causing hospital-acquired infections, as well as the **resistant sexually transmitted infections,** including *N. gonorrhoea* and **resistant enteric infections** (Salmonellae and Shigellae in particular), along with the emerging threat from ***Candida auris*.**

While entirely new drugs will be needed, there are **existing drugs that need to be trialled,** with monotherapies tested against combinations, and pharmacokinetics and pharmacodynamics, notably for neglected populations such as in neonates and infants. Indeed, neonatal ICUs would probably be the entry point to evaluate the ESKAPE pathogens.

New, **rapid point-of-care (PoC) tests to distinguish bacterial from viral infections, as well as pathogen-specific tests, are vital**. Evidence for reducing prescribing antibiotics for respiratory tract infections in high-income settings, by using POC C-reactive protein (CRP), was highlighted. However, it was agreed that a 'fever panel' was needed to better differentiate causes of fever. Surveillance is sorely needed in order to better understand epidemics as well as resistance mutations. This will drive the type of diagnostics developed. The diagnostic could also give an indication of the resistance level.

Group 2: Key elements of ensuring stewardship and sustainable access to new treatments
What does stewardship mean?
How do we foster and sustain stewardship?
How do we ensure access but also promote responsibility?
Use of existing treatments and new treatments

Priorities: It was emphasised that **diagnostics support is essential for stewardship**, including laboratory infrastructure, training and consumables. Diagnostic tools for surveillance are essential to gain fundamental insight into the most common bacterial infections in countries and the resistance levels. In many countries, outside of university hospitals, there will never feasibly be laboratories, so point of care diagnostics need to be simple enough for non-lab staff to use, affordable, and the results need to be trusted by staff (the field of malaria RDTs has shown in some countries that RDT results are only trusted if positive and that treatment is still started if negative). This could require capacity building at all levels of healthcare provision.

In terms of policies, legislation is needed, and must be enforceable (a current weakness in LMICs), to ensure implementation and accountability. Glaring gaps remain in terms of the required human resources/training/infrastructure. Learning from the fields of HIV, TB, and malaria, it was strongly suggested that for AMR, a framework for national guidelines, staff training, and supply chain is required. **AMR should be seen as providing an opportunity to build capacity, task shift appropriately,and overall to strengthen health systems**. However, low-resource countries will not be able to afford stewardship programmes without donor funding. Regional collaborations for surveillance and having sentinel sites should be encouraged in light of limited resources, interstate commerce, and undefined borders through which infections are partly spread - including resistant strains.

Finally, **a mentality shift is needed for antibiotics to be seen more as an 'emergency treatment' rather than a 'commercial product'**. TB is a good example, and progress can also be made from, for example, holding drug companies accountable if irresponsible marketing results in excessive use and resistance. As resistant bacteria cross borders, so will medication if highly restricted in one country and not accessible in neighbouring countries. Therefore, stewardship cannot be seen as a national effort; it must be regionally harmonised. For access, while regulation and limiting prescribing rights and easy access to the precious and newer antibiotics in particular was considered unacceptable, means must be found to promote appropriate use. Ensuring access to current antibiotics that work, without jumping to new treatments too quickly, is important. Indeed, access to the current antibiotics is an obstacle in most LMICs.

Group 3: Clinical research for antibiotic treatments in and for Africa: Potential for regional collaboration and clinical trials networks

- Morbidity and mortality data
- Knowledge and attitudes of healthcare providers and clients towards use and importance of antimicrobial agents
- Collaboration between clinicians and laboratories
- Lessons learnt from regional collaborative clinical research networks for accelerating the introduction of new treatments

Priorities: The group emphasised the **need for an African-driven and coordinated AMR clinical trial network that should capitalise on several existing networks**. There is a need to bring together existing registers of African clinical trials, and to map out where and what types of expertise there is in African countries, not only for clinical trials *stricto sensu*, but more broadly for surveillance as well. An action point included a questionnaire to evaluate sites based on key criteria as a minimum requirement for sites and to determine where capacity exists or needs to be built, considering, for example, that the skill sets required for different clinical trial phases are quite specific.

Indeed, **capacity will have to be built for sites in order to bring more diversity to the trial activities** (whether diversity applies to syndromes or to activities such as monitoring), to create more attractive **centres of excellence** for such research, and to **better manage 'down time' by ensuring that sites maintain activities and thus retain capacities**. Some services should also be mutualised and/or standardised, such as procurement or standard operating procedures. Data management support will be needed, as will resource assessment. Capacity that exists should be reinforced such as for pharmacy structure, management, IT and financial structures, biobanks, and disease-specific expertise. Key to the entire issue is both prioritisation and public leadership from Africa, including financing, which would need to be both international and regional. Regional collaboration was clearly a key point, but leadership will need to be taken to bring together a 'network of networks' and ensure it is managed in a fluid way. It was clear that **non-duplication of effort and resources will be key**.

Panel discussion

A panel discussion was held to discuss some of the main issues raised in the workshop. The panel members were Ranmini Kularatne, Chikwe Ihekweazu, and Glaudina Loots.

One of the important questions asked was how to **maximise existing resources**. Introducing AMR stewardship into the curriculum for both doctors and nurses was cited as a step in this direction. There needs to be leadership and accountability in hospitals. Without this, there can be no hope of introducing simple yet life-saving changes. In resource-poor settings, interventions need to be cost-effective, easily accessible, and practical given other considerations, such as work load and resources. It is vital to implement interventions in hospitals as hospital-associated infections can be easily prevented by, for example, hand washing. It is however, difficult to change behaviour and accountability is required. To help address fundamental problems in the resource-limited health systems, **disseminating national guidelines to GPs, private practitioners, and hospitals would help support standardisation of care**.

In terms of addressing the culture of prescribing antibiotics, ensuring access to treatment is balanced with the issue of resistance was noted. While complex, it was agreed that **fear of resistance should not impede access, and that stewardship solutions should always be framed in this way**. It was, however, acknowledged that access will still need to be restricted in certain situations. Relying on the development of new treatments will not be the panacea for AMR and the human element must always be taken into account.

Sounding board group discussion and way forward

Participants agreed that the outcomes from all the workshops should be implemented, starting by **capitalising on existing networks** in South Africa and beyond. **Avoiding duplication of research efforts** was a clear priority, but donor-driven duplication can be a challenge. Identifying the important stakeholders that are action-oriented is key. In order to grow confidence in any solutions implemented, it will be important to **start with the low-hanging fruit**. This will allow successes to be made early on, which will encourage buy-in from yet other stakeholders. One way to do this is to identify the commonalities between all the countries within the continent in order to make a start.

More information and input from the group will be needed on how to implement this in reality. The structure will need to be clearly developed. It was also noted that government funding is decreasing and it is now becoming necessary to do more with less. The only way to do this is by **making smarter use of technology**. Overall the group was supportive of the approach proposed by GARDP and the SAMRC and enthusiasm from the group to continue to work together as a group was expressed.

In moving forward, the SAMRC will issue two calls within the next six months. The outcomes from this workshop will inform the content of the calls. The SAMRC will start introducing AMR in the research funding agreements (RFAs), and working within neonatal clinics, i.e. start a neonatal programme. It was emphasised that when applying for the funding for these projects, ethical approval will be essential.