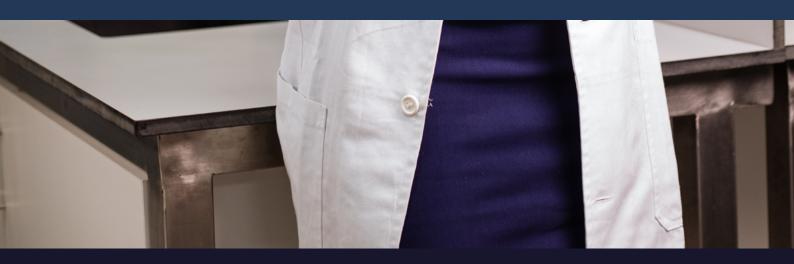


# **The Race Against Resistance:** what it means for affected communities in the Global South and global health security



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## Foreword from Catherine West MP, Chair of the All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases

Resistance to drugs and insecticides is one of the most pressing threats facing humanity today. Some of the key global health interventions are already becoming less effective at preventing and treating infectious disease.



As the Chair of the APPG on Malaria and Neglected Tropical Diseases, I have seen first-hand the progress that has been made against some of the world's oldest and deadliest diseases in the past twenty years. The difference that tools like insecticide-treated nets and antimalarial drugs make to endemic communities is remarkable.

But we know that these tools are becoming less effective due to the increasing challenge of drug and insecticide resistance. And resistance is a growing threat across a number of other diseases – both here in the UK and further afield. It is imperative that we act now to prevent the world from losing the gains against infectious diseases made in recent years.

Against the backdrop of the COVID-19 pandemic, we know that tackling global health security threats is more important than ever. The pandemic showed us that strong, resilient health systems are the building blocks of the response to global health emergencies. To secure our health security, the UK must play a part in strengthening health systems all around the world: in the words of one of the participants of the discussion on which this report is based, 'no-one is safe until everyone is safe.'

This report is based on an APPG roundtable discussion between Parliamentarians and experts from across global health, civil society, scientists, researchers and advocates. The discussion was fascinating and urgent, and the report begins to highlight some of the key challenges and solutions to the growing problem of resistance.

This defining issue of our time requires more extensive discussion than can be covered within one short report. I hope that our discussion and report can provide a starting place for an ongoing conversation. The UK has a role to play in tackling resistance here at home and across the world. With renewed commitment, the UK can rise to the challenge of resistance, and, alongside our global partners, bring about the end of diseases like malaria.

#### Catherine West MP, Chair of the APPG on Malaria and Neglected Tropical Diseases

Malaria No More UK and the All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases (NTDs) partnered with a range of APPGs with cross-sectional interests to bring together an expert roundtable of scientists and Parliamentarians. The discussion focused on concerns about drug and insecticide resistance.

This short report provides an overview of this discussion, and an introduction to the issue of resistance. The report has been prepared by Malaria No More UK but includes input to discussion from all attendees of the roundtable. We hope it provides a valuable insight into this important issue, and we would welcome the opportunity to discuss it.



# Part 1 The state of resistance today

#### Resistance: a brief introduction

The global health community is united in its concerns around drug and insecticide resistance. Resistance occurs when parasites evolve and develop new ways to survive treatments which until then had been effective at killing them. Decades of progress on infectious diseases such as malaria, tuberculosis (TB) and HIV face being undermined as the effectiveness of the best global health tools is placed at risk.

This is a risk we can – and must – mitigate by taking urgent action to limit the impacts of resistance. We must:

Ensure that the medicines which are already being used are managed properly, so that they can be used for as long as possible before resistance starts to develop against them, and
Create new tools and medicines to stay ahead of resistance.

Global donors have already begun to recognise the risk resistance poses and have stepped in to raise access to medicines across global health spaces. The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), Unitaid, the President's Malaria Initiative (PMI) and the UK Government have all played a major role in beginning to tackle resistance.

One example is artemisinin. Artemisinin is a core component of the best antimalarial medicines and is combined with other drugs to create artemisinin combination therapy (ACT) regimens. Emerging resistance to artemisinin therefore poses a substantial risk to malaria management. If artemisinin resistance becomes widespread, this could also put at risk the partner drugs in ACTs, with serious impact on the future medicine pipeline that include those medicines.<sup>1</sup>

Today, three countries in the WHO African region have begun to show signs of spontaneous artemisinin resistance: Rwanda, Eritrea, and Uganda.<sup>2</sup> This resistance has occurred independently, rather than being imported from the Mekong region or another region already experiencing artemisinin resistance. Other countries are also beginning to show signs of delayed parasite clearance. If allowed to progress, the consequences of this could be far-reaching. Resistance is also significantly threatening the effort to end TB. Treatments for drug-resistant TB are more expensive and it takes longer for a patient to be treated from start to end of the treatment. Currently, around 3.5% of new and 18% of previously treated TB cases in the world have multidrug resistant or rifampicin-resistant TB (MDR/RR-TB), a figure which is expected to rise.<sup>3</sup> MDR TB is airborne, which means that it is easy to spread. There are effective treatments for TB, and prompt treatment can reduce transmission. However, treatment can be particularly expensive, making it inaccessible to many.<sup>4</sup>

Beyond drug resistance, mosquitoes are also developing increasing resistance to insecticides, making insecticide-based vector control, including insecticide-treated nets, less effective. Product Development Partnerships (PDPs) including the Liverpool-based Innovative Vector Control Consortium (IVCC) are at the forefront of developing new insecticides and insecticide-treated nets to stay ahead of developing resistance.<sup>5</sup>

#### The Mekong region: a chink in the armour

In 2008, the first signs of artemisinin resistance emerged in the Greater Mekong Subregion, a transnational region of the Mekong River basin in Southeast Asia. Multidrug-resistant malaria first emerged in Cambodia and Thailand and spread across the region. The emergence of resistance to the bedrock drug of most antimalarials, artemisinin, signalled a chink in the armour of existing drug regimens for malaria.

The quick reaction of the WHO to the emergence of resistance in the region means that it has been effectively contained. This was achieved through improved use of drugs, rotation of drug regimens, and other measures. The Global Fund launched the Regional Artemisinin-resistance Initiative (RAI) in response to the emerging threat in 2013.

The Greater Mekong Subregion is now close to eliminating malaria altogether.

Read more: https://www.who.int/news-room/questions-and-answers/item/artemisinin-resistance

## Why fight resistance?

The fight against infectious disease is continuous. Pathogens and mosquitoes keep evolving to resist treatments, making the fight against these diseases more challenging.

Malaria killed 619,000 people in 2021.<sup>6</sup> AIDS-related illnesses killed 650,000 in the same year.<sup>7</sup> And TB killed more than those two diseases combined: 1.6 million people died from TB in 2021.<sup>8</sup> Resistance has made the fight against all of these diseases harder for a number of years. The pandemic proved challenging for main-taining programming across global health areas as programming was disrupted or diverted towards tackling COVID-19, but the truth is that progress was plateauing even before COVID-19 struck.<sup>9</sup> Tools are becoming less effective at fighting infectious diseases, and progress is slowing.

As well as causing hundreds of thousands of deaths and millions of cases every year, infectious diseases have wide-reaching impacts on the economy of endemic countries. The report Global Britain and Ending Malaria: The Bottom Line, produced by EY and Malaria No More UK, showed that between 2000 and 2015 an estimated £524bn was lost from global GDP as a result of malaria, with 11 of the 20 countries most affected members of the Commonwealth. The cost of malaria to low-income countries is vast, and money which should be spent on sending children to school is, by necessity, often poured into fighting mosquitoes instead.<sup>10</sup>

However, with the right political will and commitment to delivering innovative science, it is possible to win the fight against infectious disease. Until everyone is safe, nobody is safe.

#### Sherrie's story

Sherrie Silver is a choreographer and a Zero Malaria Ambassador.

Working in Rwanda, Sherrie has seen first-hand the effect which malaria has on lives. At the Kigali Summit on Malaria and Neglected Tropical Diseases (NTDs) in 2022, Sherrie was working with a number of dancers, all of whom had had malaria at least once. One, a young boy called JJ, experienced a severe case of malaria. His mother resorted to herbal treatments, and he came close to dying. After spending two weeks in hospital, he was able to recover, but malaria took him – and many children like him – out of school for a significant period. Malaria is a leading reason why children miss school in Rwanda.

Sherrie's cousin Guyemba died at just 9 years old, only two days after being diagnosed. He was funny, he loved school, and malaria stole his dreams from him.

Guyemba didn't have an opportunity to fight for himself, but we have an opportunity to fight for him now, by working towards the end of malaria.

#### Harun's story

Harun Tulunay is a health advocate and a member of UK-Community Advisory Board, a network for community HIV treatment advocates across the UK.

Harun spoke about his experience accessing treatment for HIV. He said that he is lucky because he is able to access treatment and doesn't have any issues with drug resistance. In the UK, accessing treatment is comparatively easy, with only 10% of those on HIV medication experience drug resistance.

However, access to HIV drugs and healthcare in lower income countries, particularly on the African continent, is more challenging. Particularly expensive is access to resistance testing. New medications are only available in high-income countries, but to end HIV anywhere, it must be ended everywhere. If countries cannot test for HIV drug resistance, the entire global fight against HIV will be held back.



#### The effect of resistance on health security

Global health security is, according to the CDC, 'the existence of strong and resilient public health systems that can prevent, detect, and respond to infectious disease threats, wherever they occur in the world.' <sup>11</sup> Resistance poses a significant threat to global health security, as responding to infectious disease threats becomes more challenging in the face of the decreased effectiveness of key medicines and tools. Most resistance found in the UK has been imported from elsewhere, so it is in the UK's interest to fight resistance wherever it emerges by investing in healthcare facilities in low-income countries and sharing learning across borders to tackle emerging resistance threats.<sup>12</sup>

In the words of Catherine West MP, health security is 'often left out of the jigsaw'. However, in the aftermath of the COVID-19 pandemic, there is a compelling reason to act now on global health security. A World Bank report showed that over 28 million people were at risk of falling into extreme poverty in the case of high prevalence of antimicrobial resistance, mostly in low-income countries.<sup>13</sup>

Building resilient, inclusive local health systems and creating strong pipelines for researching and developing new drugs for existing and emerging diseases are two crucial ways to build pandemic preparedness. Without action, tools for fighting infectious diseases which are effective now will become less effective, without others to take their place.

The development and deployment of preventative tools reduces pressure on effective medicines. For example, seasonal strategies such as seasonal malaria chemoprevention (SMC) have had a huge impact on reducing cases to reduce the window for resistance to develop.<sup>14</sup> Strong local health systems can deploy new tools and encourage the responsible use of tests, treatment and prevention to decrease the likelihood of resistance emerging.

The UK Government's Integrated Review (IR) refresh, published in March 2023, attempts to bring together security, foreign policy and development into one coherent strategy.<sup>15</sup> Threats like resistance are global, and pose a significant strategic risk to the UK and the world. The IR refresh focuses on building UK resilience. Responding to resistance is vital for the UK's resilience, not least because populations experiencing ill health are more likely to seek to migrate.

Likewise, the fight to reach zero HIV transmission is not a globally equal fight. Resistance to drugs which manage HIV and prevent its onward transmission is a threat to global health security. Resistance can be spread across borders, so if low-income countries are unable to afford consistent testing for drug resistance, the effects will be felt globally. The fight against HIV is global, but it is disproportionately felt in low-income countries. Investment in new solutions and access to medicines is necessary to achieve more equitable health outcomes and end AIDS-related deaths.



#### Fighting resistance: innovation and delivery

Resistance means that some of the tools which health workers have available to fight diseases like malaria, HIV and TB are not as effective as they once were. Developing new tools, including medicines and insecticides, which are not hindered by resistance will allow the response to these diseases to get back on track.

Product Development Partnerships (PDPs) bring together the best of industry, academia and the public sector to overcome market failures in creating new and innovative interventions for global health problems.<sup>16</sup> PDPs facilitate research and development of new tools to tackle resistance and have been successful in creating numerous life-saving interventions. These interventions include tafenoquine, a new antimalarial developed by British company GSK and Medicines for Malaria Venture (MMV),<sup>17</sup> and next-generation insecticide treated nets, tested by Innovative Vector Control Consortium (IVCC) and the London School of Hygiene and Tropical Medicine (LSHTM).<sup>18</sup>

Organisations like MMV, founded in 1999, have decades of experience developing innovative medicines for malaria and work successfully with UK-based partner organisations, including pharmaceutical company GSK, and the UK government. MMV is a PDP, bringing together industry and academic partners, and has developed over 15 new products currently treating patients since its inception. Managing a portfolio of over 65 antimalarial medicines, MMV's interventions have saved over 13.6 million lives.<sup>19</sup>

PDPs have been effective in developing new tools which tackle resistance, as they are able to work with countries and programmes closely to set priorities for development, absorbing national situations and priorities. For example, Seasonal Malaria Chemoprevention (SMC) was scaled up in five countries across the Sahel region of Africa by Malaria Consortium, MMV, LSHTM and Catholic Relief Services (CRS) in 2021.<sup>20</sup> SMC is the intermittent administration of full treatment courses of an antimalarial during the malaria season. Countries and programmes expressed a need for this programming and a PDP, along with its partners, was able to scale this up. Being receptive to what endemic countries need and want is vital, and PDPs are in a strong position to work to develop new tools which address these needs.

However, it is not enough to simply research and develop new tools to fight resistance. It is also vital that these are delivered to the communities that need them.

One challenge facing efforts to end drug-resistant TB in particular is the exorbitant cost of medicines. Effective treatments for high drug-resistant TB exist, but they are unaffordable. Clinical trials have shown that a 9-month oral regimen for TB is highly effective, in comparison with an injectable regimen.<sup>21</sup> However, the oral treatment (which contains bedaquiline, the first FDA-approved TB drug in 50 years) is very expensive, which makes it inaccessible for many. If drugs are inaccessible, onward transmission is driven up.

Treatment for medically complex TB or for patients with drug resistance can exceed £15,000 per patient in the UK, not taking into account associated medical costs such as hospital stays.<sup>22</sup> Public funds paid for the development of bedaquiline, which has been reported to have 90% efficacy against highly drug-resistant TB, and a profit could still be turned on the drug were it halved in price.<sup>23</sup> Halving its cost would enable the oral MDR-TB treatment to become cost-effective in most countries.

#### Case study: Unitaid

Unitaid is a global health agency engaged in finding innovative solutions to prevent, diagnose, and treat diseases more quickly, cheaply and effectively, in low- and middle-income countries. It funds initiatives to address major diseases such as HIV, tuberculosis and malaria. Unitaid works with partners, including in the UK, to close the gap between late-stage development of health products and their widespread adoption at scale.

Around half of Unitaid's current projects address issues of resistance. Its work also focuses on optimising the use of tests and treatments to save lives and stem the rise of resistance. For example, Unitaid has worked on shorter, better treatments for multidrug-resistance TB and new insecticide-treated bed nets for insecticide-resistant mosquitoes. It works with organisations like IVCC, MMV and LSTM to develop new tools, from nets to diagnostics.

Unitaid projects can have as much as 20 times return on initial funds in health and economic benefits.



#### Surveillance and diagnostics

Tools to survey and diagnose infectious diseases are vital in building up a picture of where resistance might be bubbling up. The work of the WHO and National Malaria Control Programmes (NMCP) in building local diagnostic capacity has contributed significantly to the ability of communities to respond rapidly to outbreaks of disease, and outbreaks of any resistant disease.

However, in the Horn of Africa, diagnostic tests which recognise malaria are becoming less effective.<sup>24</sup> Pathogens continuously change their genotype makeup, which can cause false lateral flow tests. The antigen which is recognised by diagnostic tests is being deleted in some strains, causing a delay in case management. Detecting the cause is vital in treating and managing fevers. If cases of malaria or any other infectious disease return a false negative on diagnostic tests, uncontrolled spread is more likely, and correct treatments will not be accessed. Only positive results will be treated, meaning that asymptomatic and false negative cases may 'hide in the community.'

Ensuring diagnostic tools remain effective will give the world a better global picture of outbreaks of infectious disease. Keeping up funding for improving and developing diagnostic tools and building in-country capacity for delivering diagnostic tests will help communities to stay ahead of these biological challenges. Diagnostic capacity building will also support countries in implementing national action plans for surveillance and patient care, which will have a positive impact on global health security across the board.

#### Case study: Lab Skills Africa

The Royal College of Pathologists (RCPath) engages internationally on global health issues, with nearly a quarter of its members outside the UK. To address a chronic lack of investment in clinical diagnostics and global lab training, RCPath's Lab Skills Africa project aimed to improve patient management, in particular raising diagnostic testing for TB, malaria and HIV.

This project delivered 1.7 million tests annually, working with counterparts across endemic countries.

The College have also worked on educational work on AMR with the National Postgraduate Medical College of Nigeria.<sup>25</sup> Surveillance systems and microbiology capacity are lacking across many endemic countries, and AMR national action plans, including in Nigeria, have been hampered by a lack of funding. Delivered alongside in-country partners, this programme delivers training on AMR for healthcare professionals.

Read more: https://www.rcpath.org/international/projects/labskills-africa.htm



# Part 3 Responding to an emergency: what next?

#### The need for cross-cutting policy

Resistance is a threat to global and domestic health programming across the board. Working in silos is not conducive to an effective global response to resistance, whether these are disease-specific or geographical silos. Cross-border and cross-disease collaboration is needed to share learning and research and raise awareness among the public and decision-makers of the challenges presented by resistance.

At the point of use, a patient will seek treatment for a 'fever' rather than for, for example, malaria. It is therefore vital that programming in endemic countries is not purely disease-specific but has the diagnostic and treatment capabilities to handle a broad range of diseases which present as a fever or other general symptom.

Malaria researchers have the potential to learn from TB researchers, HIV scientists can learn from the findings of those researching Neglected Tropical Diseases. To tackle drug resistance effectively, it is imperative that cross-cutting fora for discussion and shared learning can be established, and that the Government response to resistance considers the issue holistically.

Infectious diseases do not observe borders, so global collaborative working is vital – at government, research and programmatic levels. During the three High Level Meetings (HLMs) in 2023 on TB; pandemic preparedness, prevention and response; and Universal Health Coverage, the UK should take a joined-up approach, adopting a coherent strategy across all three HLMs to raise the profile of resistance.

### Recommendations

o Double down on creating the next generation of tools to combat infectious diseases. New medicines, vaccines, vector control tools and diagnostics will allow us to stay ahead of the resistance curve.

- Product Development Partnerships need multi-year, reliable and adequate funding to continue breaking new ground in developing new tools to tackle infectious diseases. For example, the development of malaria drugs which do not rely on artemisinin as a foundational drug would represent a major step forward in tackling emerging resistance to artemisinin.
- The UK should maintain investment in research and development in the life sciences sector, to ensure that new tools to tackle infectious diseases can be developed.
- The UK should continue to invest in surveillance and monitoring of infectious diseases internationally, as reliable and widespread diagnostics form the early smoke signals for monitoring outbreaks of emerging and existing diseases.

o The UK should invest in delivering new and existing tools to combat infectious diseases to the communities that need them most. This will help to create resilient health systems and strong disease programming. Programmes are also able to educate on the correct use of current tools, which should enable them to be used for longer before developing resistance.

- Multilateral organisations form the backbone of major disease programming. To ensure that programming which tackles infectious disease and strengthens global health security is able to be carried out, the UK should make strong pledges to Gavi, the Vaccine Alliance, Unitaid and the Global Fund at their next replenishments in 2024/2025.
- The UK Government should demonstrate global leadership and renew its commitment to Sustainable Development Goal 3, which includes a commitment to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases by 2030.<sup>26</sup>
- The UK and Rwanda are the past and current Chair in Office of the Commonwealth, and both showed extraordinary leadership in ensuring commitments to ending malaria in Commonwealth Heads of Government Meeting outcome statements. There is now a good opportunity for both countries to work together to continue leadership on malaria to drive accountability.
- One attendee suggested that a Global Health Security Act could be delivered as primary legislation, which could marshal resources across Government departments to deal with the cross-cutting issue of resistance and other global health challenges.
- Government departments need to work together across Whitehall to ensure an increasingly streamlined, coherent and cohesive approach to tackling resistance, ensuring that all relevant departments are convening regularly on delivering the UK's AMR strategy.
- At the upcoming 2023 High Level Meetings (HLMs) on TB, Pandemic Preparedness, Prevention and Response, and Universal Heath Coverage (UHC), the UK should send high-level representation from Government. A coherent strategy across all three HLMs should be adopted. At the HLM on TB, the UK Government should insist on global action to lower the price of bedaquiline and other drugs currently inaccessible to many.

## References

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<sup>4</sup> <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4012799/</u>

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<sup>7</sup> <u>https://www.unaids.org/en/resources/fact-sheet</u>

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<sup>20</sup> https://www.malariaconsortium.org/news-centre/smc-extended-to-more-countries-thanks-to-smc-impact-project.htm

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<sup>22</sup> https://www.gov.uk/government/publications/health-matters-reducing-the-burden-of-tuberculosis/health-matters-reducing-the-burden-of-tuberculosis

<sup>23</sup> <u>https://www.nejm.org/doi/full/10.1056/NEJMoa2119430</u>

<sup>24</sup> https://www.who.int/news/item/28-05-2021-statement-by-the-malaria-policy-advisory-group-on-the-urgent-need-to-addressthe-high-prevalence-of-pfhrp2-3-gene-deletions-in-the-horn-of-africa-and-beyond

#### The Race Against Resistance: what it means for affected communities in the Global South and global health security

This report has been produced by Malaria No More UK based on the conversation at a parliamentary roundtable of 14 March 2023 on the theme of **the race against resistance: what it means for affected communities in the Global South and global health security**. The roundtable was hosted by Malaria No More UK and the APPG on Malaria and Neglected Tropical Diseases and was chaired by **Catherine West MP** and **Lord Des Browne**.

The roundtable was attended by:

- Dr Khalid Beshir (Assistant Professor, London School of Hygiene and Tropical Medicine)
- Dr Nicholas Brown (Consultant Medical Microbiologist and Associate Lecturer, University of Cambridge)
- Michael Corley (Head of Policy and Public Affairs, British Society for Antimicrobial Chemotherapy)
- Professor Angharad Davies (Vice President, Learning, Royal College of Pathologists)
- Janet Ginnard (Director of Strategy, Unitaid)
- George Jagoe (Executive Vice President, Access and Product Management, Medicines for Malaria Venture)
- Simon Lee (Policy Lead on Malaria, Foreign, Commonwealth and Development Office)
- Mark Lewis (Coordinator, APPG on HIV/AIDS)
- Dr Kerry Millington (Research Uptake Manager, Liverpool School of Tropical Medicine)
- Dr Jo Mulligan (Senior Health Advisor and Team Leader, Foreign, Commonwealth and Development Office)
- Laura Rosu (Health Economist, Liverpool School of Tropical Medicine)
- Sherrie Silver (choreographer and Zero Malaria Ambassador)
- James Sunderland MP
- Derek Thomas MP
- Yami Torbieu (Policy and Programme Manager, Foreign, Commonwealth and Development Office)
- Harun Tulunay (online advocate and speaker, UK-CAB)
- Martha Varney (Coordinator, APPG on Malaria and NTDs)
- Vinny Wooding (Coordinator, APPG on Global TB)
- Victoria Fowler, Colette Morlino, Robin White & Lucy Tiller (Malaria No More UK)

Apologies were received from:

- Lord Ray Collins
- Vageesh Jain (Public Health Registrar and Health Advisor, Foreign, Commonwealth and Development Office)
- Justin McBeath (CEO, Innovative Vector Control Consortium)
- Lord Jonny Oates
- **Dr Jessica Potter** (Consultant in Respiratory Medicine & Clinical Lead on Tuberculosis, North Middlesex University Hospital NHS Trust)
- Danny Scarsbrook (Policy Officer, Royal College of Pathologists)
- Professor Colin Sutherland (Professor of Parasitology, London School of Hygiene and Tropical Medicine)



Malaria & Neglected Tropical Diseases