WHO draft outline of global action plan on antimicrobial resistance

Response by the Wellcome Trust

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Key Points

- Antimicrobial resistance (AMR) is a global health crisis which no government can tackle on its own. Since the first World Health Assembly resolution on AMR in 1998, there has been little concerted progress – there must be a step change if we are to tackle AMR.
- Leadership and coordinated international action is urgently required. Clarity is needed in terms of how such an initiative will be structured and led, and the actions delivered. Lessons must be learnt from successful models that work with but are not controlled by WHO, such as the IPCC, and thereby allowing other agencies and industry to be fully involved in the process.
- AMR can only be tackled with a 'one-health' approach and yet key stakeholders for this approach are not clearly involved in the draft strategy. Multi-sector engagement at the earliest stage is vital to ensure that a truly joint strategy is shaped, rather than simply endorsed after the fact.
- Despite being a global action plan for AMR, the primary focus is antibiotic resistance in the human context. Animal health is largely overlooked, as is drug-resistant viruses, parasites and fungi.
- Although we appreciate that different countries may have differing priorities with respect to AMR, tackling AMR requires concurrent action across all *Building Block* areas otherwise actions towards one or another might be undermined.
- Surveillance continues to receive disproportionate attention given it does not solve the problem of AMR. Basic research is fundamental for finding long-term solutions to tackling AMR and this is not given sufficient focus in the draft strategy.
- This response also provides an update on relevant Wellcome Trust activities.

OVERARCHING POINTS

1. Antimicrobial resistance (AMR) is a pressing issue[1] which, despite numerous World Health Assembly resolutions commencing 1998,[2] has seen little concerted progress. A step change is needed to ensure an action oriented response without delay.

2. As a truly global health crisis, no government can tackle AMR on its own and yet national efforts are currently disconnected. Leadership and coordinated international action is

[1] See Annex A – C for a number of examples regarding the rate of global resistance.
[2] http://www.who.int/drugresistance/AMR_DC_Resolutions/en/

urgently needed across a number of sectors to organise evidence and catalyse policy. There needs to be greater clarity about how such an initiative will be structured and led, and the actions delivered.

3. Clarity is needed in terms of how the strategy will be implemented and where authority and accountability for this will lie. It is important to consider who will provide the leadership and where WHO and other partners will be actively involved in delivery and where they will act in a supportive role. Specific and tangible actions and responsibilities are needed.

4. Urgent consideration must be given to the structure of a successful international multi-stakeholder initiative. Lessons can be learnt from previously successful models, including the Intergovernmental Panel on Climate Change (IPCC), UNAIDS, Medicines for Malaria Venture (MMV) and HIV Vaccines Trial Network. Common across these initiatives is that they are linked to, but not controlled by, WHO. In the AMR context, this flexibility is vital given it will be necessary to link with a wide-range of sectors, including the pharmaceutical industry and NGOs such as Médecins Sans Frontières, which WHO may not be able or best placed to do.
5. AMR is an issue that extends beyond human health and can only be tackled with a 'one-health' approach, which considers human and veterinary medicine in parallel and in the context of environmental factors. An effective AMR strategy must be developed in partnership across these key sectors, not simply endorsed by them. We would want detailed consideration of key stakeholders to be engaged in partnership and how they will work together.

BUILDING BLOCKS

6. Although we appreciate that different countries start at different places, tackling AMR requires concurrent action across all *Building Block* areas otherwise actions towards one or another might be undermined.

7. We are disappointed that although the strategy is a global action plan for AMR, many of the objectives, actions and illustrative examples suggest that the primary focus is in fact human antibiotic resistance. For example, *"recognition of antibiotics as a public good"*. Drug-resistant viruses, parasites and fungi are a looming threat and tackling them requires very different considerations to resistant bacteria, yet these are largely overlooked, as is the interface between human and animal health.

8. All actions must move forward underpinned by evidence. Research must be integrated into each *Building Block* to evaluate their impact and inform strategic development.

Specific comments on each *Building Block*

9. We have made key comments in relation to specific *Building Blocks* where we feel we are well placed to do so.

Building block 1: Increasing awareness, insight, education and engagement about AMR and of the actions and changes needed

10. Engagement and education across society is rightly given high priority in the strategy. In raising public awareness it is reasoned that public understanding should build and

ultimately support behaviour change. Evidence must underpin this reasoning to understand when awareness raising activity engenders a response. An effective strategy requires an evidence-based approach to public engagement, and this must be embedded in *Building Block 1*.

11. Promoting training and development opportunities to strengthen relevant professionals' understanding of AMR is vital, and must cover the full breadth of the workforce in community, primary, secondary and tertiary care. This must be an on-going process embedded within education, professional training and throughout peoples' careers.

12. We would want to see much greater consideration of engagement activities, both public and professional, which articulate why acting to tackle AMR is of immediate self-interest to the individual rather than relying on public good reasoning.

Building block 2: Identifying the most important approaches for preventing the development of infections and the steps needed to move beyond guidance to more effective implementation of such approaches

13. Infection prevention is illustrated as a priority for the reduction of antibiotic use, but the strategies highlighted focus on minimising the need to use antibacterial drugs. Significant scope exists to broaden this, both in terms of considering what other prevention measures might be available beyond infection control, and what prevention measures should be considered in the context of growing fungal, parasite and viral resistance. Vaccination is rightly highlighted, and improved diagnostics tools should be too.

14. In the healthcare setting mandatory surveillance of key pathogens, verifiable hospital, national and regional 'league tables' of incidence and fines encourage accountability. Although these measures have been effective for the targeted pathogen, and may warrant consideration, concentrating campaigns on one specific problem can be to the detriment of others and obscure the overall picture. We would encourage a broader approach to prevention strategies, rather than simply redefining targets to account for emerging threats.

Building block 3: Optimizing the use of existing antimicrobials for human and animal health and in agriculture

15. We agree that it is vital to consider agriculture, human and veterinary medicine in parallel and in the context of environmental factors. There is a need to strengthen the evidence base around the 'one-health agenda' and work collaboratively where synergies are identified.

Prescribing

16. Our understanding of what the optimal use of existing antimicrobials may constitute is in its infancy and further research is needed to ensure evidence-based prescribing guidelines. Current prescribing guidelines increasingly determine the dosage and treatment choice, which is limited by the type of evidence considered appropriate. Optimum antimicrobial usage must start with evidence-based prescribing guidelines; this includes pharmacology research examining pharmacokinetic and pharmacodynamic factors for informing dosage, treatment regimes and the impact of narrowing diversity in the range of drugs used.

17. Optimal guidelines are of course useless if these don't translate into practice. Prescribing guidelines must be developed with consideration for the delivery context, including getting practitioners to abide by the correct set of procedures and recognising the complexity of behaviour.

Stewardship

18. We continue to be concerned that while there is agreement that responsible use of society's medicines – stewardship – should be high priority, we do not have a framework for determining optimum stewardship. Understanding what research is required to optimise stewardship continues to be a pressing question, and while it remains unanswered stewardship strategies may be undermined.

19. Engendering drug stewardship requires an understanding of how prescribing and health behaviours have an impact. This includes understanding why, in the presence of evidence, examples of positive change are not adopted. It might be important to consider here what incentivises behaviour change, how this is likely to differ across cultures, and how this can be adopted to promote stewardship. To answer these questions an interdisciplinary response is needed, which engages a wide range of stakeholders.

Diagnostics

20. Rapid, precise and accurate diagnosis of pathogen and resistance is a formidable but important challenge that will ultimately be critical for optimising antimicrobial drug use. Rapid diagnostic tools are crucial for delivering personalised treatment, and reducing prescription rates for viral infections. Lack of precise diagnostics is also driving the use of broad-spectrum antimicrobial drugs.

Legislation and Regulation

21. Legislation can have a significant impact on the amount of antimicrobial drugs prescribed, however these measures have not been universally implemented. Impactful legislation adopted in the UK and countries across the world has included the banning of financial incentives for selling antimicrobial drugs for both animals and humans, and banning the use of antibiotics as growth promoters in animal husbandry. Denmark has documented the impact of these measures, reporting a 30% decrease in antibiotic prescriptions when profiting was banned without compromising production efficiency.[3] There is a need to influence globally to encourage a consistent legislative approach, which considers how this will be enforced and implications for trade. This must move forward alongside engagement and guidance.

22. Innovations in antimicrobial regulation are urgently needed. Regulatory bottlenecks in terms of a limited choice of indications, limited ability to label for resistance and lack of alignment globally have a significant impact and should be considered as a matter of urgency. Complexities in terms of trial requirements are a key bottleneck in drug development and warrant further consideration. We are particularly concerned that promising combination therapy approaches do not clearly align within the current regulatory framework and approvals are particularly difficult to obtain.

[3] http://wwwnc.cdc.gov/eid/article/13/11/07-0421_article.htm

Building block 4: Identifying and closing critical gaps in knowledge needed to address AMR

23. Coordinated data on antimicrobial distribution in humans, animals and the environment, and the trends of resistance are crucial for understanding the magnitude of resistance and how selection pressures drive its spread. Surveillance is highlighted as an important area, and we agree this certainly needs to be improved, but we have continued to raise concern that cataloguing receives disproportionate focus given it does not solve the problem of AMR. Any surveillance strategy must make clear how cataloguing will translate into actions – we are deeply concerned that we have yet to match our ability to survey with our ability to act.

24. Basic research is fundamental for finding long-term solutions to tackling AMR and this is not given sufficient focus in the draft strategy. Tackling the challenges raised by AMR will require expertise from a broad range of scientific disciplines including epidemiology, pharmacology, ethics, mathematical modelling, health systems, social sciences, animal health, economics and policy as well as classical microbiology and pathogen genetics. A multifaceted, long term research strategy which draws on expertise across disciplines is urgently required.

25. As well as knowledge gaps, there is a critical gap in the scientific workforce which compromises our ability to tackle AMR. More could be done to develop skills and competence necessary to tackle AMR and preserve our existing drugs. The lack of skills in the specialisms of clinical bacteriology, medical microbiology, pharmacology and animal health is particularly concerning. We are also concerned about the lack of interdisciplinary working, especially at the human-animal-environmental interface.

Building block 5: Developing an innovative and sustainable approach to develop and distribute critical products and technologies needed to address AMR

Incentivising new drug development

26. There is a shortage of new antimicrobial drugs being developed to replace the ones to which organisms have developed resistance. Big pharmaceutical companies as a group have substantially reduced their R&D investment in antimicrobials, focussing their efforts in late stage development. Companies still active in antimicrobial R&D are predominantly small and medium-size enterprises conducting discovery and early clinical studies so there remains a need to incentivise downstream drug development.

27. There are a number of proposed market incentives that warrant consideration and some examples are highlighted below, but it is vital that we consider how each of these actions might impact on the sector as a whole and across the different scales, and in particular if an incentive compromises the activities in small and medium-size enterprises.

28. Consideration of incentives to entice pharmaceutical companies to resume R&D could include fee waivers, extended patent protections and priority review vouchers. One such initiative is the Generation Antibiotics Incentives Act (GAIN) in the USA which provides automatic priority review and a patent extension of 5-7 years for infectious disease products. Alternative de-linkage models may be Payor Licenses, whereby an upfront global payment would be agreed by relevant private and public payors for an antimicrobial thereby incentivising companies to commit funds to research and development.

29. Further insights into this important area will likely come from the work of *Driving Re-Investment in R&D and Responsible Antibiotic Use (DRIVE-AB),* which is an *Innovative Medicines Initiative* proposal from a multidisciplinary and multi-stakeholder consortium, composed of 16 public and 7 private partners from 12 countries. They will examine alternative models that can create incentives for the discovery of novel antibiotics.[4]

Other treatments and methods

30. Greater clarity is needed on the scope of this *Building Block 5* and particularly whether alternative therapies are included. Promising alternative therapies include methods to target the pathogen, such as anti-virulence initiatives and bacteriophage viruses, and methods to enhance the immune response, such as probiotics and vaccinations. Although these methods are at a relatively early stage, and substantial research is required to support these innovations, a long-term strategy to tackle AMR must consider how to overcome the inevitable resistance cycle associated with drug treatments and embrace alternative approaches

Building block 6: Assessing the long term economic impact, developmental and social costs and implications of AMR as a basis for sustainable investment and action

31. Significant work in this important area is underway, including initiatives by the World Bank, Chatham House and the Independent Review on AMR (see paragraph 44 for more details). We would welcome collaborations across the sector to further this work.

32. It is crucial to engage the expertise and insight from industry to address *Building Block 6,* and we are disappointed that their contribution is not given necessary primacy.

33. Full consideration of the context in low and middle income countries and the impact that rationing the use of antimicrobials would have on their health and economy is needed. For example, in some countries, such as India, over-the-counter antibiotics have been introduced many years before comprehensive immunisation coverage or basic sanitation is improved nationally.[5]

RELEVANT WELLCOME TRUST ACTIVITIES

34. Our work to tackle AMR spans direct funding, advocacy and partnership working. Specially convened focus groups continue to appraise our action in these areas and provide strategic planning and support. A brief overview of our work in AMR follows, which we will be happy to discuss further.

Our funding into AMR

35. The Wellcome Trust has directly awarded a significant number of grants relevant to tackling AMR. Grants are awarded for AMR research through personal awards, at all career stages, projects and programme grants, and strategic awards. Our funding covers a broad-range of work, from basic research, surveillance, technology advancement, drug discovery, diagnostic development and vaccine development. The majority of funding has been allocated to bacteria and parasite resistance. Pathogens that have received particular attention include TB, malaria and HIV.

[4] http://www.imi.europa.eu/webfm_send/914
[5] http://www.cddep.org/sites/cddep.org/files/publication_files/India-report-web.pdf

36. Funding relevant to AMR is also awarded through our humanities programmes, including public engagement activities and societal and ethics research.

37. The Trust supports research into AMR through our core funding of our five Major Overseas Programmes, in Kenya[6], Thailand and Laos[7], Malawi[8], South Africa[9] and Vietnam.[10] For example, our programme in Thailand and Laos, The Wellcome Trust-Mahidol-Oxford Tropical Medicine Research Programme, is part of the Task Force on Antimalarial Drug Resistance in Cambodia, and has carried out research on understanding the molecular level of resistance as well as mathematical modelling to guide containment efforts.

38. Significant research projects undertaken at the Wellcome Trust Sanger Institute focus on AMR. Relevant research includes the studies by the microbial pathogenesis team, which is focusing on the genetic analysis of the interactions between bacteria and their hosts to shed light on how humans and other animals respond to infection.

Our advocacy for tackling AMR

39. We have been a prominent advocate for tackling AMR. Indeed, Jeremy Farrar used his first major interview since taking the post of Director to focus on the threat posed by the emergence of infections that have become drug resistant, and we continue to work to raise the profile of this important issue.

40. The Trust has hosted a number of meetings relevant to AMR, including a one-day symposium on *Lessons to be learnt from Pharma about drug discovery and development of new antibacterial drugs*[11], in collaboration with BBSRC and MRC (May 2013). We are the secretariat for the Biomedicine Forum, which met in November 2013 to discuss AMR. Bringing together relevant experts to inform our strategic planning on AMR is an on-going activity, and we would welcome WHO representation at relevant points.

Our partnerships for tackling AMR

41. To tackle AMR we work in partnership with Government organisations, industry, research funders, learned societies and charities.

42. We are a member of the AMR Funders Forum, which brings together bring together the Research Councils, Health Departments, Governmental bodies as well as charities. This cross-council initiative takes a thematic approach across four themes:
    - Understanding resistant bacteria in context of the host.
    - Accelerating therapeutic and diagnostics development.
    - Understanding the real world interactions.
    - Behaviour within and beyond the health care setting.

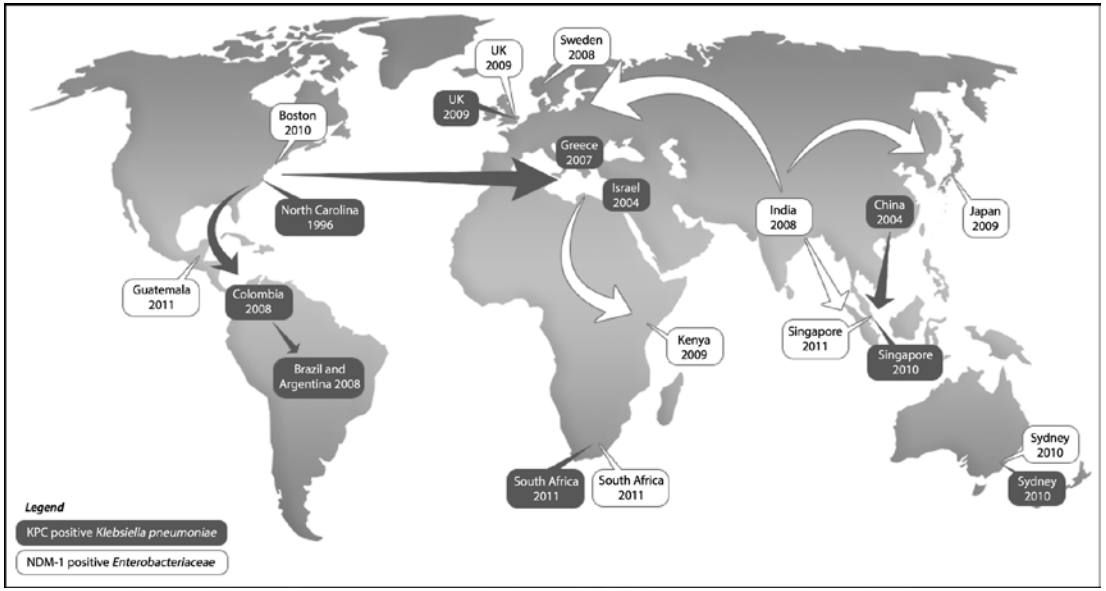
[6] The Kenya MOP was funded by a core award of £20 million, which will expire in September 2011 and be replaced by a renewal award worth £32.5 million for 2011 - 2015. The Trust also supports the MOP through a substantial strategic award aimed at capacity-building, and a relatively large number of fellowships, project and programme grants, which in total amount to over £21 million.
[7] The Thailand Unit's core award is £23 million for 2010 to 2015. The Thailand Programme started in 1979. The number of staff is 370. It has satellite units in Vientiane, Laos and Mae Sot, Thailand among others.
[8] There is approximately £8.9 million including supplements in the current core award, awarded in 2008 for five years. Approximately 250 staff are employed by the programme.
[9] The first core award to the Africa Centre was ZAR 237m (£16m) and core support was renewed for a further 5 years in 2012.
[10] The core award is £21 million for 2010 to 2015.
[11] http://antibiotic-action.com/wp-content/uploads/2013/08/Learning-Lessons-report.pdf

43. In July 2014, the Independent Review on AMR, hosted and co- funded by the Wellcome Trust, was announced by the UK Prime Minister. This major international review will look broadly at the economic issues surrounding AMR, including how to incentivise the drug pipeline so that new drugs are developed. The review will be led by renowned economist Jim O'Neill, with backing from the UK Department of Health and HM Treasury.

44. In collaboration with the Department of Health we are commissioning work on *Antimicrobial Resistance: Alternative therapies*. This is to be a scientific 'think-piece' on emerging viable alternative therapies to antibiotic/antimicrobial drugs, to inform policy and decision makers. The report will primarily review emerging technologies, ideas and innovations for alternatives to currently used antimicrobials, focusing on leading viable options and considering the value in investigating these further. This assessment will include analysis of what the barriers might be to the development of emerging alternative technologies and innovations and their eventual use.

Annex A: Global dissemination of Klebsiella pneumoniae carbapenemase–producing K. pneumoniae and New Delhi metallo-β-lactamase-1–producing Enterobacteriaceae.

Figure 4 from The Global Spread of Healthcare-Associated Multidrug-Resistant Bacteria: A Perspective From Asia[12]

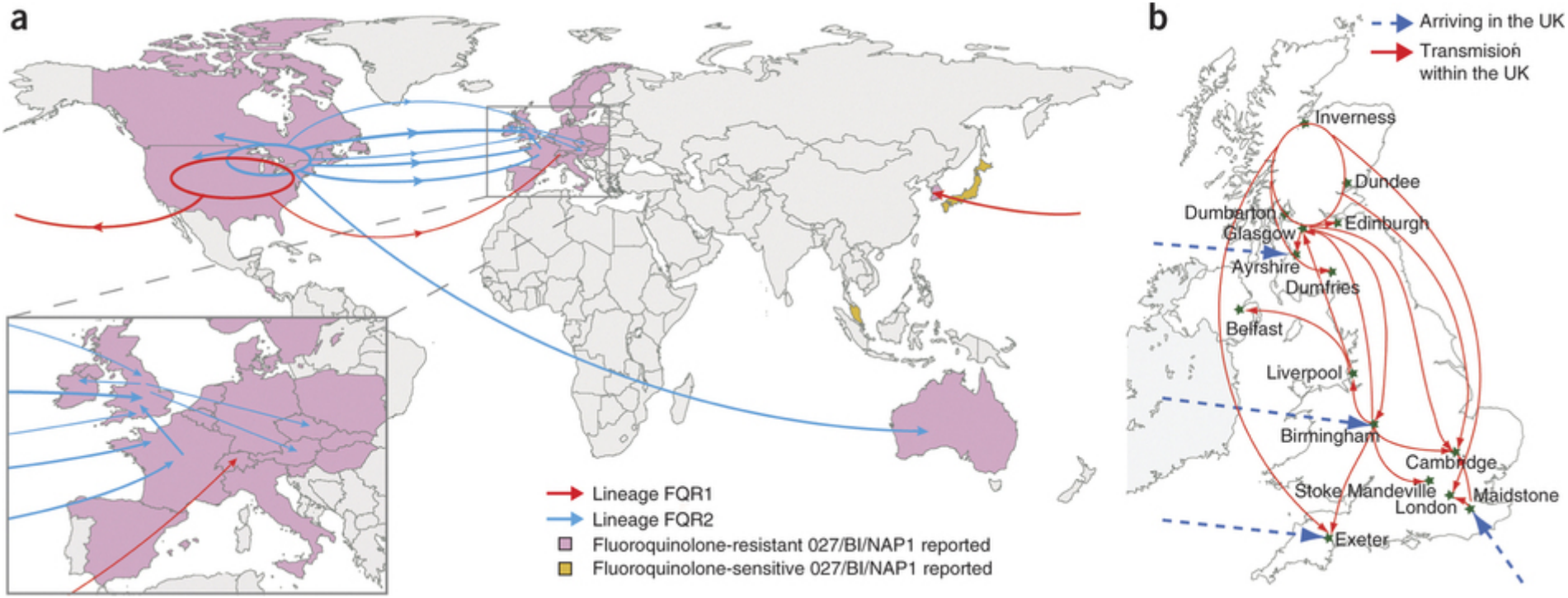


The earliest reported cases in each continent are shown. Arrows indicate the significant international movements of these organisms. Abbreviations: KPC, Klebsiella pneumoniae carbapenemase; NDM-1, New Delhi metallo-β-lactamase–1; UK, United Kingdom.

[12] J. S. Molton et al. Healthcare epidemiology (2013).

Annex B: Transmission events inferred for epidemic *C. difficile* 027/BI/NAP1.

Figure 2 from Emergence and global spread of epidemic healthcare-associated *Clostridium difficile*[13]



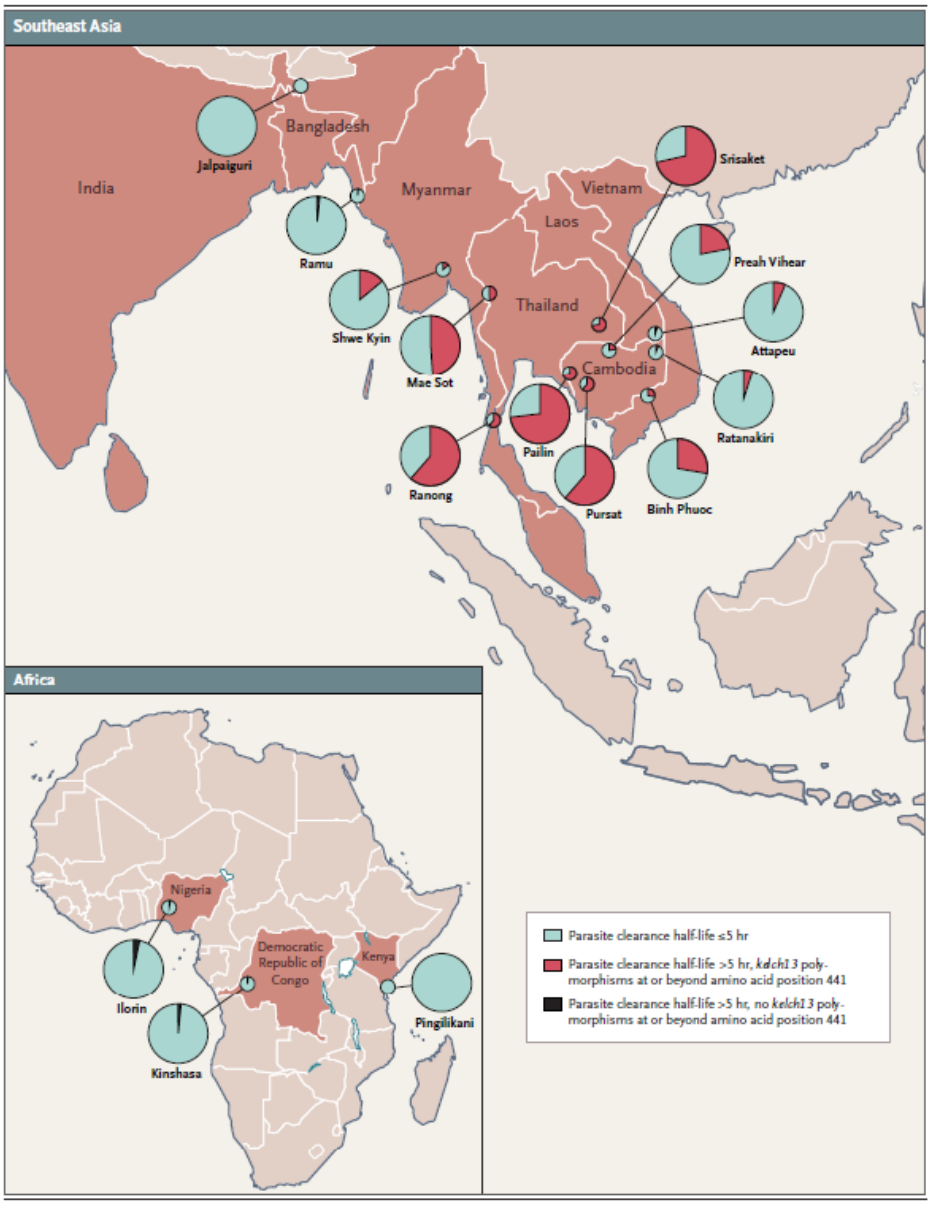
(a) Global spread (arrows) of lineages FQR1 and FQR2 inferred from phylogeographic analysis (Supplementary Fig. 5). Country color indicates where fluoroquinolone-resistant and fluoroquinolone-sensitive *C. difficile* 027/BI/NAP1 isolates have been reported[6]. The width of the arrow is approximately proportional to the number of descendents from each sublineage. Inset, enlarged view of the transmission within Europe.

(b) (**b**) Inferred arrivals and transmissions of the FQR2 lineage into and within the UK based on phylogeographic analysis (Supplementary Fig. 5) and maximum-likelihood phylogeny (Fig. 1b).

[13] M. He et al. Nature Genetics (2013)

Annex C: Location of study sites and proportion of patients with artemisinin resistance

Figure 1 from Spread of Artemisinin Resistance in Plasmodium falciparum Malaria[14]



[14] E. A. Ashley et al. for the Tracking Resistance to Artemisinin Collaboration (TRAC). New England Journal of Medicine (2014)