Microsimulations and other modelling approaches could prove instrumental to optimise interventions to curb and ultimately eliminate Ebola virus disease in the region, especially as an Ebola vaccine might materialise in the near future.

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Shortening treatment of tuberculosis: lessons from fluoroquinolone trials

In clinical trial settings the standard 6-month treatment regimen for drug-sensitive pulmonary tuberculosis can achieve relapse-free cure in more than 95% of people. However, poor adherence might increase the risk of relapse and lead to drug resistance. Shortening the duration of treatment has become a major priority for global control of tuberculosis—it will benefit patients and reduce the selection pressures that lead to the evolution of new drug-resistant strains.1,2

Attempts to use shorter courses of standard regimen drugs have not been successful except for smear-negative disease,3,4 and recent research has focused on fluoroquinolones. The authors of a Cochrane review of five studies assessing 6-month fluoroquinolone-containing regimens to treat drug-sensitive disease concluded that the available evidence was of low quality: the only consistently reported clinical outcome was all-cause mortality.5 However, data from studies of mice and phase 2 trials suggested that use of fluoroquinolones could shorten treatment for drug-sensitive tuberculosis from 6 months to 4 months.6 This possibility has now been assessed in human beings in four large phase 3 randomised controlled trials.7–10

Although fluoroquinolone-containing regimens led to more negative culture results at 2 months, this did not translate into improved clinical outcomes when treatment was shortened (figure). The RIFAQUIN,7 OFLOTUB,8 and REMoxTB9 trials benefitted from large numbers of patients, more than 18 months of follow-up, and robust methods (such as the ability to differentiate relapse from reinfection by strain typing). A trial done by the Indian National Institute for Research in Tuberculosis was discontinued early on account of an unacceptable number of relapses.10 The non-inferior result of the RIFAQUIN 6-month group, in which high-dose rifapentine and moxifloxacin were given once weekly in the continuation phase, seems consistent with findings from previous trials of 6-months’ treatment with fluoroquinolones, suggesting that they are broadly equivalent to the standard regimen. Apart from the 6-month RIFAQUIN once-weekly regimen, which could be useful in some settings, it is disappointing that, despite these large trials—each costing several million dollars and lasting up to 10 years—we remain with the same 6-month regimen used in the 1970s. Since fluoroquinolones alone do not seem to allow treatment to be shortened, it is...
important to establish which other new drugs might be successful and how the process of evaluation in clinical trials can be sped up.

Ideally, a treatment regimen would be given to all patients, but this might mean that most patients receive unnecessarily prolonged treatment. An alternative approach would be to revisit the stratification of cases. A 4-month regimen of rifampicin, isoniazid, pyrazinamide, and ethambutol was shown to be effective for smear-negative disease in Hong Kong in the 1980s;3 recent trials have focused exclusively on sputum smear-positive disease. With the advent of molecular diagnostics and the scaling up of active case finding, it might be possible to define a group of patients who might benefit from shortened treatment.

Other simple markers of severity could include smoking, HIV infection, and chest radiographic cavitation. Shortening treatment in patients with cavitation who also have negative cultures after 8 weeks is associated with more relapses, although a modest increase might be acceptable for a shorter regimen.3,11,12

Stratified analysis of data from the recent 4-month fluoroquinolone trials might provide further evidence to support this hypothesis. Stratification could also be made possible through the development of an effective biomarker for disease burden or response to treatment. For example, the semiquantitative outputs from GeneXpert or the Molecular Bacterial Load assay are associated with probability of relapse and changes in bacillary load on liquid and solid culture over the first 14 days of treatment.13

Previous attempts to assess new treatment combinations involved initial animal studies and early phase human studies before progressing to large randomised controlled trials of one or two regimens. The new trial results show two things. First, the present mouse model of human tuberculosis does not fully represent the course of human infection. And second, 8-week culture conversion is not a completely reliable marker of the later course of human infection, perhaps as a result of bacterial persisters. Using animal models might inadvertently mean that effective drugs are screened out, thereby increasing the chances of failed phase 3 trials.

A solution might be to accelerate clinical trials, including safety analyses of new drugs and assessment of combinations in trials in human beings, to assess efficacy as soon as possible. Multi-group multi-stage studies identify the best regimen through parallel evaluation of several different regimens, with sequential interim analyses to stop recruitment to groups unlikely to be sufficiently effective.14 Two such studies are PanACEA MAMS-TB (ClinicalTrials.gov number NCT01785186) and TRUNCATE-TB. PanACEA MAMS-TB is a four-arm phase 2b study assessing combinations of high-dose rifampicin, moxifloxacin, and the new drug SQ109 for drug-sensitive tuberculosis. This approach allowed two SQ109 treatment groups to be dropped after the first interim analysis. TRUNCATE-TB is a phase 2/3 trial of several novel combination regimens (recruitment will start in 2015). Even when a classic multi-group multi-stage design is not possible, inclusion of several arms would increase efficiency, as for the STREAM trial (ISRCTN78372190), which will investigate short regimens for multidrug-resistant tuberculosis.

Because of the disappointing results of the 4-month fluoroquinolone trials, the lessons learnt should be combined with well established clinical trial infrastructure to accelerate the next phase of efforts to improve
Climate change and infectious disease: time for a new normal?

At present, there is a clarion call for action on climate change across the global health landscape. At the recent WHO-sponsored conference on health and climate (held in Geneva, Switzerland, on Aug 27–29, 2014) and the UN Climate Summit (New York, USA, on Sept 23, 2014), participants were encouraged to act decisively to change the current trajectory of climate disruption. Health inequalities, including those related to infectious diseases, have now been pushed to centre stage. This approach represents a step-change in thinking. But as we are urged toward collective action, is it time to rethink our approach to research, especially in relation to climate change and infectious disease?

For a long time, climate change has been the proverbial unwanted guest at the global health table. Causal relations remain elusive to many researchers, even for infectious diseases with clear climate effects such as vector-borne, arboviral, and parasitic disease. An equally prevalent view was that climate change was the crucial game changer in terms of our understanding of infectious disease. Indeed, there have been calls for global warming to be viewed as a health threat itself. 3

Part of the problem is that much of the early research into climate change and infectious disease focused on proving how “coupled” or “decoupled” particular diseases are with climate effects. 4 Thus, climate change was often viewed as a unique and discreet driver of disease. 5 Unsurprisingly, this conceptualisation forged an evidence base that is both highly specific and often polarised.

Yet climate change is clearly an embedded context in which changes to the susceptibility and infectiousness of human and animal diseases—and thereby their emergence or transmission—occur. We know that climate change has direct and indirect effects on a range of diseases. Furthermore, climate disruption is likely to have multiplier effects between both diseases and drivers. Finally, climate warming could potentially forge a cascade of both biotic and abiotic events or factors leading to disease emergence and re-emergence. Such a cumulative or cascade effect could clearly set the scene for collective disease events in global health.