Improving the health of the tuberculosis drug pipeline

After 40 years of no new therapies, approval of bedaquiline and delamanid for the treatment of tuberculosis is a cause for optimism. But is that hope well founded? Talha Burki investigates.

For more on **the tuberculosis drug pipeline** see http://www.newtbdrugs.org/pipeline.php

On the face of it, the pipeline for tuberculosis drugs seems to be in fine shape. In little more than a year the armamentarium for treatment of multidrug-resistant tuberculosis has grown by two. Bedaquiline gained approval from the US Food and Drug Administration (FDA) in December, 2012, the first novel tuberculosis drug to do so in more than 40 years (panel). And in November, 2013, the European Medicines Agency (EMA) recommended granting a conditional market authorisation for delamanid, another novel agent.

Both drugs have only been tested up to phase 2b trials, so there remain questions over their safety and efficacy, but a phase 3 trial of delamanid is in progress, as are phase 2b trials of bedaquiline that should shed light on its potential for treatment of drug-sensitive tuberculosis.

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Elsewhere there is further cause for optimism. The Global Alliance for TB Drug Development is testing a fluoroquinolone-containing four-drug regimen for drug-sensitive tuberculosis that aims to cut treatment time from 6 months to 4 months. Results will be available in the next few months. Another trial by the same organisation is testing a combination therapy based on bedaquiline and PA-824, which, being a nitroimidazole antibiotic, has the same mechanism of action as delamanid. Early results are encouraging.

Meanwhile, there are high hopes for oxazolidinones, three examples of which are in phase 2b development. In terms of vaccines, there are ten candidates in various stages of clinical development and two immunotherapeutic candidates in latter stage trials.

All of which bodes well for the short-term (although, of the ten drugs in late stage clinical development, six are repurposed, which has implications in terms of resistance). But the outlook for the medium-term is far less promising, and it has prompted experts to question whether the present system is simply incapable of delivering the advances needed to arrest the tuberculosis epidemic.

As things stand, there are no candidate drug compounds in phase 1 trials (figure). So the health of the pipeline rests on the nine candidates in preclinical development. "We need the pipeline to be fuller in late preclinical and early clinical", stresses Mel Spigelman (The Global Alliance for TB Drug Development, New York, NY, USA).

According to the Treatment Action Group, total funding for tuberculosis research and development stood at US$627·4 million in 2012, a decrease of $30·4 million on the previous year. The private sector cut their funding on the disease by 22·1%. Private funds now represent less than 20% of total spending on tuberculosis research and development. Pfizer has left the field entirely; Otsuka, the producers of delamanid, reduced their investment in drug discovery programmes; and AstraZeneca decreased funding for its compound AZD5847, currently in phase 2 trials, by almost $3 million.

Exactly how much would constitute a meaningful investment in tuberculosis research and development is not entirely clear. But WHO's Mario Raviglione believes that $2 billion is a reasonable estimate for all kinds of research. "We certainly need a much increased investment in the basic science of tuberculosis—we do not know all the details of pathogenesis", he said. Without this investment, Raviglione is sceptical about the immediate prospects for, for example, a point-of-care rapid and easily delivered diagnostic test.

But the picture is more complicated than the scarcity of resources. Wim Parys is Research and Development Lead for Global Public Health at Janssen Pharmaceuticals, the producers of bedaquiline. "Even if the funds are sufficient, it is important to realise that there still need to be other incentives to make this a sustainable endeavour, because the tuberculosis field is not going to return profits to

***Panel:* Tuberculosis treatment and prevention**

1901: UK establishes Royal Commission to Inquire Into the Relations of Human and Animal Tuberculosis.

1921: Bacillus Calmette–Guérin (BCG) vaccine first used in people.

1944: Seth Waksman and colleagues at Rutgers University in the USA identify streptomycin. In Sweden, Jorgen Lehman synthesises the para-amino salt of salicylic acid (PAS).

1947–48: The UK Medical Research Council does a randomised controlled clinical trial—the first of its kind—on streptomycin and PAS. They show that combination therapy improves effectiveness and delays resistance.

1952: Isoniazid, first isolated in 1912, is added to the armamentarium. Triple therapy can cure 90–95% of patients.

1954: Discovery of pyrazinamide.

1955–56: World's first national drug-resistance survey done in the UK finds resistance to streptomycin, PAS, and isoniazid.

1961: Introduction of ethambutol, which comes to replace PAS. Treatment time can now be reduced to 18 months.

1967: Rifampicin begins to be used therapeutically. A new standard 6 month treatment is soon established.

2012: US Food and Drug Administration approves bedaquiline, the first novel tuberculosis drug in more than 40 years.

2013: European Medicines Agency recommends granting a conditional market authorisation for delamanid, another novel drug.

offset the expensive development costs", he told *TLID*.

Parys believes that push and pull mechanisms offer the best means of encouraging companies to invest in the disease. Grants are an example of a push mechanism, as are commitments to share research and development costs. Examples of pull mechanisms include the transferable priority review voucher scheme run by the FDA, which offers an accelerated review process for qualifying drugs, and milestone prizes for organisations that achieve a stipulated goal. An advance market commitment negotiated by a range of interested parties, including the US Agency for International Development, the President's Emergency Plan for AIDS Relief, UNITAID, and the Bill & Melinda Gates Foundation, prompted the producers of the Xpert MTB/RIF diagnostic to reduce its cost to $9·98 per test cartridge for 145 eligible countries.

Parys suggests offering companies that develop a suitable drug to treat a neglected tropical disease extended exclusivity for another drug in their portfolio. "These are all mechanisms that could increase the likelihood that the pharmaceutical industry would invest in tuberculosis", he noted.

Spigelman points out that bedaquiline is, at least initially, likely to be used in very few patients. "Small production needs make production costs and therefore prices more expensive." If pharmaceutical companies can make economies of scale, then they will be better placed to cut prices. But this is not always happening. "If we look at the models that have been used recently to get drugs like bedaquiline approved, they're going to market with a very narrow indication. We need to ensure that development is done in ways that mean new drugs or regimens will apply to the largest number of patients with tuberculosis."

In a candidate demonstration project, Médicins Sans Frontières (MSF) suggested a new model for tuberculosis research and development based on push and pull mechanisms, but with the addition of pooled intellectual property. "Without the impediment of restrictive patents, especially the high tuberculosis burden countries, multiple players, including producers, could work in the field and manufacturers could obtain sublicences to manufacture and sell new tuberculosis regimens once they are approved", noted MSF.

The overarching aim is to delink the cost of drug development from the price at which the drug is sold. In their project proposal, MSF argued that the new model would reduce duplication of research efforts, accelerate the testing of drugs in combination, and reduce the risk of resistance to new compounds.

In early December, 2013, WHO decided not to pursue the proposal. MSF's Grania Brigden was disappointed by the decision. "We need to have companies willing to work together and share information, because these drugs need to be developed in combination." Brigden believes that the existing model means that combination trials are happening too late. She cites the example of delamanid and bedaquiline. "There is now the potential that these two drugs will be available but we'll have absolutely no evidence on how to combine them."

Spigelman welcomes MSF's idea. "There is much to be said for not letting the patent situation get in the way of the development of products for tuberculosis."

Parys disagrees. "I don't think there is a patent issue to make combination studies impossible—we've been discussing them and we're very open to the combination studies that are in preparation." His colleague Myriam Haxaire Theeuwers believes that the bottleneck lies in the arduous clinical research phases. Data were first reported on bedaquiline in 2005, and by 2009, the The Global Alliance for TB Drug Development had agreed to test the drug in combination. Parys points out that this is a reasonable timetable. "I really think that incentives alone can create a lot of interest in the industry to invest in tuberculosis", he concluded.

Raviglione is involved in finalising the new strategy for tuberculosis control before its presentation at the World Health Assembly this year. It is founded on three pillars: treatment, diagnosis, and prevention; policy, systems and social determinants; and promotion of research. He notes that the enormous investments in HIV/AIDS have resulted in substantial advances in a matter of decades. Despite killing roughly the same number of people, tuberculosis has never attracted similar investment. More money has to be made available, and, most importantly, this money should not be diverted from the already inadequate funds that exist for the disease.

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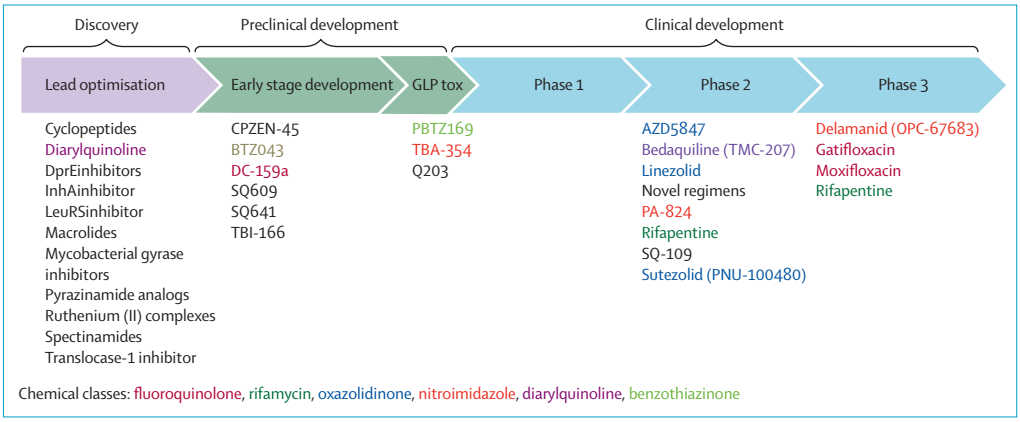

Figure: **Global tuberculosis drug pipeline**
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For the **MSF candidate demonstration project** see http://www.msfaccess.org/push-pull-pool-who-tb-demo-project