Tuberculosis, a neglected opportunity?

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Historically, tuberculosis (TB) has fallen firmly in the group of 'neglected diseases'—diseases in which pharmaceutical companies have been reluctant to invest due to a perception of low commercial potential. According to the World Health Organization (WHO), an estimated 1.7 million deaths resulted in 2004 from TB, and the global prevalence of TB was 14.6 million[1]. However, more than 80% of people with TB live in sub-Saharan Africa or Asia[2], where spending on healthcare is low and access to drugs is limited. Owing to the low commercial interest in treating TB, no new drug class has been introduced for over 30 years. The current market is dominated by generic products. Relatively few international drug manufacturers market TB therapies; exceptions are Sanofi-Aventis, Pfizer and Sandoz (Novartis's generics division). However, over the past 10–15 years, several factors have emerged, which are contributing to increased research and development (R&D) activity in TB treatment.

The prevalence of TB grew significantly in the late 1980s and 1990s, driven by cases in sub-Saharan Africa, but also by a resurgence in both the US and Europe, where TB had been considered an eradicated disease. The WHO identified TB as a global health emergency in 1993 and launched the Global Plan to Stop TB, which focused on early TB diagnosis and reliable access to treatment.

In areas of high HIV prevalence, coinfection with TB and HIV has become a critical issue, fuelling the increase in TB cases. Coinfection not only increases the proportion of individuals with TB who develop active disease, but also presents treatment challenges owing to interactions between TB and HIV drugs. Increased incidence of multidrug-resistant TB (MDR-TB) has further complicated effective disease management and created a demand for new treatments that are effective against resistant disease strains.

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The Global TB Alliance, a nonprofit organization working with public and private sectors to accelerate R&D in TB, was established in 2000. The TB Alliance has raised substantial funding for clinical research and is now the leading developer of new TB drugs, with agents in all phases of development. Nonprofit investment has been a key factor in stimulating interest in TB R&D within the pharmaceutical industry. Most products in the TB pipeline are joint projects between private and nonprofit organizations. The TB Alliance received donations of $39 million and $14 million from the Dutch and Irish governments, respectively[3,4]. In addition, the Bill & Melinda Gates Foundation provided grants of $25 million in 2000 and a further $104 million in 2006 (ref. 5).

Cost of TB

Given the geographic distribution of TB, its burden is overwhelmingly centered on developing markets (**Fig. 1**). It has been estimated that $10 billion is spent annually on global TB control and $3 billion of this is spent by established market economies[6]. From a market dynamic perspective, the incidence of TB is now stable or falling in five out of six WHO regions but growing in Africa, where the TB epidemic is still driven by the high rate of HIV infection.

Developed markets. Improvements in housing and nutrition together with treatment and immunization programs were considered to have largely eradicated TB in developed nations. However, following years of constant decline, a resurgence in TB in both the US and Europe in the late 1980s and early 1990s attracted significant attention. Outbreaks were concentrated in large cities, among immigrant and homeless populations, and triggered reviews of screening and control programs. For example, in 2005 the UK government introduced a program of TB screening for all immigrants entering the UK from countries with high TB prevalence.

In both the US and Europe, increases in TB incidence peaked in the early 1990s and are now falling again. Key exceptions are the UK and several Eastern European markets. New figures released by the UK Health Protection Agency (HPA)[7] in November 2006 showed a 10.8% increase in cases of TB in England, Wales and Northern Ireland, from 7,321 cases reported in 2004 to 8,113 cases in 2005. In the UK, TB continues to be concentrated among communities in deprived areas, whereas in Eastern Europe, low domestic funding for TB programs has contributed to the problem.

One of the significant issues arising from these outbreaks from a clinical and economic perspective was the high prevalence of MDR-TB in some areas. MDR-TB resistance is usually defined as resistance to the two most effective TB treatments—rifampicin and isoniazid (see below)—and requires the use of more costly second-line treatments that must be taken for longer periods of time. A TB outbreak in New York City between 1991 and 1992 claimed more than 500 lives[8], and the Health Department estimated that the total cost of the outbreak was around $1 billion, driven by extended hospital stays.

High-burden markets. The economic impact of TB in high-burden countries is huge. More than 75% of TB deaths affect the population aged 15–54, the most economically active segment. TB is estimated to cause lost productivity of 4–7% of GDP and to deplete the economies of developing countries by a total of $12 billion per year[9]. In India, the country with the world's highest number of TB cases, it is estimated that indirect costs associated with TB amount to $3 billion, and direct costs total around $3 million[10].

Multi-drug resistance is also a growing problem in high-burden TB markets. In South Africa, a form of TB known as extremely drug resistant TB (XDR-TB) that cannot be effectively treated with first- or second-line therapies has emerged. In 2006, of 53 people infected with XDR-TB in one rural South African hospital, 52 died from the disease[11]. Of these 53 with XDR-TB, more than 80% (all 44 who were tested) were known to be HIV positive[12]. Cases of XDR-TB have been reported worldwide, including in the US. In Russia, the only nation in the WHO Europe region classified as a high-burden TB country,

15% of resistant cases are also resistant to second-line therapies[11].

WHO-led global control programs aim to reverse the rise in TB incidence by 2015 and to halve the 1990 prevalence and morbidity rates globally. The costs of reaching these targets will be substantial: the WHO estimates a total cost of $56 billion over 10 years to implement its global plan to stop TB, but anticipates that funding of only around 45% of this total will be available. An important cost driver is the policy of directly observed therapy, in which individuals take each dose of their treatment under observation of a health worker. Owing partly to the success of this program, which is aimed at increasing treatment adherence, there has been progress in controlling TB, but targets are unlikely to be met in sub-Saharan Africa (**Fig. 2**).

Current treatment of TB

Several anti-infective agents are available which are effective against the bacterium that causes TB. These agents are grouped into first- and second-line agents on the basis of efficacy and potential for adverse events.

The five mainstay TB treatments—rifampicin (also referred to as rifamycin), isoniazid, pyrazinamide, ethambutol and streptomycin—were introduced between 1948 and 1963, and are all available generically[13]. Streptomycin was the first available TB therapy, but its benefits were limited by the emergence of drug resistance, as well as by the requirement for intramuscular administration. As new agents with different characteristics became available, they were used in combination to optimize efficacy and limit the possibility of treatment relapse (**Table 1**).

The current gold-standard treatment for active TB is a six-month regimen with rifampicin and isoniazid, supplemented in the initial two months with pyrazinamide and either ethambutol or streptomycin[14]. This combination has the three properties required for effective TB management: antibacterial activity, capacity to inhibit the development of resistance and efficacy against persisting organisms.

The recommended regimen for those with latent TB (who are infected with TB but do not express symptoms and are not infectious) is a single-agent treatment with either isoniazid (six- to nine-month regimen) or rifampicin (four-month regimen). This is recommended to reduce the risk of progression to active disease in high-risk groups (for example, those coinfected with HIV)[15].

First-line therapies. Sanofi-Aventis markets a branded version of rifampicin in both established and developing markets. It is supplied as a single agent (Rifadin), and in fixed combination with isoniazid or a combination of isoniazid (Rifanah) and pyrazinamide (Rifater); fixed-dose combinations are strongly advocated in the treatment of TB to reduce treatment complexity and pill burden. Sandoz also manufactures a generic rifampicin-isoniazid fixed-dose combination (Rimactazid). Companies do not report sales for these products, but estimates are that US sales of generic rifampicin in 2005 were around $14.5 million[16].

In 2001, Pharmacia (now Pfizer) introduced rifabutin (Mycobutin), a rifampicin derivative that, unlike rifampicin, is not associated with significant decreases in blood concentration of the protease inhibitors or non-nucleoside reverse transcriptase inhibitors that are used in treatment of HIV. In developed markets, rifabutin is used for prevention of TB infection in HIV-positive individuals.

As single agents, isoniazid, pyrazinamide and ethambutol are available as unbranded generics, supplied primarily by local generics manufacturers. To address the reliable supply and low cost of TB agents, the WHO established in 2001 the Global Drug Facility (GDF), which procures and supplies TB drugs to low-income countries. Four manufacturers have been designated preferred suppliers—Svizera Europe, Lupin Pharmaceuticals, Cadila and Strides-Sandoz (Sandoz is partnering with the Indian manufacturer Strides to produce both TB and HIV drugs). Between 2005 and 2006, the GDF supplied TB therapy worth $28 million to 55 countries[17].

Second-line TB therapies. If adhered to, first-line therapy can have around a 95% success rate[18]. However, a high proportion of individuals do not adhere to the 6–9 month first-line regimen. They frequently discontinue therapy after 1–2 months as their symptoms subside. As a result, TB treatment is associated with relatively high relapse rates.

Several therapies that can be used as second-line treatment are available, but they are less effective, more expensive and typically associated with more significant side effects than first-line agents. Given their lower efficacy and increased risk of side effects, some guidelines refer to these agents as reserve therapies, rather than true second-line options.

Second-line antibiotics are typically older generic products not specifically developed to treat TB. They include kanamycin, marketed by Sandoz as Kantrex, and capreomycin (Capastat) and cycloserine (Seromycin), both marketed by Eli Lilly.

Market value. Defining the value of the TB market is difficult. Reliable sales data are not available for several of the markets with the highest TB burdens. The market is largely generic and highly fragmented, with several local manufacturers involved, together with large generics manufacturers such as Sandoz. The market is further segmented by the role of the GDF in supplying TB drugs to low-income markets. Furthermore, the GDF has also driven down the cost of tuberculosis therapies; it is estimated[19] that the average cost for a course of TB therapy procured through the GDF is between $14–18.

Reflecting the low degree of interest from drugs manufacturers in the TB market, few reviews of the value of the global TB market are available. A report by the TB Alliance estimated that in 2000 the market was worth between $412.5 and $470.5 million per year[20]. This figure includes an estimated $275–318 million worldwide private TB market (based on IMS

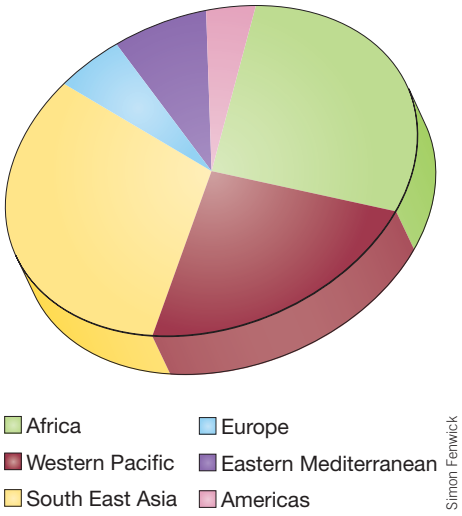

Figure 1 Proportion of tuberculosis cases by world region in 2004, as defined by the WHO.

Table 1 Overview of key TB therapies and launch dates

Agent	Description	Launch date	Launched by
Rifampicin	Broad spectrum antibiotic, also used in treatment of leprosy	1963	CIBA Ltd (now Novartis)
Isoniazid	Hydrazide antibiotic, only effective against mycobacteria	1952	Roche
Pyrazinamide	Bacteriostatic & bactericidal activity	1954	Lederle (now Wyeth)
Ethambutol	Bacteriostatic antimycobacterial drug	1962	Lederle (now Wyeth)
Streptomycin	Aminoglycoside antibiotic	1948	Merck

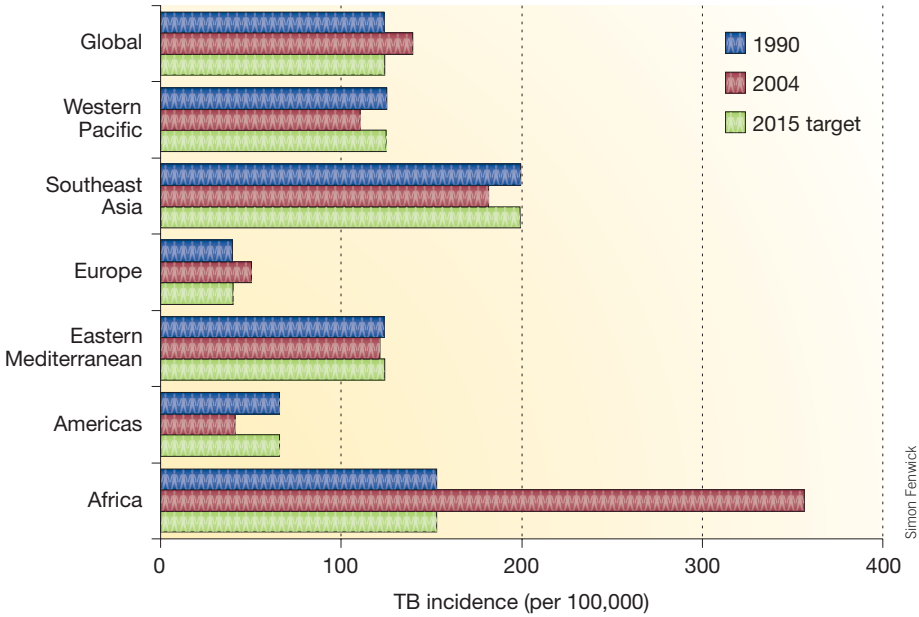

Figure 2 Incidence of tuberculosis, 1990–2004. The figure also includes the targets for 2015.

Health sales data for anti-TB drugs), an estimated $125–140 million tender market and an estimated $12.5 million for drugs to treat MDR-TB. It was estimated that the global TB market would grow to between $612–630 million by 2010. This was based on assumptions that the private TB market would remain constant from 2000, but that increases would be seen in the tender market due to expansion of TB control programs together with increases in the proportion of MDR-TB and people with latent TB receiving treatment[20].

IMS sales and unit volume data were provided from 1997 to 2000. Over this period, sales fell from $314 million to $275 million, whereas unit sales remained relatively constant, indicating a decrease in unit price of TB drugs during this time.

Similarly, limited data are available to provide a robust assessment of current market share. In the TB Alliance's economic report, based on 1998 IMS data, Sanofi-Aventis (then Aventis) was estimated to be the market leader in TB, with a 17% share of the private market. Other key manufacturers included Novartis (through Sandoz) with a 14% share and Pfizer (then Pharmacia) with a 7% market share (**Fig. 3**).

Emerging therapies

Although available first-line agents are effective, they are associated with significant unmet needs. Recommended regimens require therapy to be continued for 6–9 months and can involve a high pill burden and a cost that is restrictive for people with low incomes. Furthermore, current drugs are associated with significant adverse effects, as well as with interactions with antiretroviral therapies, which can be a critical factor limiting their use. Although the WHO's promotion of directly observed therapy has contributed to significant improvements in treatment adherence and success rates, reducing the length of treatment is viewed as a priority for new TB therapies. In fact, the TB Alliance has outlined ideal characteristics that new TB therapies should possess to represent a significant advance in TB treatment. These include activity against drug-resistant TB strains, lack of interaction with antiretroviral agents, and shorter treatment duration.

There are several agents in clinical trials for TB and in the discovery and preclinical pipelines (**Table 2**). Notably, most current trial programs are in partnership with nonprofit organizations, such as the TB Alliance and the WHO.

Fluoroquinolones. Moxifloxacin is a synthetic fluoroquinolone antibiotic manufactured by Bayer and sold as Avelox for the treatment of bacterial infections of the skin and respiratory tract. In 2005, Bayer entered into a collaboration with the TB Alliance to launch a clinical trial program, evaluating moxifloxacin for treatment of TB[21]. Under the terms of the agreement, Bayer will cover the costs of regulatory filings, and the TB Alliance will coordinate and pay for the clinical trials with additional support from the US Centers for Disease Control and Prevention (CDC), the Orphan Products Development Center of the US Food and Drug Administration (FDA), the European and Developing Countries Clinical Trials Partnership (EDCTP) and the British Medical Research Council[22].

A phase 2-3 trial with moxifloxacin is underway, and will compare a four-month moxifloxacin regimen versus a standard six-month isoniazid regimen, both in combination with ethambutol, pyrazinamide and rifampicin. If successful, Bayer's intention is to make moxifloxacin available at a reasonable price in developing markets.

Gatifloxacin, another fluoroquinolone similar to moxifloxacin, has also shown encouraging results in preclinical studies. As with moxifloxacin, gatifloxacin is a marketed product available in the US as Tequin, where it is sold under license by Bristol-Myers Squibb for treatment of respiratory infections.

Table 2 Current TB pipeline

Drug	Trial sponsor	Class	Status	Comments
Gatifloxacin	Bayer, TB Alliance	Fluoroquinolone	Phase 2–3	May shorten treatment from 6 to 4 months
Moxifloxacin	Institut de Recherche pour le Developpement, WHO, European Commission	Fluoroquinolone	Phase 3	May shorten treatment from 6 to 4 months
TMC207	Tibotec (subsidiary of J&J)	Diarylquinoline	Phase 2	May allow once weekly dosing; high potency against drug resistant strains and low potential for drug interactions
OPC-67683	Otsuka, TB Alliance	Nitroimidazole derivative	Phase 2	May shorter duration of therapy in active TB and MDR-TB
PA-824	TB Alliance (acquired rights from the former Chiron)	ATP modulator	Phase 1	Combines most effective features of rifampicin and isoniazid
LL-3858	Lupin Pharmaceuticals	Pyrrole	Phase 1	May reduce treatment duration to 2–3 months
SQ-109	Sequella Pharmaceuticals, NIH	Diamine	Phase 1	Could replace 2 current TB agents and reduce treatment time by 25%

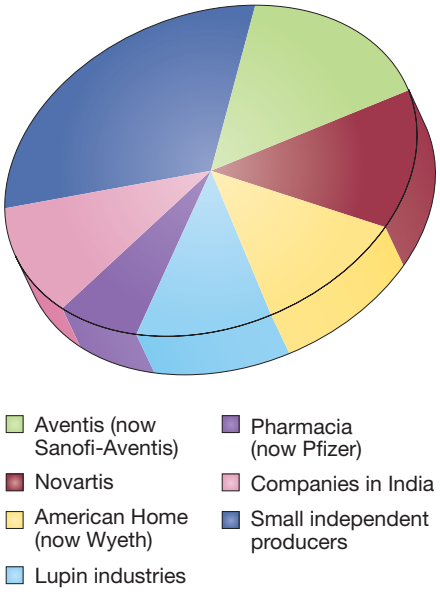

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Figure 3 Anti-TB drug market share within the private market, 1998.

Following successful phase 2 studies in TB, the *Institut de Recherche pour le Developpement*, together with the WHO and the European Commission, is sponsoring a 2,500-person, multicenter, open-label phase 3 trial to evaluate the safety and efficacy of a four-month gatifloxacin-containing regimen. The trial is expected to end in June 2009 (ref. 23). However, gatifloxacin has been claimed to be associated with "life-threatening" side effects, including severe diabetes, and there have been calls for the FDA to issue a black-box warning for Tequin[24]. Bristol-Myers Squibb announced that it would cease manufacturing Tequin and return all rights to licensor Kyorin. It is unclear how this will affect development plans for TB.

Moxifloxacin and gatifloxacin have significant potential in TB as a new drug class, owing to reduced treatment duration, lack of interactions with antiretroviral drugs, new mechanism of action and potential efficacy in MDR-TB. However, as a four-month treatment taken in combination with three other drugs, neither agent provides the ideal profile that the TB Alliance expects to revolutionize TB treatment.

ATP modulators. Tibotec (a subsidiary of Johnson & Johnson) is developing TMC207 for treatment of TB. TMC207 is the lead product in the diarylquinoline-derivative ATP-modulator class. TMC207 holds the promise of being active against latent and active TB. Its long half-life and bactericidal potency also give TMC207 the potential to reduce the duration and the pill burden of TB treatment.

Others. PA-824 is a promising molecule in phase 1 of development by the TB Alliance. The Alliance obtained worldwide rights to PA-824 and its derivatives from Chiron with Chiron's commitment to make the drug available for TB without royalties in countries where TB is endemic.

Lupin Pharmaceuticals manufactures and markets several branded generic TB treatments in high-burden markets and is also involved in the development of new therapies. Their lead molecule, LL-3858 is in phase 1 trials.

Sequella is a biopharmaceutical company that focuses on infectious diseases that "pose serious risk to public health and have both significant market opportunities and clear commercialization pathways"[25]. In addition to a diagnostic agent in phase 3 trials, Sequella's lead TB treatment, the orally active small molecule antibiotic SQ-109, is in phase 1.

GlaxoSmithKline, AstraZeneca and Novartis each have set up research centers focused on tropical diseases, including TB. GlaxoSmithKline and AstraZeneca have announced TB candidate products in early stage development, and both companies are working in collaboration with the TB Alliance. Another major company, Lilly, which has second-line TB drugs in its pipeline, has also established a "multi-pronged philanthropic program" to tackle the issue of MDR-TB[26].

Conclusions

TB remains a major public health issue, particularly in developing markets, and is a disease characterized by significant unmet need. The availability of effective new agents will be critical to controlling TB, particularly in addressing issues such as MDR strains and TB-HIV coinfection.

The TB market has been stagnant for several years, with no major new products launched since the 1960s. In the near term, some market growth may result from the spread of MDR-TB and the associated higher treatment costs. However, this growth is likely to be offset by the pressure on pricing and the slowing in the number of new TB cases. In short, it seems unlikely that we will see any real market growth within the next 3–5 years.

The recent increase in R&D activity could produce a number of new advances in TB treatment within the next 5–10 years. A number of these agents, notably TMC207, which has promise to reduce treatment frequency from once a day to once a week, have the potential to make a real difference to future TB treatment.

However, from a commercial perspective, the key issue for the pharmaceutical industry is that TB does not represent a significant enough medical burden in the core markets of the US, Europe and Japan to make TB a truly attractive prospect. In developing markets, new therapies will be welcomed, but only if they are made affordable.

But perhaps commercial interests should take a back seat to philanthropy. It would do no harm to the industry's tarnished public image if new products for the treatment of TB were to be advanced with only humanity and medical interest in mind. Encouragingly in this regard, the availability of significant amounts of public funding for TB, together with social responsibility programs at individual companies, seem to be a significant catalyst for private investment in TB.

This commitment must remain in place to maintain R&D momentum and to bring much needed new products to market. Assuming that approach, everybody can gain and the fight against TB can be engaged with renewed vigor.

COMPETING INTERESTS STATEMENT
The authors declare that they have no competing financial interests.

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