

Inhaled therapies for tuberculosis: A viable approach for spray-dried drugs delivered by handheld dry powder inhaler

Inhalation may enhance efficacy and reduce adverse effects compared to oral and parenteral therapies

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Abstract

Treatment for multidrug-resistant tuberculosis requires lengthy and complicated regimens. These include oral, poorly absorbed, toxic drugs and daily intra-muscular injections of high quantities of parenteral agents, for a duration of several months. Reformulating such medications into dry powders suitable for inhalation and deposition to the deep lung shows promise. Indications are that healthcare workers would be in favor of such an option.

Worldwide incidence and classifications of tuberculosis

Tuberculosis (TB) is an airborne, bacterial infectious disease, caused by the organism *Mycobacterium tuberculosis* (Mtb), which spreads directly from person to person. Most people who are infected, however, do not develop active TB, but remain symptomless and contain the infection lifelong.¹ From an epidemiological perspective, Mtb has been very successful in maintaining transmission in populations throughout the world for several thousand years.

TB continues to be a leading killer disease. Despite the fact that it is curable in more than 98% of cases, an estimated 9.0 million people developed TB worldwide in 2013 and 1.5 million died from the disease.² The highest TB burden occurs in the southeast Asian and western Pacific Regions (56%), with India and China contributing 24% and 11% of all cases respectively. Africa has approximately 25% of the global burden, but also has the highest rates of cases and deaths relative to population (Figure 1). Over the past two decades, much of the rise in TB incidence rates in these regions, in particular in sub-Saharan Africa, can be ascribed to joint infection with HIV. Diminished immunological defenses allowed



"La Miseria by Cristóbal Rojas (1886). The artist, suffering from tuberculosis, depicts the social aspect of the disease and its relation to living conditions at the close of the 19th century." (Quoted from http://en.wikipedia.org/wiki/History_of_tuberculosis)

a large pool of persons with latent TB infection to progress to active disease.

Compounding the problem is the emergence of a growing number of multi-drug resistant cases of TB (MDR-TB), and in particular, cases that are extensively multi-drug resistant (XDR-TB).³ These cases are mainly the result of inadequate case management, particularly due to poor compliance with first-line chemotherapy, leaving very limited options for treatment with less-potent reserve (second-line) drugs. In 2013, 3.5% of all TB patients were estimated to be suffering from MDR-TB.²

Current oral and injectable TB therapies

Treating TB requires daily oral dosing of several antibiotics, taken for at least six months to be effective. For new cases, the World Health Organization (WHO) recommends two months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of isoniazid and rifampicin.⁴ High doses are required because only a small fraction of the total dose reaches the lung following oral administration and that dosage fraction is cleared systemically in a few hours.

Not all patients, however, successfully complete this treatment course. In addition, many who fail first-line treatment efforts are at risk of developing resistance to one or more first-line drugs. Resistance to the two anchor drugs in first-line therapy, rifampicin and isoniazid, is defined as multi-drug resistance (MDR-TB).

To treat MDR-TB, more costly, second-line antibiotics are needed and treatment lasts up to two years.⁴ The treatment regimen, representing various drug groups (Table 1), typically combines at least four or five drugs, which may include pyrazinamide (Group 1), a fluoroquinolone (Group 2), an injectable agent (Group 3) and a drug from Group 4. The injectable agent is used until negative sputum cultures have been documented for at least 6 months. Several other second- and third-line drugs are available as substitutes. Based on WHO reports about MDR-TB treatment schedules started in patients in 2013,² it is estimated in that year worldwide, some 97,000 patients received injectable drugs long-term as part of their therapy.

The need for alternative TB therapies

Public health agencies, such as the WHO Global Tuberculosis Programme and the Stop TB Partnership, have been campaigning for simpler, affordable and more effective TB medications. In recent years, scientists and service providers have begun to investigate regimens as short as nine months for treatment of MDR-TB.⁵ This concept was greatly enhanced by the 2012 introduction of two potent new drugs, bedaquiline (Janssen Pharmaceuticals, Titusville, NJ) and delamanid (Otsuka Pharmaceuticals, Princeton, NJ).

Still, injectable drugs (e.g., capreomycin, kanamycin or amikacin) or poorly absorbed oral compounds (e.g., clofazimine) can be associated with varying degrees of

adverse effects, some extremely toxic. In addition, the pain and discomfort associated with intramuscular (IM) injections of high quantities of drug, daily for several months, in patients who are severely emaciated cannot easily be discounted.

Inhaled therapy may enhance efficacy and reduce adverse effects

Over the past decade, growing interest has also been shown in inhaled therapies for MDR-TB. The hypothesis is based on the fact that tuberculosis is predominantly, but not exclusively, a pulmonary disease.⁶ Directly targeting the lung for introduction of potent medicines that would be amenable to such a route of administration could have several advantages. These include lower dose requirement and bypassing first stage metabolism in the liver, limiting adverse effects. However, the most important effect would be in the dramatic reduction of bacterial load at the primary site of infection, leaving an optimized, background oral regimen to support sterilization of the lung and eliminate infection foci at other tissue sites. Ideally, drugs administered to the lung would be used as adjunct therapy, rather than primary therapy.

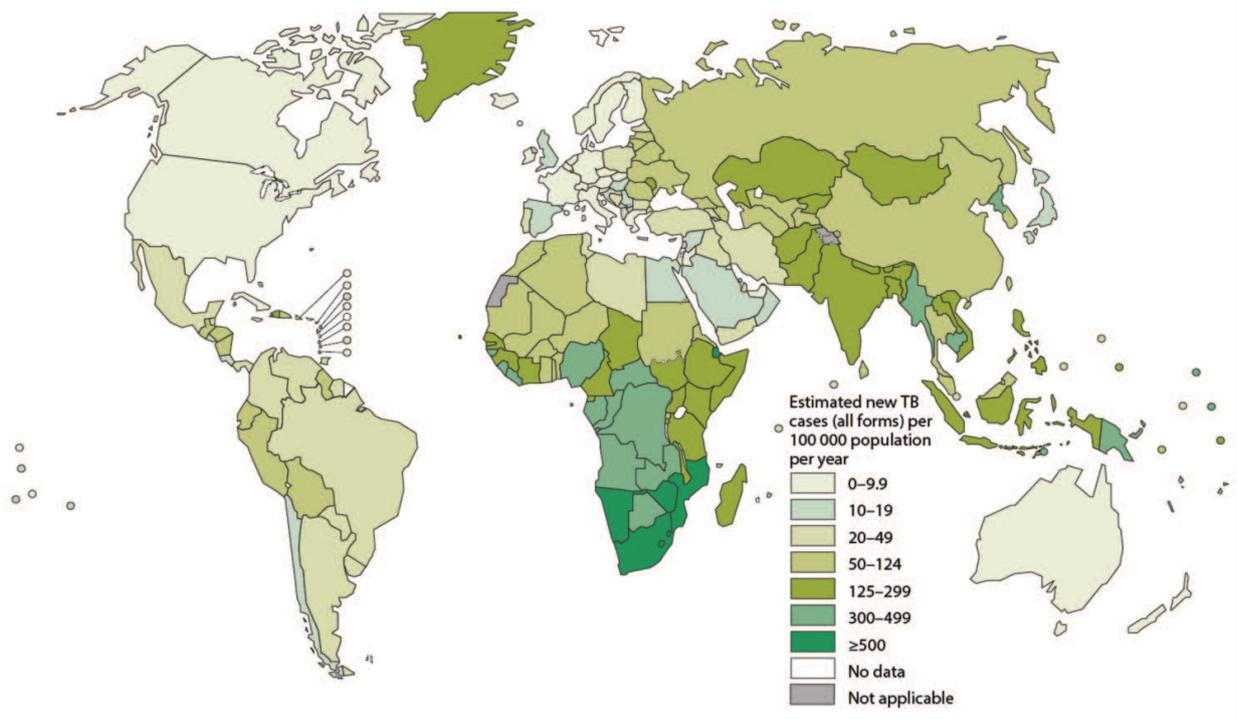
Animal and human inhaled therapy studies

Evidence from animal studies and several human studies strongly support the rationale for inhaled therapies

Figure 1

Estimated TB incidence rates, 2013

Estimated TB incidence rates, 2013



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2014*. WHO, 2014.

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for tuberculosis.⁶ For example, in a well-controlled study⁷ of inhaled dry powder capreomycin in guinea pigs, spray-dried powders delivered directly to the lung led to higher local tissue concentration at significantly lower doses than those administered by injection, with good systemic absorption and efficacy against pulmonary tuberculosis. During the study, animals were infected with tuberculosis. Four weeks after infection, they were given capreomycin, either by intramuscular injection or by inhalation, daily for 4 weeks. Animals that received an estimated 1.8 mg/kg deposited dose (14.5 mg/kg delivered dose) of aerosolized capreomycin particles showed a reduction in TB infection, measured by colony-forming units, similar to that achieved by IM injection of 20 mg/kg capreomycin solution. The reduction of TB infection in the lungs was also significantly lower than in the untreated controls. In humans, at least three published accounts of kanamycin nebulized to the lung had significant efficacy over parenteral administration.⁶

Inhaled delivery of spray-dried formulations

The viability of pulmonary administration of anti-tuberculosis therapy depends on the successful formulation of drugs into powders or similar compounds that would allow for inhalation and deposition of drug particles in the alveolar regions of the lung. To be operational, the approach must be linked to the use of easy-to-use inhaler devices for delivery.

Several recent studies have examined delivery of known injectable or orally administered anti-TB agents as spray-dried powder formulations. The most important developments from those studies are summarized here:

- **Capreomycin** (CM, 2nd-line anti-TB injectable agent, 1,000 mg/dose): In a Phase I trial of self-administered, single dose, inhaled CM (25 mg, 75 mg, 150 mg or 300 mg nominal dose). The single 300 mg dose rapidly achieved serum drug concentrations above the minimum inhibitory concentration for *Mycobacterium*

Table 1

Drugs used to treat multi-drug resistant tuberculosis (MDR-TB)⁴

Group	Drugs (Abbreviations)
Group 1: First-line oral agents	• Pyrazinamide (Z)
Group 2: Injectable agents	• Kanamycin (Km) • Amikacin (Am) • Capreomycin (Cm)
Group 3: Fluoroquinolones	• Levofloxacin (Lfx) • Moxifloxacin (Mfx) • Gatifloxacin (Gfx) • Ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	• Ethionamide (Eto) • Prothionamide (Pto) • Cycloserine (Cs) • Terizidone (Trd) • Para-aminosalicylic acid (PAS)
Group 5: Agents with unclear role in treatment of drug resistant-TB	• Clofazimine (CFM) • Linezolid (Lzd) • Amoxicillin/Clavulanate (Amx/Clv) • Clarithromycin (Clr)

Principles for composition of regimens for MDR-TB:⁴

- Include at least four second-line anti-TB drugs likely to be effective as well as pyrazinamide during the intensive phase of treatment. The regimen should include pyrazinamide, a parenteral agent, ethionamide (or prothionamide) and cycloserine, or PAS if cycloserine cannot be used.
- Note: Recently, market authorizations were issued for two new drugs, bedaquiline and delamanid, for use in the treatment of MDR-TB; both are regarded as Group 5 drugs by the World Health Organization. Guidelines for their use as part of treatment regimens are being developed. (Personal communications to P. Bernard Fourie, October 2014.)

Table 2

Results from a qualitative study in 48 healthcare workers from five multi-drug resistant tuberculosis (MDR-TB) care facilities in South Africa. The study evaluated attitudes and perceptions toward dry powder formulations, inhaled from simple handheld devices, as replacements for injectable anti-TB agents.

- 92% believed patients would be comfortable using the inhaler
- 84% found the inhaler easy to use
- 88% would use the inhaler with adult patients if it were available
- Some respondents had concerns about actuating the inhaler
- 22% found the inhaler's durability in repeated use somewhat questionable
- 26% queried the safety and hygiene of the procedure
- No major foreseeable barriers to product adoption (medical or cultural) were found
- The educational gap that characterizes the array of patients normally requiring injectable anti-TB agents would need to be taken into consideration when the technology is introduced

tuberculosis. The Plastiap RS01 handheld inhaler (Plastiap SpA, Milan, Italy) used for administration and inhaled drug were well-tolerated by 20 healthy, normal, volunteer human subjects. Multiple-dose Phase I and Phase 2 trials are in planning to further explore the potential of inhaled therapy as part of an MDR-TB treatment regimen.⁷

- **Rifapentine** (RPT, 1st-line oral anti-TB agent, 12-18 mg/kg): RPT's long half-life and powerful anti-TB activity make it an attractive candidate for treatment simplification and shortening. Currently, it is licensed for intermittent administration against TB. Early work shows that the drug can be formulated into an inhalable dry powder, which might potentially accelerate cure in patients with pulmonary TB.⁸

- **Pyrazinamide** (PZA, 1st-line and 2nd-line oral anti-TB agent, 20-30 mg/kg): Increasing the dose of PZA is desirable, but is limited by its toxicity profile. An alternative approach might be to use pyrazinoic acid in its inhaled form, as an adjunct to standard oral therapy. This would acidify pulmonary lesions, thus increasing the bactericidal activity of concomitant orally-administered PZA.⁹

- **Clofazimine** (CFM, oral anti-leprosy riminophenazine, 2nd-line anti-TB Group 5 agent): Anti-TB activity of this drug class might benefit from pulmonary rather than oral administration. CFM, a lipophilic riminophenazine antibiotic, possesses both anti-mycobacterial and anti-inflammatory activity. Inhalable CFM-containing dry powder microparticles and native CFM were evaluated for activity against *Mycobacterium tuberculosis* in human monocyte-derived macrophage cultures and in mice infected with a low-dose aerosol. It was concluded that spray-dried clofazimine was suitable for deep lung delivery, retained the *in vitro* kill characteristics of the native compound and demonstrated superior efficacy in preliminary *in vivo* experiments.^{10,11}

A qualitative study of perceptions about inhalation therapy

The concept of pulmonary administration is new to the practice of TB management so it is essential to gain an understanding of the perceptions of patients and service providers about inhaled therapy. Their perceptions about a device by which an inhaled drug would be delivered also should be considered and it is especially relevant to inquire about their prevailing experiences with injectable TB drugs.

Accordingly, we piloted a small qualitative study among 48 healthcare providers (doctors, nurses or treatment supporters) treating MDR-TB patients in South Africa. We used an opinion-based questionnaire to gauge the acceptability of inhalation (versus parenteral therapy) as a viable route of administration for anti-tuberculosis therapy.

The opinion-based survey focused largely on the provider's experience with administering injections for TB treatment and introduced, in a descriptive manner, the concept of inhalation therapy. Furthermore, the questionnaire solicited opinions about ease of use, product acceptability, predictors of obstacles to adoption and suggestions for product improvement. In all cases, use of a handheld inhaler was demonstrated, but not with active powder ingredient.

Results of the study are shown in Table 2. Of the providers surveyed, almost all respondents (92%) believed patients would be comfortable using the inhaler and most (84%) found the inhaler easy to use. There were some concerns about actuating the inhaler, with 22% finding its durability on repeated use somewhat questionable and 26% querying whether the device might pose a risk for cross-infection or self-infection if used repeatedly.

Challenges and opportunities for inhaled therapy

Inhaled therapies offer major opportunities for low dose adjunctive therapy to existing regimens, without additional risk of adverse effects associated with first pass metabolism. Recent research provides strong evidence for enhanced efficacy at lower doses for several anti-TB agents formulated in dry powder form. Preliminary qualitative studies indicate that dry powder inhaled agents delivered by easy-to-use devices might be feasible and acceptable to clinical staff managing TB patients.

It is important to anticipate that inhaled therapy would need to fit in with existing national TB program strategies and form part of TB control policies. In addition, cost-effectiveness would have to be determined, infection control to prevent device-associated cross-infections and/or risk to health personnel strictly enforced, and drug administration supervised. These requirements might limit the extent to which inhaled therapies would be implemented, particularly in developing countries.

The large-scale production of stable drug formulations at an affordable cost will be the fundamental and decisive obstacle that needs to be overcome before embarking on operational demonstration of the technology.⁶ Nevertheless, the rationale behind anti-tuberculosis inhaled therapy is convincing and will hopefully inspire the progression of this concept towards definitive clinical trials, ultimately eliminating injections for MDR-TB patients and providing supplementary treatment options for TB patients in general.

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The third international TB meeting, "Inhaled Therapies for Tuberculosis and Other Infectious Diseases" will be held October 14-16, 2015 in Parma, Italy.
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