Contents lists available at ScienceDirect

European Journal of Integrative Medicine

Opinion paper

Urgent global action is needed on multi drug-resistant tuberculosis (MDR-TB) – can small cone moxa contribute to a global response?

Merlin Young*, Jenny Craig

Members of Toyohari Medical association, Tokyo, Japan

ABSTRACT

Introduction: Many critical dilemmas currently face global authorities in TB control. This article highlights one of the most challenging which is drug-resistance. MDR-TB is estimated to account for at least one third of all deaths associated with anti-microbial resistance, but remains largely undiagnosed and untreated, particularly in countries with inadequate health infrastructures which also have a high prevalence of latent infection. This article considers the growing primary evidence that a Traditional Japanese Moxibustion (TJM) technique with known immunomodulatory effects may help significantly improve treatment outcomes with MDR-TB.
Methods: Data from three recent primary research programs in resource-limited environments (in Uganda and the DPRK) are discussed and evaluated in terms of outcomes, as well as in respect of the therapy's low-cost and low-tech nature.
Results: These data suggest that the therapy may be helpful in developing countries in reducing infectivity in TB cases (including those co-infected with HIV) as well as in accelerating recoveries, and significantly enhancing recoveries in MDR-TB cases. They also suggest that TJM may also prevent the emergence of MDR-TB from latent infection.
Conclusion: There is an urgent need for better understanding of these effects. A model for further investigation of moxa treatment for MDR-TB is presented. This could generate further data that might be used by WHO and Member States, potentially enabling them to integrate TJM into their TB treatment programmes, thereby benefitting large numbers of vulnerable patients at very little extra cost.

1. Introduction

Multi-drug resistant TB (MDR-TB) is the child of tuberculosis, paradoxically propagated by the very efforts to defeat the parent using TB drugs. It comprises the single most sizeable component of Anti-Microbial Resistance (AMR), causing the most deaths [1,2] and comprising the only anti-microbial resistant pathogen (so far) that is infectious through inhalation. As such it poses a unique and significant threat to global health.

These dilemmas contribute to a cycle of programmatically untreatable infectious disease which is posing an increasingly serious challenge for global authorities, national TB programmes and NGOs, especially where resources are limited. This is partly because most TB occurs where health infrastructures are deficient, partly because the very drugs used to treat TB inevitably put pressures on the mycobacteria that result in drug-resistance, and partly because the resources needed to combat MDR-TB itself (in terms of appropriate public health resource, and access to second line or new drugs and their necessary

pharmaco-management) are inherently deficient in high incident environments. In addition, human immune systems in these environments are often not robust enough to keep the disease in check naturally.

This article focuses on a Traditional and Complementary Medicine (T&CM) therapy that is well-known in East Asia, but little-known outside this region. This is moxibustion (described below) – specifically small cone direct moxibustion which is a part of Japan's traditional medical heritage. Three separate complementary sets of evidence of this therapy's potential for helping address key aspects of the tuberculosis AMR crisis have now emerged from Africa and East Asia. They are presented in this paper collectively suggesting that this therapy may be a useful tool in controlling MDR-TB as the crisis deepens.

1.1. A retrospective view of drug-resistance

In 1882 Robert Koch, arguably the founding father of the science of bacteriology, made a famous presentation to the Physiological Society in Berlin, Germany [3], identifying the pathogen that was killing

---

millions in Europe at the height of its industrial revolution. He called it *Mycobacterium tuberculosis.*

Forty-seven years later (in 1929), a Japanese physician by the name of Dr Shimetaro Hara published an article describing how he had deliberately infected groups of marmots with TB and then administered various regimens of moxa on them to see how they might respond [4]. His motive for doing so was because he had been treating his own hospitalised TB patients with moxa and had recorded many recoveries. Dr Hara's results (which compared various moxa regimens using blood and organ analysis) remain compelling though, as far as we know, he published no further controlled data relating to any human recoveries. Not only do the animal data provide evidence that the treatment provokes a host immune response, but they also appear to confirm the results he saw in his patients. It should be noted that this research was published in the pre-antibiotic era when there were no drug treatments for TB or any antibiotics, and of course no sign of drug-resistance because of this.

Sixteen years later (in 1945) Alexander Fleming while receiving a Nobel Prize for developing the first major antibiotic (penicillin) offered a warning to the world: *"It is not difficult to make microbes resistant … by exposing them to concentrations [of the drug] not sufficient to kill them"* [5]. Just three years afterwards the first anti-tuberculosis drug (streptomycin) was discovered and the crisis that has become multi-drug-resistant tuberculosis began to slowly unfold exactly as Fleming predicted in his famous speech.

1.2. About tuberculosis

TB mycobacteria replicate slowly and have thick and waxy cell walls, which delay the penetration of drugs [6], necessitating lengthy treatment regimens. Drug-resistance in TB develops slowly as well [7], with viable hotspots of infection often thought to appear around fifteen years after the introduction of a new drug [8].

Today the standard first line treatment of TB uses four drugs over a period of at least six months [9]. It is a challenging treatment, not least because those who are most vulnerable to TB generally have limited access to quality supportive health care.

An infection that is resistant to the two strongest first line drugs (rifampicin and isoniazid) is defined as multi-drug resistant or MDR-TB and treatment takes 9–24 months, often failing. MDR-TB is now a significant global public health threat, particularly in low-income countries with inadequate health infrastructures where the incidence of MDR disease is estimated with uncertainty based only on limited surveillance data [10]. MDR-TB has furthermore been identified by the World Health Organisation (WHO) as being a public health crisis in its own right [1].

TB is also complex because it exists in the body in two clinically distinct states - sub-clinically (as a latent infection) and reactivated (as a potentially lethal infectious disease). Both the progression of disease and its prognosis are affected by a variety of risk factors which are closely related to the relative strength of host immunity, along with the quality and quantity of medical resource available to confront and contain the infection. Put most simply, if host immunity is relatively strong then the likelihood of a latent infection reactivating is considerably reduced (and vice versa).

Since 1993 (when TB was officially declared by the WHO to be a Global Emergency) a series of global initiatives have targeted TB, but have so far achieved disappointing results. The Millennium Development Goal target of beginning to reduce incidence and mortality from TB was achieved by 2005 but, despite this, probably 40 million have still died from the disease since 2000 and nearly 2 million are still dying each year. Additionally, TB is the leading cause of death of those living with HIV, as well as being the leading cause of death by infectious disease worldwide [1].

Meanwhile all targets so far set specifically for MDR-TB have been missed by significant margins and the death toll of this part of the pandemic is growing [8]. It has further been forecast that 75 million lives will have been prematurely lost to MDR-TB by 2050 [2] mostly in Africa and South Asia. What is of real concern is that there is currently nothing in the way of affordable clinical options to counter this latter threat at the necessary scale where needed.

Recent estimates suggest that around half a million new cases of MDR-TB are now emerging annually [1] adding to a currently un-estimated accumulation of prevalent cases. Given the paucity of diagnostic capacity in many countries with the highest burdens of TB it is also possible that many national estimates may be conservative. Most MDR cases will be infectious until they are either cured (doing so in fewer than 70,000 cases annually according to recent reports) or die (of which there are no current accurate numbers available). Without treatment the average duration of an active TB infection is conservatively estimated to be around 3 years [11], and a single infectious case is estimated to potentially infect between 10 and 15 people in any given year. That these drug-resistant strains of disease are growing where there is least capacity to respond to them is beyond debate, but the specific threat to low-income countries has yet to be properly assessed and addressed by the global authorities.

A further definitive category of TB is 'programmatically untreatable TB'. Given the wide variability of resource available globally to treat MDR-TB, this effectively defines any strain of TB in terms of the quality and quantity of critical resource available to diagnose and treat it. Since at least 70% of MDR-TB is undiagnosed and untreated, this category of 'programmatically untreatable disease' may seem clinically vague but from the perspective of those infected it is perhaps the most pertinent, not least because it is estimated that 98% of the annual 1.7 million TB deaths worldwide currently occur amongst the poor [12]. Because of this, all new interventions need to be both low-tech and low-cost. This is even more the case for MDR-TB given the complexity for those strained national TB programmes treating MDR-TB compared with treating TB that is susceptible to first line TB drugs. It is therefore specifically in respect of MDR-TB that a low-tech intervention might be most helpful.

The global success rate of treating diagnosed MDR-TB cases is currently just 56% [1]. Meanwhile, with the estimated death rates from MDR-TB rising, the costs of treatment remain too high for developing countries [13]. Drug-resistance thus threatens the goal of defeating TB (which is currently being targeted by SDG3 (Sustainable Development Goal) to occur by 2030), while MDR-TB also accounts for at least a third of all AMR deaths [2]. This means that controlling MDR-TB is simultaneously a crucial component in containing AMR as well as in ending tuberculosis.

The UN has set country-specific targets for diagnosis and treatment of MDR-TB for all member nations dependant on current estimated disease burden [28], but achieving them is beyond the reach of almost all African countries as well as many in Asia, all of whom already have serious problems with MDR-TB.

Furthermore, signs already exist that two of the three targets for preventative treatment of TB are also off track and will not be met [1], [29]. It is logical therefore that the proportion of the TB pandemic that is currently drug-resistant will rise. (The Russian Federation, which has had an MDR-TB problem longer than any other country now reports MDR-TB occurring in over one-in-three new TB cases and should thus be seen as the potential future of this pandemic [30]).

1.3. The complexities of sub-clinical 'latent' TB that is MDR

It is estimated that about 1.7 billion people worldwide currently have latent TB infections meaning that nearly a quarter of humanity has been infected with TB through an infectious contact [14]. These infections are effectively 'walled off' by a host immune response, the mycobacteria disabled from replication but still surviving within tiny granuloma, neutralised and effectively reduced to being sleeper cells of infection which can break out at any opportunistic moment. These 1.7

billion people thus provide the feeder pool from which around 10 million new TB cases persistently emerge each year [1], a cycle which is proving challenging to disrupt.

How many of these latent infections may be MDR? This fundamental question cannot be answered because it is currently impossible to tell whether a latent infection is drug-resistant until it reactivates and breaks out. A recent study in the Lancet [15] used mathematical modelling to estimate this, suggesting that in 2014 (the baseline year used) there were 19 million cases within this immense pool of latent infection who were multi-drug resistant. Another UK paper published in 2016 [14] had already suggested, however, that 10.9% of those who had latent TB carried a strain of disease that is mono-resistant to isoniazid. Isoniazid is the most frequently used therapy for treating latent TB, so this percentage amounted to nearly 200 million latent infections for which isoniazid preventative therapy would have been ineffective.

As a result of these estimates, the number of latent TB cases who are now being targeted for prophylactic treatment following last year's High-Level Meeting at the UN (and more importantly those who are prioritised for treatment) are of significant concern. The current UN target for preventative treatment of latent TB, set in 2018, is for at least 30 million cases of latent TB infection to be treated by 2022 [16]. This amounts to a massive increase in the number of latent TB cases who are currently being treated prophylactically (with the most recent WHO report recording that this goal is worryingly off target). [1].

It is self-evident that 30 million is a long way short of 1.7 billion, but the UN's target sensibly focuses on particularly vulnerable sub-groups – specifically children who are in close contact with infectious cases, along with other active close contacts, and also those living with HIV in high incident areas. These three sub-groups are considered to be at highest risk of reactivated disease, but (particularly because of their known compromised immunity and more recent infection) they also simultaneously carry a higher risk of their latent infection being MDR [14], [17]. This makes for a huge clinical challenge that will be discussed in more detail later.

2. Japanese traditional moxa and tuberculosis

Moxa (or moxibustion) comprises the smouldering of a preparation of dried mugwort leaves (*Artemisia princeps*) on or over the skin [18]. It should be noted that the umbrella terms 'moxa' and 'moxibustion' are commonly used to apply to a variety of approaches and techniques. Most involve the smouldering of dried mugwort, with occasional references to immunomodulatory effects, but few reflect the techniques traditionally used in Japan, nor the specific method discussed in this paper.

In this paper the term 'moxa' exclusively refers to the Traditional Japanese Moxibustion (TJM) technique of smouldering tiny 1 mg 'cones' of refined mugwort leaves on specific acupoints until the patient feels the heat (at which point the moxa is snuffed out).

This photo shows a Ugandan TB patient self-administering the tiny moxa at the key acupoint on his leg.

It is this particular style of moxa therapy that is being proposed as being potentially appropriate to help treat MDR-TB, a suggestion that is based on documentary and scientific evidence of moxa use in Japan at the height of its TB epidemic in the immediate pre-antibiotic era [4] as well as the results of recent research in Uganda [19] and associated research on both MDR and latent TB cases conducted in the DPRK, which is so far unreported but is recorded below.

It is widely recognized in Japan that TJM can provoke a host immune response in an immune-deficient patient [20]. Whilst this was first scientifically established in Japan in the pre-antibiotic era (including contemporary claims that it promoted recoveries from TB) these reports are now strongly supported by the evidence from the following three recent studies on TB, the first of which was published in 2018.

3. Moxa and drug-susceptible TB: the results of a Ugandan RCT

This randomized-control trial (RCT) was conducted by Makerere University in collaboration with and sponsored by the Moxafrica charity [19]. It compared two groups of 90 drug-susceptible pulmonary TB patients, one assigned to an adjunctive low-dosed self-administered moxa protocol alongside the standard WHO-approved first line drug therapy, the other to the same drug therapy over the same period.

The adjunctive moxa group was found to respond to their drug therapy faster in terms of sputum conversion rates, with a higher number of successful treatment outcomes. There was simultaneous evidence of better adherence to TB drugs, along with complementary signs of immune reconstitution. Similar (but slower) responses were also seen in TB cases who were co-infected with HIV. This latter finding was of particular relevance given the impact of HIV co-infection on TB incidence and mortality in Africa.

These responses, however, related only to low dose adjunctive moxa therapy in drug-susceptible cases. In other words, neither the older Japanese evidence nor the Moxafrica/Makerere Ugandan study could provide any direct evidence of moxibustion's possible benefit for MDR-TB.

This study report thus concluded that these results identified an urgent need to investigate the usefulness of moxibustion as a tool for helping treat drug-resistant TB (again including cases of co-infection with HIV) adding, however, that a higher dosage of moxa might be needed to compensate for the relatively weaker second line drugs.

4. Moxa and MDR-TB: unpublished research results from North Korea

There is now unpublished evidence of positive effects from adjunctive TJM on reactivated MDR-TB disease reported by the Ministry of Public Health in the DPRK (North Korea).

North Korea has a very serious problem with MDR-TB, afflicting its undernourished and vulnerable population at scale. North Korean TB experts became aware of the Ugandan study's results soon after its completion, and (given their familiarity with Traditional East Asian Medicine including moxa) invited the Moxafrica charity to present the Ugandan findings. They then quickly (in 2017) implemented their own research comparing a total of 64 MDR-TB patients, half treated with a higher dosed adjunctive moxa protocol and the other half a control group only given the standard second line drug treatment (i.e. this research used the higher treatment dosage initially used by Dr Hara in Japan in the pre-antibiotic era; a maximum of seven cones daily on ten points, two on the lower leg and eight on the lower back).

The fact that these original data are unpublished and remain unvalidated must be noted (and regrettably we do not have access to the individual raw data because we were not actively involved in this research). Nevertheless the authors (and the Moxafrica charity) consider them to be of potential importance and, given that the Moxafrica charity was given specific permission to share as it sees fit and key results provided are given in the following graphs.

Fig. 1a suggests that the MDR-TB patients experienced a reduction of TB-related symptoms during their therapy, with Fig. 1b showing that these reductions manifested more rapidly in the group receiving moxa.

Fig. 2a shows that treatment success rates (as defined by the WHO [13]) were significantly higher in the moxa group. Fig. 2b shows a significant median weight increase in the moxa group compared with a median weight loss in the no-moxa patients.

If these original unpublished data could be validated in other populations and then extrapolated against current global MDR-TB success rates, the results in Fig. 2a suggest that the current success rate of 56% for MDR-TB [1] could possibly be increased to 79% with adjunctive moxa (a rate not far short of the current 81% global success rate for treating drug-susceptible TB). If this sort of outcome improvement were corroborated by further research, it suggests that a significant
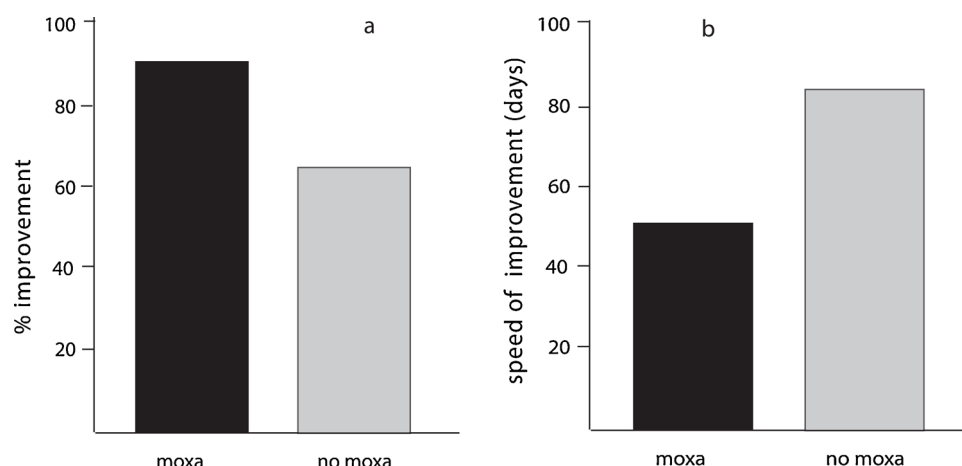
Fig. 1. XXX.

epidemiological impact could be made on the burgeoning MDR-TB epidemics in low-income countries before they become entrenched, as well as in existing hotspots of MDR-TB in middle-income countries (Photo 1).

5. Moxa and latent TB: original data from further unpublished North Korean research

The North Korean Ministry of Public Health also launched a second lengthier study to review the prophylactic use of moxa as a tool to reduce the cycle of TB re-infection. This study reported on disease re-activation rates in individuals with confirmed latent TB who were in close contact with 'smear-positive' (i.e. potentially infectious) pulmonary TB cases. Such contacts are known to be at higher risk of re-activated disease.

Again, the fact that these original data are unpublished and remain unvalidated must be noted (and regrettably again we do not have full access to raw data) but may have potential importance.

A total of 294 close contacts were monitored over twelve months. Of these, 152 used a daily dose of small cone moxa at a single acupoint (St36 *Zusanli*) for a three month period (maximum seven cones daily), with a further 142 close contacts of infectious cases using the standard WHO-approved isoniazid preventative therapy (10 mg/kg per day) for a period of six months. A low-dosed moxa protocol was thus being tested directly against the most commonly used WHO-approved preventative

therapy. The numbers of reactivated TB disease in the two groups were then compared after a 12-month period to see if there were any differences in rates or reactivated disease.

The study's final results are expected in 2020, but preliminary unpublished original data provided to Moxafrica suggested no differences in the numbers of reactivated disease in the two groups (with a 1.31% and 1.41% incidence rate in each group respectively). In other words, moxa appears to be neither worse nor better in preventing reactivation of disease from latency than standard isoniazid preventative therapy.

They further reported a 'trend' of raised WBCs and lymphocytes in the moxa group, suggesting (again) that moxa provokes a host immune response that is beneficial in TB infection, but this time doing so at an early sub-clinical stage of disease rather than after reactivation into clinical disease.

Preliminary immunological data pre- and post-treatment for the moxa group are given in Table 1.

An immediate issue can be seen with the low numbers serologically tested, along with the fact that no comparative haematological data for the control isoniazid group was provided. The explanation for this was simple: there was only enough chemical reagent to test 20 of those 294 studied because the national TB programme had no supplies of drugs and diagnostics.

Nevertheless, despite these small numbers, the leader of the research reported to Moxafrica that their laboratory studies "were particularly trending elevated lymphocytes", and on this basis (along with
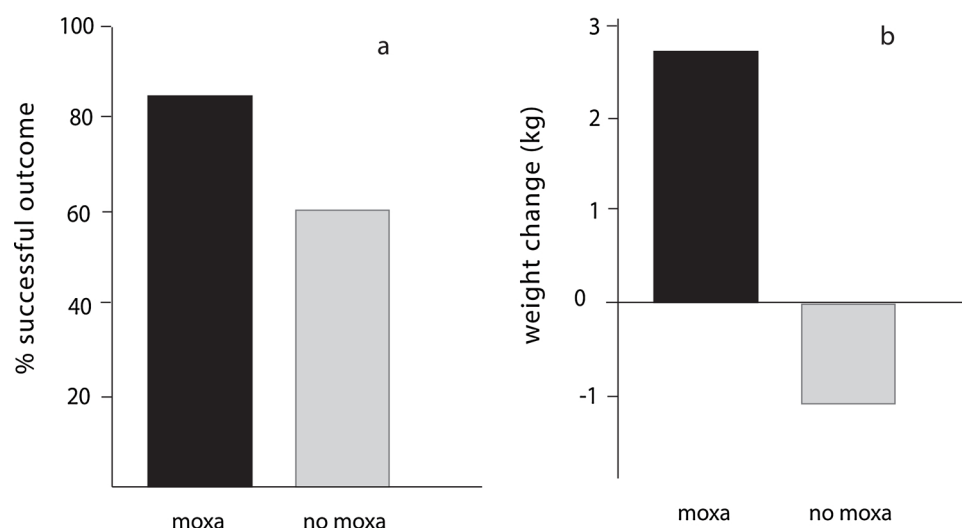

Fig. 2. XXX.

Photo 1. XXX.

Table 1
Hematological change (n = 20).

WBC(M ± SD,G/L)		Lymphocyte(M ± SD,%)	
Pre-treatment	Pre-treatment	Pre-treatment	Pre-treatment
5.7 ± 1.5	6.6 ± 1.3	22.7 ± 1.0	27.9 ± 4.9

their other data) he stated that the intention was to begin to roll out the use of moxa in the DPRK as a preventative therapy.

6. Discussion

Interest in immunomodulation for treating cases of *M. tuberculosis* has revived in recent years [21], both for the development of vaccines with post-exposure efficacy and also as adjuncts to drug therapy, but investigations so far have proved technically complex, potentially expensive, fraught with safety issues and largely disappointing [22].

Any safe and effective immunomodulation for treating *M. tuberculosis* needs to meet specific criteria. It must firstly be appropriately broad and/or balanced because of the dynamic interaction between the host and the TB mycobacterium (with the bacteria at times understood to capitalise from the host immune response). As such, stimulating the expression of high levels of particular immune cells at specific stages of disease progression can be pathology-generating rather than therapeutic. Likewise, generating high levels of antigen-specific immune cells may not help a patient if the response to them is blocked by the pathogen (something which is also believed to be the case at particular stages of the disease).

This need for both a balanced and broad response appears to be exactly what has made immunomodulatory research for TB such a challenge. A consistent theme in the existing investigations into immunomodulatory treatments for TB has concerned the fact that effects are either too strong and therefore potentially dangerous, or too transient to be clinically useful. This issue is certainly a problem for an immunomodulatory vaccine, for instance, where a single effective safe

dose needs to last for as long as possible, but it is not the case for T&CM moxa therapy for the following reasons.

Firstly, it can still be suggested (particularly given the slow-replicating nature of TB infections) that provoking a low-level and balanced inflammatory response could be beneficial to patients whose response to infection is implicitly low (e.g. in immune-compromised cases). The responses and the safety profile of the moxa therapy used in both Uganda and North Korea certainly support this possibility both in sub-clinical and reactivated disease, and the long-term traditional use of moxa therapy in Japan further testifies to its general safety.

Secondly, daily 'transient' low-dosed moxa therapy is traditionally accepted to be the norm in terms of treatment delivery (in fact there is a centuries old tradition of daily moxa therapy for health and longevity in Japan [18] which may be related to the promotion of Heat Shock Proteins [23]).

Thirdly, its application is implicitly low-tech, traditionally being either self-administered or administered by a family member, meaning that regular treatment can be extremely cheap and easy to administer.

Given that this style of moxa now has documented clinical evidence of benefit for TB patients, it suggests that low-to-moderate daily stimulation of a broad immune response is both safe and potentially effective with TB. As such the issue of transient effect turns out to be an intrinsic strength for moxa because daily low dosages are normally applied, apparently creating a cumulative and broad immunomodulatory effect, doing so at a low cost by being safely and practically administered by the patients themselves or by family members.

As previously discussed, whilst there are several drugs used to treat latent infections, there is currently no approved treatment for latent TB which can cope with multi-drug resistance. In all such cases the approved preventative therapies cannot reasonably be expected to be of benefit, with six months of ineffective antibiotic treatment potentially leaving an infected patient in a weaker state which may provide a surviving drug-resistant infection more opportunity to reactivate rather than less. In other words, successfully meeting the target (of treating 30 million latent cases by 2022) may end up stoking the MDR-TB pandemic at the same time as it may successfully reduce incidence of drug-susceptible TB.

A practical method to strengthen non-specific host immunity could provide a solution to this clinical dilemma and the above original unpublished data from North Korea suggest that moxa, as a cheap and easily implemented treatment, might help. If used alongside existing treatments it could both aid recovery from active disease and reduce the risk of promoting MDR-TB. This explains why moxa has been adopted in North Korea for prevention of TB – not simply because they have problems with supply of drugs but also because they have a lot of latent MDR-TB and they know that their only pharmaceutical option (if available) will not work in such MDR cases. Their own data now suggests that moxa works as well as isoniazid in preventing activation of TB (both 'normal' and drug resistant) and so could help staunch their MDR epidemic at less than US $10 per patient alongside isoniazid or on its own.

Without detailed reporting of the DPRK studies in peer-reviewed journals, however, (something which has so far proved impossible) these results must, of course, be viewed with some scepticism. Given what they imply, however, this should not stop other parties testing the data elsewhere, particularly because control of drug-resistant tuberculosis is in crisis in all TB endemic countries.

Further research (ideally in high-incidence MDR-TB hotspots) is now necessary, to examine disease reactivation rates in close contacts using isoniazid preventative therapy (IPT) on its own, compared with IPT plus adjunctive moxa. Longitudinal monitoring of incidence of both TB and of MDR-TB could then be undertaken.

The general aim of any further research into reactivated MDR-TB, meanwhile, would be to test whether improved outcomes in treating MDR-TB (currently reported globally as low) can be achieved using

adjunctive moxa. Data on the following would require measurement:

1. Treatment outcomes in MDR patients using moxa and TB drugs compared with outcomes of patients using TB drugs alone (using WHO standard definitions of treatment outcomes);
2. Treatment outcomes of cases confirmed at time of MDR-TB diagnosis as also being HIV positive (HIV co-infection being a hallmark of the African TB epidemic and a main reason for the high mortality rates for the region);
3. Side-effects of treatment;
4. Drop-out and/or relapse rates amongst the moxa patients;
5. Measurements of immune markers, general well-being, monitoring of weight changes etc.

Any such future study of adjunctive moxa for MDR-TB can be developed directly from the RCT previously conducted by Makerere University [19] and from the original unpublished data provided from the DPRK research. For practical purposes such research should only include MDR-TB patients with bacteriologically confirmed pulmonary TB with the pharmaceutical treatment used also carefully defined.

The cheapest treatment (approved by the WHO) [24] for MDR-TB is currently the all-oral bedaquiline-containing shorter regimen. This consists of an intensive phase of 4 months (that may be extended to 6 months), and a continuation phase of 5 months (giving a total duration of nine to eleven months). Given the UN's demand that 1.5 million more MDR-TB cases must be treated by 2022 and the relative cost of meeting this demand, most TB endemic nations (both middle- and low-income) will choose to opt for this shorter injection-free protocol in order to treat as many patients as possible. While this regimen is not believed to be inferior compared to a longer more expensive regimen [25] it should be noted that the WHO's Guideline Development Group has nevertheless stated that current certainty in the evidence of the efficacy of this all-oral shorter regimen is still "very low" so treatment success rates may still be difficult to improve even while more patients are treated with this new regimen. The possibility that treatment outcomes might be improved by using moxa alongside this shorter for a tiny extra cost per patient is therefore compelling.

As such it is believed that moxibustion therapy used under research conditions should exactly mirror this nine-eleven month regimen, with the intensive phase using a higher-dosed daily moxa treatment (as historically used in Japan and now more recently in the DPRK) administered alongside any in-patient administration of MDR-TB drugs, and the continuation phase using lower-dosed daily moxa self-administered (as in the previous Ugandan study) by the patients themselves. Bacteriological confirmation of the infectivity of the patients could be monitored monthly while the patients are in the MDR-TB unit, and on a bi-monthly basis as out-patients.

Patient follow-up could be conducted for the following two years after completion of all therapy to check for relapse and monitor general health indices.

Given the prevalence of HIV in many high burden TB countries and its association with higher rates both of mortality and incidence with MDR-TB, it is strongly suggested that HIV cases should not be excluded from such research. In fact, such co-infected cases could be monitored as a sub-group particularly in relation to CD4+ T-cell expression, and ideally other immune markers could be regularly monitored as well.

In 2013 the UK government commissioned a series of reports into the possible impact of AMR on the global economy. The study was led by world-renowned economist Lord Jim O'Neill with the first report published in 2014 [2]. Along with the expected economic forecasts, the team broke down their mathematical models into different categories defined by types of AMR infection. They thus estimated the numbers of anticipatable premature deaths from each infection by 2050, using existing WHO estimates as their baselines. This included predictions about MDR-TB given that it is the most prevalent AMR infection and also the most frequent cause of death.

Their report predicted that, on current trends, 75 million lives may be prematurely lost to MDR-TB by 2050, mostly in Africa and South Asia. As already discussed, diagnosis of MDR-TB is currently deficient in all TB-endemic countries, and variable depending on local health infrastructure. While most MDR-TB cases never see bacteriological confirmation of their disease let alone treatment, even of those who do, most only see confirmation of resistance to one drug (rifampicin) because of the limit of available drug-susceptibility testing [1]. Drug-susceptibility testing to all groups of anti-TB drugs, which is always required in high-income countries, is relatively rare in TB endemic ones (i.e. treatment is generally begun without full bacteriological confirmation - an approach which is guaranteed to promote drug-resistance in the longer term). Moxa might help fill this resource gap until better diagnostic solutions are found, by reducing infectivity and symptoms, and by promoting recoveries.

Such implementation would be fully in line with WHO policies. Recent years have seen a rise in interest into research into Traditional and Complementary Medicine (T&CM) worldwide, a trend which has been recognized and endorsed by both the WHO [31] and the G20 [32]. Acceptance of T&CM is still handicapped, however, by persistent deficiencies in credible data. Better data on therapies such as moxa could be of benefit to WHO Member States both by better elucidating the landscape of T&CM and each country's relation to it, and simultaneously benefitting vulnerable patients. Such research could be particularly important for any country which is culturally unfamiliar with any particular T&CM (as is the case with an East Asian traditional therapy like moxa in any country in the African region).

In respect of this, the Director of WHO's Department of Service Delivery and Safety, Edward Kelley, recorded in the WHO's 2019 Global Report on Traditional and Complementary Medicine [31] that, *"It is clear that the role of traditional medicine in meeting the health needs of populations has come to the fore, and this report is another call to harness its potential to contribute to UHC and the SDGs through primary health care."*

Developing any new drug normally takes years and billions of dollars of investment. Despite treatment of tuberculosis having been regularly shown to be of huge national economic benefit [26], research into TB has nevertheless been lacking because of low expectations of significant profit by drug companies. The development of any biomedically orthodox pharmaceutical response to this crisis thus now requires enormous incentives from governments of richer countries, some of which are currently stalling or generally reducing their support for developing nations. At the same time, there is growing evidence that the effects of climate change will have significant negative impact on poorer countries (especially in Africa) in terms of individuals' health and host immunity [27], not least because of fragile and diminishing nutritional resources the reduction of which will in turn negatively impact on immune responses to infectious diseases (including tuberculosis).

Table 2 identifies critical factors in this pandemic in this perspective, comparing categories of TB, global incidence, treatment durations, average total costs of treatment, add-on moxa costs, existing success rates and possible improvements in these rates with moxa added.

It further compares potential treatment success rates with and without adjunctive moxibustion both for drug-susceptible tuberculosis (including with HIV co-infection) and MDR-TB.

7. Conclusions

There is universal agreement that MDR-TB control is in crisis. It is likely that the proportion of the TB pandemic that is currently drug-resistant will rise and the number who already suffer from no treatment at all because of lack of diagnosis and treatment of MDR-TB in low income countries (and therefore in most cases die) will increase. Moxa could contribute to slowing these increases down, potentially preventing many deaths which are currently otherwise inevitable.

Developing the necessary evidence base with a view to integrating a

Table 2
Summarising critical factors.

	DS-TB	MDR-TB
Resistant to:	No resistance to drugs	2 strongest first line drugs
Global news cases p.a.	c. 10 million	c. 0.5 million
Treatment time	6 months	9-24 months
Treatment cost (total) [1]	US$973	US$6,430
Add-on moxa costs	<US$10	c. US$20-30
Existing global success rates (2018) [1]	81% (all cases) 78% (TB + HIV)	56%
Potential improvements in treatment success rates with adjunctive moxa	88% (all cases) 88% (TB + HIV) (*extrapolated from Ugandan study data*)	79% (*extrapolated from DPRK study data*)

T&CM practice like moxa into national health systems could see it rapidly regulated and safely practised alongside and complementary to orthodox biomedicine in order to improve treatment outcomes. A compelling argument can thus be made for further urgent research into moxa for MDR-TB, and this would be fully coherent with existing published WHO policies.

Finally, as is well known, MDR-TB is not the only anti-microbial resistant infection that threatens human health. Others include HIV/AIDS, malaria, sexually transmitted diseases, urinary tract infections, pneumonia, blood-stream infections and food poisoning. This opinion paper has only addressed TB but, given that all of these others also occur extensively in low-resource settings, should the potential benefit of a low-tech T&CM intervention such as moxa be demonstrated, then others that may also help might be more readily considered to help fill these other widening gaps in treatment provision.

Funding

Author contributions

MY conceived the concept. MY and JC wrote/edited the manuscript and agreed for submission

Declaration of Competing Interest

Both authors confirm that there have been no involvements of any kind (financial or otherwise) that might raise the question of bias in the work reported within this opinion piece, nor in its conclusions or the implications discussed within it.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eujim.2020.101072.

References

[1] WHO, Global Tuberculosis Report, World Health Organization, Geneva, Switzerland, 2019.

[2] J. O'Neill, et al., Review on Antimicrobial Resistance – Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations' – Chaired by Jim O'NeillJ. (2014) (last accessed 30th November 2019), https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

[3] Studies of tuberculosis and cholera, Encyclopedia Britannica, (2019) (last accessed 30th November 2019, www.britannica.com/biography/Robert-Koch/Studies-of-tuberculosis-and-cholera.

[4] S. Hara, Recovery Tendencies of Tuberculous Animal Treated With Moxibustion 22 Fukuoka University Fukuoka Univ. Med. J, 2016, p. 5 (originally published in 1929). (In Japanese.).

[5] N. Rosenblatt-Farrel, The landscape of antibiotic resistance, Environ. Health Perspect. 117 (June 6) (2009) A244–A250.

[6] E.C. Hett, E.J. Rubin, Bacterial growth and cell division: a mycobacterial perspective, Microbiol. Mol. Biol. Rev. 72 (1) (2008) 126–156, https://doi.org/10.1128/MMBR.00028-07.

[7] D.E. Goldberg, R.F. Siliciano, W.R. Jacobs Jr, Outwitting evolution: fighting drug-resistant TB, malaria, and HIV, Cell 148 (6) (2012) 1271–1283, https://doi.org/10.1016/j.cell.2012.02.021.

[8] M. Young, Blowing in the Wind: Drug-Resistant TB and the Poor, Moxafrica, 2014.

[9] World Health Organisation, Treatment of Tuberculosis: Guidelines for National Programmes, WHO, 2020 / (last accessed 7th January 2020) https://www.who.int/tb/features_archive/new_treatment_guidelines_may2010/en.

[10] T. Cohen, J. Manjourides, B. Hedt-Gauthier, Linking surveillance with action against drug-resistant tuberculosis, Am. J. Respir. Crit. Care Med. 186 (5) (2012) 399–401, https://doi.org/10.1164/rccm.201203-0394PP.

[11] Edine W. Tiemersma, Marieke J. van der Werf, Martien W. Borgdorff, Brian G. Williams, Nico J.D. Nagelkerke, Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review, PLoS One 6 (4) (2011) e17601, , https://doi.org/10.1371/journal.pone.0017601.

[12] J. Kim, A. Shakow, A. Castro, C. Vande, P. Farmer, Tuberculosis Control, World Health Organisation, 2019 (last accessed 30th November 2019), https://www.who.int/trade/distance_learning/gpgh/gpgh3/en/index5.html.

[13] Medecins Sans Frontieres, TB Drug Remains Too Expensive Despite New Price (last accessed 7th January 2020), https://www.doctorswithoutborders.org/what-we-do/news-stories/news/tuberculosis-drug-remains-too-expensive-despite-new-price.

[14] R.M.G.J. Houben, P.J. Dodd, The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling, PLoS Med. (2016), https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002152.

[15] G. Knight, C.F. McQuaid, P.H. Dodd, R.M.G. Houben, Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling, Lancet Infect. Dis. 19 (8) (2019) 903–912, https://doi.org/10.1016/S1473-3099(19)30307-X.

[16] United Nations, Political Declaration of the High-level Meeting of the General Assembly on the Fight Against Tuberculosis, (2018) - see paragraph 25. (last accessed 30th November 2019) https://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3.

[17] N. Saldanha, K. Runwal, C. Ghanekar, S. Gaikwad, S. Sane, S. Pujari, High prevalence of multi drug resistant tuberculosis in people living with HIV in Western India, BMC Infect. Dis. 19 (1) (2019) 391, https://doi.org/10.1186/s12879-019-4042-z.

[18] M. Young, The Moon Over Matsushima: Insights Into Moxa and Mugwort, Godiva Books, UK, 2012.

[19] I. Hood, et al., Adjunctive moxibustion treatment for tuberculosis: a randomised clinical trial investigating potential efficacy and comparative safety, Eur. J. Integr. Med. 20 (2018) 90–97 https://www.sciencedirect.com/science/article/pii/S1876382018301690.

[20] K. Tohya, et al., Literature documentation of basic research on immunological effect by acupuncture and/or moxibustion treatment by the immunological research committee for acupuncture and moxibustion, Japan J. Acupuncture and Moxibustion 56 (5) (2006) 7670778(in Japanese, abstract in english).

[21] A. Zumla, M. Rao, E. Dodoo, M. Maeurer, Potential of immunomodulatory agents as adjunct host-directed therapies for multidrug-resistant tuberculosis, BMC Med. 14 (2016) 89, https://doi.org/10.1186/s12916-016-0635-1.

[22] T. Mark Doherty, Immunotherapy for TB, Immunotherapy 4 (6) (2012) 629–664.

[23] A. Murshid, T. Eguchi, S.K. Calderwood, Stress proteins in aging and life span, Int. J. Hyperthermia 29 (5) (2013) 442–447.

[24] WHO, Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-resistant Tuberculosis Treatment, World Health Organization, Geneva, 2020 Licence: CC BY-NC-SA 3.0 IGO, .

[25] A.J. Nunn, et al., A trial of a shorter regimen for rifampin-resistant tuberculosis, N. Engl. J. Med. 28 (March 13) (2019) 1201–1213, https://doi.org/10.1056/NEJMoa1811867 380.

[26] R. Laxminarayan, et al., Economic Benefit of Tuberculosis Control, World Health Organisation, 2020 (last accessed 7th January 2020), https://www.who.int/management/EconomicBenefitofTuberculosisControl.pdf.

[27] World Health Organisation, Climate Change and Health, WHO, 2018 (last accessed 7th January 2020), https://www.who.int/news-room/fact-sheets/detail/climate-change-and-health.

[28] Stop TB Partnership, MDR TB Diagnosis and Treatment Targets, (2019) (last accessed 30th November 2019), http://www.stoptb.org/assets/documents/global/advocacy/unhlm/2.%20UNHLM%20DR-TB%20Country%20Targets.pdf.

[29] Moxafrica, HLM Targets, (2019) Website blog 2019 – https://www.moxafrica.org/single-post/2019/08/07/ Latent-tuberculosis—the-invisible-plague (last accessed 30th November 2019).

[30] WHO, Russian Federation Tuberculosis Profile, World Health Organisation, 2019 (last accessed 30th November 2019), https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=RU&LAN=EN&outtype=html.

[31] WHO, Global Report on Traditional and Complementary Medicine, (2019) (last accessed 30th November 2019), https://apps.who.int/iris/bitstream/handle/10665/312342/9789241515436-eng.pdf?ua=1.

[32] G20 Information Centre, G20 Leaders' Declaration: Building Consensus for Fair and Sustainable Development, (2018) (See Paragraph 15)http://www.g20.utoronto.ca/2018/2018-leaders-declaration.html (last accessed 30th November 2019).