

Debate

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Critical reflections on evidence, ethics and effectiveness in the management of tuberculosis: public health and global perspectives

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Abstract

Background: Tuberculosis is a major cause of morbidity and mortality globally. Recent scholarly attention to public health ethics provides an opportunity to analyze several ethical issues raised by the global tuberculosis pandemic.

Discussion: Recently articulated frameworks for public health ethics emphasize the importance of effectiveness in the justification of public health action. This paper critically reviews the relationship between these frameworks and the published evidence of effectiveness of tuberculosis interventions, with a specific focus on the controversies engendered by the endorsement of programs of service delivery that emphasize direct observation of therapy. The role of global economic inequities in perpetuating the tuberculosis pandemic is also discussed.

Summary: Tuberculosis is a complex but well understood disease that raises important ethical challenges for emerging frameworks in public health ethics. The exact role of effectiveness as a criterion for judging the ethics of interventions needs greater discussion and analysis. Emerging frameworks are silent about the economic conditions contributing to the global burden of illness associated with tuberculosis and this requires remediation.

Background

As a disease with a known causal agent, pathogenesis, mode of transmission and predisposing factors, as well as an effective cure, the goal of eradication of tuberculosis (TB) should be a plausible one [1]. The decline of TB in the developed world in the mid to late 20th century gave rise to an expectation that this could be achieved. However, with changing socioeconomic conditions and the arrival of HIV/AIDS came an increase in the number of TB cases, a much higher risk of active (and therefore, commu-

nicable) TB, and the emergence of strains of TB resistant to available treatments and more likely to cause death.

At present TB is the world's leading infectious killer; 8 million people annually develop active disease and 2 million die from their disease [2]. The most vulnerable populations remain the poor, the homeless, people in and from developing nations, those with HIV infections, substance abusers and the prison population. As such, it is a highly stigmatized illness, and those most often affected have the

most limited access to necessary resources. Since TB regained its alarming profile and was declared a global emergency by the World Health Organization, there have been renewed and concentrated efforts for its control.

This renewed effort raises important issues relating to the just and humane treatment of persons with tuberculosis infections. This paper will discuss ethical issues in the control of tuberculosis. The paper will analyze the problematic issues entailed in the relationship between the effectiveness of therapy and justifications for the limitation of individual autonomy as applied in tuberculosis control. The analysis will draw on recent frameworks for the analysis of ethical issues in public health and standards of evidence assessment as articulated by proponents of evidence based medicine. Finally, the ethical implications of global inequities in health will be discussed as they relate to tuberculosis.

Discussion

Ethics

Efforts to control TB involve unique social and cultural concerns [3] as well as complex ethical considerations involving medical and public health ethics [4,5]. Traditional medical ethics focuses on the physician-patient relationship, and the preservation of autonomy and human dignity, and is very strongly individualistic in perspective. Public health ethics, on the other hand, focuses on populations and the protection and promotion of health in communities.

Tuberculosis control raises several issues including stigmatization of infected individuals, and the cultural [6] and economic consequences of acquiring TB [7,8]. One central ethical problem concerning TB control consists of balancing the patient's rights and autonomy with the protection of the public's health [9]. Interventions such as directly observed therapy, detention and mandatory treatment entail a substantial reduction of autonomy not customarily found in clinical medicine. On a larger scale, TB is also a human rights issue, raising important questions about equity regarding who suffers the most from disease, and the global imbalance with regard to disease burden as well as reciprocal social obligation to alleviate suffering [10]. Therefore, the evidential standard supporting tuberculosis intervention should be high, in order for interventions that infringe human rights to be justified both scientifically and ethically.

Individual rights vs. public health

Given its nature and impact, TB is indeed a serious threat to communities, which deserve protection from exposure to TB and attention to the means to curtail its spread. Simultaneously, individuals within communities, particularly those in liberal democracies, have the right to per-

sonal autonomy and privacy. Achieving a balance between these seemingly conflicting goals can only result from an understanding of the underlying ethical principles [11]. It is possible to justify breaches of civil liberty when the goal is to prevent harm to the community, and the means to achieve this end are ethically and legally appropriate [12]. However, if individuals are required to sacrifice their autonomy for the good of the community, then it is the community's responsibility to attend to the individual's health requirements and to support and facilitate the discharge of the individual's obligations [13].

Public health ethics

There has been a recent expanded interest in the relationship between public health and ethics. In the last years, several commentators have provided frameworks for the analysis of ethical issues in public health. As tuberculosis control is one of the primary concerns, both of historic and modern public health, it is instructive to see the extent to which the frameworks articulated for public health ethics match up with the current provision of tuberculosis care. In particular, two frameworks will be evaluated in terms of their relationship to tuberculosis and ethics.

Nancy Kass, in the American Journal of Public Health, articulated an ethics framework for public health [14]. In this framework, there are six primary questions that need to be answered.

1. What are the public health goals of the proposed program?
2. How effective is the program in achieving its stated goals?
3. What are the potential burdens of the program?
4. Can burdens be minimized or are there alternative approaches?
5. Is the program implemented fairly?
6. How can the burdens of the program be fairly balanced?

A second framework articulated by Childress et al. enumerate five considerations that need to be weighed when considering the ethical dimensions of public health action [15]. These include effectiveness, proportionality, necessity, least infringement and public justification.

Both of these frameworks share significant overlap but it is important to note that among the primary considerations in each of these frameworks are effectiveness and

what can be termed least restrictive means. Effectiveness in these frameworks relates to the published scientific evidence indicating that any proposed intervention will do more good than harm. Neither framework states a standard of effectiveness that should be met. Kass writes: "As a rule of thumb, the greater the burdens posed by a [public health] program – for example, in terms of cost, constraints on liberty, or targeting particular, already vulnerable segments of the population – the stronger the evidence must be to demonstrate that the program will achieve its goals" [14].

The concept of an evidence hierarchy as articulated by proponents of evidence based medicine is not mentioned, but may serve as a useful and increasingly agreed upon standard of the strength of evidence required to justify a public health program. Such a hierarchy was initially introduced as a means of evaluating preventive health care. Evidence hierarchies regard systematic reviews and randomized trials as providing stronger evidence than observational studies and expert opinion [16]. In terms of tuberculosis management, then, programs that impose burdens such as curtailing individual freedoms should come from as high as possible on this evidence hierarchy in order to be regarded as both scientifically and ethically justified.

The concept of least infringement or the minimization of burdens and use of alternative approaches indicate the need for proportionality of public health response to public health problems. This will be discussed below.

The effectiveness of tuberculosis interventions

The empirical research literature on tuberculosis can be regarded as complementary to an analysis of the ethical issues. Interventions that have the potential to impede autonomy or infringe upon established rights should have evidence of effectiveness. In terms of interventions, it can be argued that an approach to tuberculosis involving least restrictive means is an appropriate approach to tuberculosis care. A schema of least restrictive means in tuberculosis care would entail progression through the following steps.

- Self management
- Directly observed therapy (DOT)
- Provision of a therapeutic milieu
- Detention in a health care setting

Consequently, self-management assures the most autonomy and dignity and least intrusion in a person's life, whereas detention is decidedly autonomy denying. Hence there should be an evidence gradient with the highest

probable benefits provided for interventions that reduce or diminish autonomy and voluntariness.

Failure to complete an appropriate course of chemotherapy for tuberculosis is the chief cause of antibiotic resistance and a substantial cause of morbidity and mortality from tuberculosis. The successful administration and completion of a complex antibiotic regimen over prolonged periods of time has been problematic. As a consequence treatment regimens and programs incorporating direct observation as an integral component of chemotherapy have been developed and variously called DOT, or DOTS, when a shorter course of antibiotic therapy is employed within an overall TB control strategy. Direct observation, among other program elements is hypothesized to enhance and facilitate adherence and consequently improve treatment outcomes. For the purposes of our discussion, we are concerned with the requirement of direct observation of therapy by someone other than the individual with the disease, and not with the programmatic aspects of delivery programs such as political commitment, provision of medication, technical support (such as sputum microscopy) education, etc which arguably could be present for the management of other chronic and communicable diseases such as coronary artery disease and HIV/AIDS where patient adherence is problematic and direct observation is not advocated.

This logic underlies the WHO's recommendation of directly observed therapy as the international method of TB control and is supported by data reflecting decreased relapse and resistance rates as a result of its implementation [17]. A review of the DOTS strategy in six WHO regions extrapolated that DOTS can reduce deaths by TB and incidence of infection on the condition that detection and cure rates improved [18]. However, this analysis relied upon complex mathematical modeling and projections, and not only on direct empirical evidence of effectiveness from randomized trials. DOTS implementation in India in 1993 has led to a significant increase in case detection and treatment [19]. Limitations on its success in India and potentially other low-income countries with high disease burden include regional discrepancies in the functioning of health services, and the degree of private sector regulation. A randomized trial of DOTS in Pakistan did not demonstrate its superiority over self-administered treatment, which was thought to be a reflection of the overall state of health care delivery in Pakistan and decentralized care [20]. This study, however, was conducted perhaps too soon after implementation of DOTS in Pakistan to effectively evaluate its impact [21].

However, directly observed modes of therapy may not always be superior to self management and the problems of determining a priori which patients will fail to adhere

to therapy calls for reflection on both the autonomy denying aspects and potential harms of such therapy and on the all embracing designation of all people in some nations as requiring directly observed therapy programs [22]. A recent Cochrane systematic review concluded that "randomized trials provide no evidence that directly observed therapy in low and middle income country settings improves cure or treatment completion rates in patients with tuberculosis" [23].

The results of providing a "therapeutic milieu" of mental health techniques to both foster behavioural changes and to increase adherence and address some other health concerns of the patients in an inpatient setting were favourable. Outcomes included an increase in compliance, with the majority of patients discharged to complete treatment in an outpatient setting [24]. It is important to realize that efforts are required to enhance adherence to tuberculosis treatment, including increasing the level of community support available to patients. A growing literature on incentives has identified effective strategies [25]. The evidence, though is far from complete and further research is required.

Detention of TB patients is generally considered a method of last resort [26]. A New York study found that regulatory orders were written on 4% of 8,000 patients known to have tuberculosis [27]. A history of leaving the hospital against medical advice and previous noncompliance were the strongest indicators for regulatory intervention. The findings of a study of non-adherent TB patients in California indicate that detention measures target the homeless, substance abusers, the mentally ill and people in correctional facilities. 1.3% of patients were detained. Furthermore, while 84% of detained patients completed treatment, only half of them did so within 12 months (thus reducing the risk of developing multi-drug resistant tuberculosis (MDRTB) and they were four times more likely than non-detained patients to be lost to follow-up after their release[28]. Therefore, the success of this measure is limited and may, in fact, lead to harm if detention leads to loss of follow-up.

In summary, although there is unequivocal evidence of the effectiveness of clinical treatment of tuberculosis, the empirical evidence under-girding public health support for direct observation is not overwhelmingly superior in terms of effectiveness. Evidence of effectiveness is sparse and becomes attenuated as one moves through more restrictive means of ensuring treatment adherence. There may be important and positive impacts thus far from an internationally recommended TB control strategy on global TB control, but this entails recognizing the ethical implications of imposing a strategy that lacks evidence of superiority on vulnerable populations in societies that

may lack infrastructure to effectively execute this strategy. If evidence of effectiveness is to be a *sine qua non* of the ethicality of public health programming, as noted in the frameworks above, then a debate must ensue in order to clarify support for such measures, particularly direct observation, with the recognition that it may not be superior to self-care.

The issue here is how we conceptualize and understand effectiveness, specifically as it relates to public health programs and the normative implications of how we understand effectiveness. As evidence-based medicine attracts increasing interest and support in the medical community, it is important to note that central to evidence-based medicine is the concept of an evidence hierarchy. These hierarchies give preference to systematic reviews and meta-analysis over non-randomized or observational study designs, as the latter form of inquiry can be biased particularly with regard to therapy.

The issues relating to the effectiveness of direct observation are controversial, as noted in a recent set of papers in the British Medical Journal. Arguments have been made suggesting that perhaps randomized controlled trials are not the gold standard for evaluating complex programs such as DOTS, which entail more than simply direct observation of therapy (DOT), and that the diminished autonomy entailed by DOTS is counterbalanced by its focus on supporting adherence [29]. However, the added benefit of DOTS in comparison to DOT have not been rigorously evaluated, and some have argued that RCT's are not the gold standard in this domain. Volmink and Garner have argued that : "Enthusiasts make the world go round, but there is a belief among specialists in tuberculosis that it is unethical not to provide direct observation. This attitude stifles debate and good research into alternatives to direct observation is replaced by semantics." [30]

Several points of debate require clarification. Why should more credence be given to a non-randomized trial over a systematic review that provides a concept of quality and has fairly precise and clear inclusion and exclusion criteria? If such other studies are to be preferred to a systematic review, then supportive arguments must be provided. Further there are specific normative consequences to this debate because any form of observed therapy is in principle, and in fact, autonomy denying, and the burden of proof to deny people the right to self-management must be correspondingly higher on those who believe studies based on less rigorous forms of evidence. Either public health effectiveness is defined in terms other than those articulated by evidence-based medicine, or another relevant ethical principle must be invoked to justify support of DOT that supercedes effectiveness. The current ethical frameworks do not provide such a trump.

Furthermore, there is a need for an open and critical discussion on the magnitude of difference or enhanced benefit that is needed for one therapy to be considered superior to another, particularly when individual liberties are in question. Such decisions cannot be made conditional on p values and confidence intervals alone, but instead require an open discussion on how much evidence and what types of evidence are required for such limitations of autonomy to be warranted. The extent to which those individuals and communities affected by high level policy decisions are to be involved in the discussions as to the acceptability of varied interventions is unclear.

Decisions to use autonomy reducing strategies in public health may be better justified by legal standards of sufficient evidence that are not necessarily commensurate with scientific concepts of evidence articulated in evidence-based medicine. Internationally, the Siracusa principles can be applied to public health interventions as a means of ensuring that restrictions of liberty and uses of coercion for public health ends are legitimate, legal, necessary, non-discriminatory and represent the least restrictive means appropriate to the reasonable achievement of public health goals [31]. Most would agree that TB control is a legitimate social goal and that it is necessary to conduct programs to achieve this end. Most democratic societies have legal structures that support and sanction public health action in the name of community protection [32]. Additionally, justifications for public health action that rely on the potential to minimize harms rather than guarantee of benefits may be more appropriate, provided there is a context of accountability and appeal [33].

Globally, there has been concern about how tuberculosis control measures have been applied. There are reports of increasing reliance on restrictive or coercive means to achieve public health goals, such as legislation passed in Russia to detain individuals for up to six months who fail to comply with screening, diagnosis and treatment [34]. The extent to which coercive measures are used for the control of tuberculosis around the world is unknown and represents a priority for empirical research in this area. Cultures vary greatly in their weight given in the balance between community goods and individual liberties. For example, sub-Saharan cultures have been characterized as more broadly communitarian than North American cultures [35]. Similar claims have been made for Asiatic cultures [36]. Of note the Singapore Tuberculosis Elimination program (STEP) includes the detention of "infectious recalcitrant defaulters" as a key component of its strategy [37]. As Doyal recently argued, coercive measures can only be justified when there is assurance that a strategy of minimal violation of autonomy in place and non-threatening treatment options available [38].

Equity and global imbalance

Unfortunately, many of the factors responsible for the conditions that create tuberculosis cannot be remedied by health care intervention. A concern for the ethics of tuberculosis that neglects these broader determinants of tuberculosis is insufficient to the task. If analysis of the relationship between evidence and effectiveness is restricted to the biomedical literature, it risks neglecting broader social and economic forces relevant to the tuberculosis epidemic. The current ethical and evidential frameworks under consideration do not address such issues leaving open questions as to their scope.

Social conditions that predispose to TB disease and its spread are well understood: over-crowding, inadequate housing, malnutrition, lack of timely access to medical care and medication, to name but a few. This makes it incumbent on public health systems to address these issues, and inter-sectorial strategies that address these broader determinants of health are to be encouraged [39,40]. TB remains a scourge of marginalised populations that continue to live in conditions that increase their vulnerability to TB, and have difficulty accessing comprehensive treatment and following it through to completion or education about their illness [41]. This reflects not only a failure of government and public health systems, but also a violation of their fundamental rights to basic medical care, as enshrined in Article 25 of the Universal Declaration of Human Rights.

It should also be acknowledged that globally, TB continues to have its greatest impact on developing nations that lack the infrastructure for even rudimentary TB control programs. TB poses the greatest threat to persons most likely to be unable to advocate for themselves. Their burden is exacerbated by ongoing economic disparities that are increasing dramatically [42]. These disparities make it difficult for many nations to address the fundamental conditions predisposing to TB without external aid, most of which comes with specifications regarding how the resources must be spent – including having to implement DOT. The disease burden thus remains largest for countries less equipped to implement internationally recommended strategies. Economic disparities create a situation in which generating the resources to even attempt remediation of the medical and social determinants of tuberculosis is thwarted by the control that more economically robust nations and trans-national corporations exert over developing nations [43]. Global public health demands an international collaborative approach and an acknowledgement of the health implications of the globalized economy, and global public health ethics demands advocacy to rectify the disparities that perpetuate tuberculosis [44]. Efforts to address TB control that ignore economic

conditions or require programs for vulnerable populations that reduce choice can be seen as further aggravating existing inequities.

Summary

Tuberculosis is a complex but well understood disease that raises important ethical challenges for emerging frameworks in public health ethics. The exact role of effectiveness as a criterion for the ethicality of interventions needs greater discussion and analysis. The silence of emerging frameworks on economic conditions contributing to the global burden of illness associated with tuberculosis requires remediation.

Competing interests

None declared.

Authors' contributions

Dr. Upshur originated the project and convened the writing team. Dr. Verma wrote the first draft and Drs. Benatar, Rea and Upshur contributed to each subsequent draft and approved of the final document. All authors stand as guarantors of the paper.

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