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Title

Triumph and Tragedy of 21st Century Tuberculosis Drug Development.

Permalink

<https://escholarship.org/uc/item/94m0r0rc>

Journal

The New England journal of medicine, 382(10)

ISSN

0028-4793

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Publication Date

2020-03-01

DOI

10.1056/nejme2000860

Peer reviewed

EDITORIALS



Triumph and Tragedy of 21st Century Tuberculosis Drug Development

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Since the discovery of the first antituberculosis drugs 75 years ago, the pursuit of a short, effective, and affordable regimen that has acceptable side effects and is capable of curing most patients most of the time has been a major public health priority. Such a “pan-tuberculosis” regimen is seen by many as essential in reducing the global tuberculosis burden.¹

The successful development of two new antituberculosis drugs — bedaquiline and pretomanid — represents an important step forward in the pursuit of pan-tuberculosis regimens fit for the 21st century. Conradie and colleagues now report in the *Journal* that when this all-oral regimen was combined with a third drug — linezolid, repurposed from its licensed indication for gram-positive bacterial infections — and given for 26 to 39 weeks to patients with extensively drug-resistant or complicated multidrug-resistant tuberculosis, it produced a favorable outcome in 98 of 109 patients (90%) at 6 months after the end of treatment.² Cure rates for extensively drug-resistant tuberculosis were less than 50% before the advent of new drugs.³ Therefore, this is a triumph, and the authors are to be congratulated for their vision and courage in tackling the most difficult-to-treat forms of tuberculosis.

The tragedy being confronted, however, is the overlapping realities of the persisting need for new regimens and the spectacular inadequacy of support for their development and the tools needed for their effective use in the field. Our current tuberculosis regimen was the product of a remarkable series of global, iterative, randomized, controlled trials conducted between 1947 and 1980.⁴ The resulting “short-course chemo-

therapy” was an oral regimen, containing rifampin, isoniazid, and pyrazinamide, that cured the large majority of people with tuberculosis if it was taken for 6 months. This regimen, despite known toxicities, has produced extraordinary gains, curing approximately 58 million people since the year 2000.⁵ However, 30 years of its global use has revealed the serious limitations of depending on a single, one-size-fits-all regimen to treat a challenging infectious disease.⁶ Predictable toxicities and the development of resistance are directly relevant to ongoing efforts to develop other regimens,⁷ including the new regimen studied by Conradie et al.

During the early global adoption of rifampin-based short-course chemotherapy, the possibility that resistance would become a barrier to ending the epidemic was considered unlikely. As a result, the development of accessible and affordable laboratory tools for the detection of drug resistance was not prioritized. Thus, when resistance did inevitably emerge, the tools to detect and manage it were too inefficient, too costly, and too far from the clinic to halt the spread of rifampin resistance. The acquisition of resistance is also a risk for the bedaquiline–pretomanid–linezolid regimen. Conradie reports one patient who had a relapse caused by bacteria with reduced susceptibility to bedaquiline. When this evidence is considered together with other reports of primary resistance to bedaquiline,⁸ along with the described toxicities of linezolid, the need for monitoring of the QT interval, and the residual uncertainty about hepatotoxicity of pretomanid,⁹ it suggests a risk of going back to where we started: a situation in which a pan-tuberculosis

regimen with known toxicities that are likely to result in pauses in or discontinuation of treatment is sent to the field without adequate tools for monitoring resistance.

The other major tragedy is that every year tuberculosis still affects approximately 10 million people and kills 1.5 million.⁵ In light of these figures, we should not be dependent on one small, single-group, single-country study for evidence of the efficacy of the newest tuberculosis regimen. The study was rigorously conducted and laudably designed to report on definitive outcomes of durable cure and relapse; however, such approaches for the development of tuberculosis regimens do not correspond with the magnitude of the problem. Tuberculosis does not present insurmountable hurdles for the conduct of clinical trials. Even the creation of multidrug regimens with new agents from different developers is feasible, as evidenced by the recent history of treatment for human immunodeficiency virus infection and hepatitis C, both of which have new regimens developed and defined through multiple large trials. In contrast and tragically, the majority of evidence available to the World Health Organization in 2020 as it formulates treatment guidelines for drug-resistant tuberculosis comes from noncomparative or observational studies.^{10,11} Such studies should serve as the adjunct to an evidence base of robust randomized, controlled clinical trials, rather than as its leading edge.

A rejuvenated program of innovative phase 2 and phase 3 clinical trials of new drugs and regimens, in conjunction with continued investment in tools for detecting and monitoring resistance, is required worldwide. It will take substantially greater investment and coordinated forms of collaboration among sponsors, industry, academic partners, and policy decision makers to develop and implement new evidence-based regi-

mens that are fitting for a disease that has killed hundreds of millions of people. Until that happens, if the current inadequate investment path is held, history is bound to repeat itself — and for all the jubilation that comes with developing a new effective regimen, there will be more tragedy yet to come.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe2000860

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Vaping-Induced Acute Lung Injury

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A number of environmental agents are known to cause acute or subacute inhalation injury to the lung parenchyma. Indeed, emergency response guidelines for medical personnel describe toxic

inhalation pneumonitis as a heterogeneous group of chemically induced injuries to the lung parenchyma as well as to the upper respiratory tract. The manifestations of such injury depend on the