DRUGS, DIAGNOSTICS, VACCINES, PREVENTIVE TECHNOLOGIES, RESEARCH TOWARD A CURE, & IMMUNE-BASED & GENE THERAPIES IN DEVELOPMENT

2016

PIPELINE REPORT

Tuberculosis Edition

TAG

i-base

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2016 PIPELINE REPORT

Tuberculosis (TB) Edition

DIAGNOSTICS, TREATMENT, PREVENTION, AND VACCINES
IN DEVELOPMENT

By Mike Frick, Erica Lessem, and Lindsay McKenna

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HIV i-BASE/TREATMENT ACTION GROUP

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ABOUT HIV i-BASE

HIV i-Base is a London-based HIV treatment activist organization.
HIV i-Base works in the United Kingdom and internationally to ensure that people living with HIV are actively engaged in their own treatment and medical care and are included in policy discussions about HIV treatment recommendations and access.

ABOUT TAG

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS.

TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

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THIS REPORT IS DEDICATED TO

Margie Garber-Steinberg
April 7, 1949 – April 14, 2016

This edition of the *Pipeline Report* is dedicated to Margie Garber-Steinberg, mother of long-time board member Jason Osher. Margie was a steadfast TAG supporter for well over a dozen years, and not only fought against the HIV/AIDS pandemic through her support and philanthropy, but also fought her own battle with cancer for ten years, undergoing two stem cell transplants and countless chemotherapies and drug combinations. She was a much adored wife, mother, grandmother, and friend. She was also a strong warrior, and showed us all how to continue to fight, despite the obstacles. Her love for TAG and its leaders, her humor, and her voice to end HIV/AIDS will be sorely missed.

THIS REPORT IS DEDICATED TO

Paul Blanchard
1964 – 2016

The 2016 *Pipeline Report* is dedicated to i-Base co-founder Paul Blanchard (1964 -2016). Paul played a unique role in establishing treatment activism in the UK, challenging doctors to continually update their views and practice with evidence from rapidly evolving research. Like many HIV activists Paul experienced the dramatic benefits of ART first hand when antiretroviral therapy was very new. He was one of the leading activists to recognize the need to use triple combination therapy to achieve optimal and sustained viral suppression and to avoid drug resistance, when UK guidelines – and many other UK HIV organizations – suggested fewer drugs might be sufficient.

Paul had a tremendous and steady intellect and a unique critical view that enabled him to comment on new advances and current practice with such masterly understatement that would make disagreeing with his conclusions extremely difficult.

He also had a wicked sense of humor, writing an article on the increases in "internet-related STIs" with a chuckle "because doctors love reading about this sort of thing" or commenting proudly on his own 7-drug salvage regimen in the late 90s that "none of them are made by Glaxo Welcome".

Paul will be deeply missed.

TABLE OF CONTENTS

The Tuberculosis Diagnostics Pipeline

By Erica Lessem

INTRODUCTION

Over the past decade, several new options for improving TB diagnosis have become available. The past year saw considerably more progress than the previous one. However, the reality of how most TB is diagnosed—or not—remains largely unchanged. The world failed to detect 3.6 million of the estimated 9.6 million new cases of TB in 2014.[1] Sputum smear microscopy—which misses over half of TB cases[2] and gives no indication of drug susceptibility to guide appropriate treatment—is still the diagnostic standard in most of the world, despite the availability of the far more sensitive GeneXpert MTB/RIF for six years.[3] Late in 2015, the World Health Organization (WHO) approved Alere's TB lipoarabinomannan (LAM) test—a very affordable, simple, rapid, noninvasive, point-of-care (POC) rule-in test for people with HIV with very low CD4 counts—but no country has begun to implement it yet. New versions of line probe assays—Hain's MTBDR*plus* and MTBDR*sl* and a product from Nipro—received WHO recommendation, facilitating rapid drug susceptibility testing (DST), but the world is still a long way from universal DST, with an estimated 59 percent of cases of multidrug-resistant TB (MDR-TB) undetected.[4]

Research and development (R&D) for TB diagnostics features some promising developments since last year (see table 1). Improvements on nucleic acid amplification tests (NAATs) such as GeneXpert Omni and Ultra and Molbio's TrueNAT are being validated, positioning them for possible WHO recommendation. Further upstream, encouraging research into gene sets that can predict active TB disease and reliably distinguish it from latent TB and other infections may eventually underpin new blood tests (currently, there is no effective serological test for active TB). Incremental advances are being made to improve detection of pediatric TB (see "Extending quality," page 133).

Yet, overall, with a mere US$65 million in 2014 funding out of an estimated annual need of $340 million,[5] the pipeline for evidence-based new diagnostics has largely remained stagnant (see table 2). Dismayingly, some companies continue to move forward with marketing for their products when the data are unavailable or scream that they should not, as is the case with Epistem, which is marketing GeneDrive in India despite the test's having flopped in studies.

With use of poor tests predominating, poor uptake of good extant options, poor evidence bases to support the introduction of new tests, and poor funding to support the development of better tests, it's no wonder we've made little headway in diagnosing TB.

Table 1. 2016 Tuberculosis Diagnostics Pipeline: Products in Later-Stage Development or on Track for Evaluation by the WHO with New Published Data or Policy Updates Since the *2015 Pipeline Report*

Test	Type	Sponsor	Status	Comments
MOLECULAR/NAAT				
BD MAX MTB assay	qPCR for MTB in automated BD MAX	BD	In 16 *M. tuberculosis* samples, 100% sensitivity, 97.1% specificity[6]	
Genedrive MTB/RIF	Portable RT-PCR for MTB + RIF resistance	Epistem	Worse sensitivity than smear [!] in 2016 study[7]	Marketed in India
GenoType MTBDR*plus*	Line probe assay for RIF + INH resistance	Hain Lifescience	WHO now recommends based on FIND evaluation[8]	WHO guidance pending
GenoType MTBDR*sl*	Line probe assay for FQ + SLID resistance	Hain Lifescience	WHO now recommends[9]	FIND's multicountry evaluation of MTBDR*sl* version 2.0 from 2015 still unpublished
MeltPro	Closed-tube RT-PCR	Zeesan Biotech	New study from China of 2,057 smear-positive TB patients shows sensitivity of detecting resistance to rifampin 94.2%, isoniazid 84.9%, ofloxacin 83.3%, amikacin 75.0%, kanamycin 63.5%[10]	
NTM+MDRTB Detection Kit 2	Line probe assay for RIF + INH resistance	Nipro	WHO now recommends based on FIND evaluation[11]	WHO guidance pending
RealTime MTB/ TB MDx m2000	Automated RT-PCR for MTB; can be added to HIV RNA platform	Abbott	Sensitivity 100%, 95% CI: 98.6–99.9 in smear-positive samples, similar to GeneXpert MTB/RIF[12]	
Truenat MTB	Chip-based NAAT with RT-PCR on handheld device for MTB	Molbio Diagnostics, Bigtec Labs	FIND and ICMR studies underway	
Xpert MTB/RIF Ultra	Next-generation cartridge-based detection of MTB + RIF resistance	Cepheid	FIND study results anticipated end 2016	
Xpert Omni	Single-cartridge mobile platform that can use single MTB/RIF or Ultra cartridge	Cepheid	FIND study pending but delayed	
Xpert XDR	NAAT	Cepheid	FIND study anticipated 2018	
ANTIBODY/ANTIGEN DETECTION				
Determine TB LAM Ag	Urine dipstick for TB LAM protein	Alere	WHO recommended use in people with HIV with CD4 count ≤100[13]	

CI: confidence interval
FLD: first-line drugs (isoniazid, rifampin, ethambutol, pyrazinamide)
FQ: fluoroquinolone
ICMR: Indian Council of Medical Research
INH: isoniazid
LAM: lipoarabinomannan
MDR-TB: multidrug-resistant tuberculosis
MTB: *Mycobacterium tuberculosis*
NAAT: nucleic-acid amplification test
qPCR: quantitative polymerase chain reaction
RIF: rifampin
RT-PCR: real-time polymerase chain reaction
SLID: second-line injectable drug (e.g., amikacin, capreomycin, or kanamycin)
WHO: World Health Organization

Table 2. Later-Stage or Marketed TB Diagnostic Test Candidates with No New Published Evaluation Data

Test	Type	Sponsor	Status
MOLECULAR/NAAT			
EasyNAT	Isothermal DNA amplification/lateral flow to detect MTB	Ustar	No new data since poor in Tanzanian field study[14]
FluoroType MTB	Semiautomated direct MTB detection; PCR in a closed system; results in 3 hours	Hain Lifescience	Marketed
FluoroType MTB RNA	MTB RNA for monitoring of anti-TB therapy	Hain Lifescience	No published data
GeneChip	RT-PCR for RIF + INH DR	CapitalBio	Marketed
LATE-PCR with Lights-On/Lights-Off Probes + PrimeSafe	Single-tube PCR to detect MTB, resistance to INH, RIF, EMB, SLID	Hain Lifescience/Brandeis University, Stellenbosch University	No published data
LiPA pyrazinamide	Line probe assay for PZA resistance	Nipro	Marketed
PureLamp	Manual NAAT by loop-mediated isothermal amplification for MTB detection	Eiken	WHO June 2015 review impeded by data quality issues; guidelines development group reexamined evidence January 2016; recommendations expected June 2016
REBA MTB-MDR	Line probe assay for RIF + INH resistance	YD Diagnostics	No new data; marketed
REBA MTB-XDR	Line probe assay for FQ + SLID DR	YD Diagnostics	No new data; marketed
TREK Sensititre MYCOTB MIC plate	Dry microdilution plate to detect MICs for FLD + SLD (except PZA)	TREK Diagnostic Systems, Thermo Fisher Scientific	No new evaluation data but used in study in Cameroon[15]
TRC Rapid MTB	Automated rapid rRNA to detect MTB	Tosoh	No new data
VOLATILE ORGANIC COMPOUNDS			
Giant African pouched rats (Cricetomys gambianus)	Trained sniffer rats to detect MTB in sputum	Apopo Foundation	No new data
AUTOMATED IMAGING			
CAD 4TB	Digital CXR for TB screening	Delft Imaging Systems	Marketed; in 2016 WHO to review available evidence on computer-aided radiographic TB detection and organize a scoping meeting to determine research needs and if guidelines should be developed[16]
ANTIBODY/ANTIGEN DETECTION			
MBio Array System	POC cartridge to measure ~57 simultaneous MTB antigen-antibody reactions	MBio Diagnostics, FIND	No new data

CXR: chest x-ray
DR: drug resistance
EMB: ethambutol
FLD: first-line drugs (isoniazid, rifampin, ethambutol, pyrazinamide)
FQ: fluoroquinolone
INH: isoniazid
MDR-TB: multidrug-resistant TB
MIC: minimum inhibitory concentration
MTB: *Mycobacterium tuberculosis*
NAAT: nucleic-acid amplification test
PCR: polymerase chain reaction
POC: point of care
PZA: pyrazinamide
RIF: rifampin
RT-PCR: real-time polymerase chain reaction
SLD: second-line drug
SLID: second-line injectable drug (e.g., amikacin, capreomycin, or kanamycin)
TB: tuberculosis
WHO: World Health Organization

TROT, TROT TO MARKET

Perhaps the most exciting advance in TB diagnostics came in late 2015, when the WHO recommended Alere's Determine LAM Ag simple urine dipstick test for ruling in TB in people with HIV with CD4 counts below 100/mm^3 or who are seriously ill.[17] The test's imperfect sensitivity (56% pooled sensitivity based on five studies of people with CD4 counts below 100/mm^3) means that a negative test must still be followed up with other testing to rule out TB.[18] However, given the extremely high mortality of people with TB and HIV (TB is thought to be the cause of death in nearly 40% of HIV-positive patients, half of which is undiagnosed)[19] and challenges in diagnosing TB in people with low CD4 counts, having an inexpensive ($2.26 per test), simple, and noninvasive test to use in this very high-risk population is a major advance. In fact, the LAM test is the first TB test to ever demonstrate a mortality benefit in a randomized controlled clinical trial: among 578 people with HIV in hospitals in South Africa, Tanzania, Zambia, and Zimbabwe, using LAM was associated with an absolute reduction of all-cause mortality at eight weeks of 4% (95% confidence interval [CI]: 1%–7%) from 25% to 21%, and a relative risk reduction of 17% (95% CI: 4%–28%).[20] This difference appeared to be attributable to the test's allowing earlier initiation (by one day on average) of anti-TB therapy.[21] Countries with large burdens of TB/HIV, including many countries in sub-Saharan Africa, should roll out LAM testing immediately, along with proper accompanying training to ensure the test is used only in the recommended population and that follow-up tests are done as necessary.[22] Whoever ends up with the rights to the test—Abbott is trying to pull out of a putative acquisition of Alere—should ensure its continued manufacture as well as marketing.[23] Further upstream, funding from the Global Health Innovative Technology Fund (GHIT Fund, which is itself funded by the Japanese government, pharmaceutical companies, the Bill & Melinda Gates Foundation, and the Wellcome Trust) to FIND and Fujifilm will support the development of what is hoped to be a more sensitive LAM test.[24,25,26]

Other policy advances can help improve timely detection of drug-resistant TB. In late 2015, the WHO extended its 2008 guidance, which recommended the use of the Hain version 1 line probe assay (LPA), to recommend the use of two alternative LPAs with the capability to detect TB and rifampin resistance: the Hain version 2 LPA (also called the GenoType MTBDR*plus* assay) and the Nipro Assay.[27] The WHO still does not recommend using LPAs on smear-negative samples. In 2014 and 2015, FIND conducted a cross-sectional noninferiority study to compare the accuracy of these two tests to that of Hain Version 1 assay, evaluating their performance both on clinical isolates and on sputum specimens from people with pulmonary TB; both tests showed comparable performance in detecting *Mycobacterium tuberculosis* (the bacterium that causes TB infection and disease) and rifampin resistance in smear-positive samples: on clinical isolates, sensitivity and specificity compared with the phenotypic reference standard for Hain V1, HainV2, and Nipro were 90.3%/98.5%, 90.3%/98.5% and 92.0%/98.5%, respectively, for detection of rifampin resistance and 89.1%/99.4%, 89.1%/99.4%, and 89.6%/100.0%, respectively, for detecting isoniazid resistance. In sputum testing, sensitivity and specificity were 97.1%/97.1%, 98.2%/97.8%, and 96.5%/97.5% for rifampin resistance and 94.4%/96.4%, 95.4%/98.8%, and 94.9%/97.6% for isoniazid resistance.[28] The WHO will update its guidance on LPAs later in 2016. While this certainly reflects progress, Hain and Nipro launched these assays in 2011; it's taken five years to optimize and fully evaluate them.

In May 2016, the WHO also recommended and issued guidance on Hain's MTBDR*sl*, an LPA capable of detecting resistance to fluoroquinolones and second-line injectables.[29] LPAs can produce results in 24–48 hours, much quicker than the two weeks that liquid culture or two to three months that solid culture take. As such, the MTBDR*sl* LPA can guide appropriate treatment selection. The announcement of the WHO's MTBDR*sl* recommendation accompanied its recommendation of the shortened or "modified Bangladesh" regimen, whose introduction the test can help facilitate, as the shortened (9- to 12-month) regimen is not suitable for fluoroquinolone- or injectable-resistant TB (pre-XDR-TB; see "Tuberculosis Treatment," page 35).[30] Countries and donors must scale up the introduction of this test and work with Hain to further reduce the price. FIND negotiated a public sector price of €7.50 (approximately $10) per test strip in 138 countries; however, the total cost of running a test (which requires other laboratory supplies) can result in costs of $20–$30. The test equipment itself can cost $8,000–$40,000, depending on its size and whether it automatically reads results or not.[31]

Newer iterations of GeneXpert are moving closer to market. Recent investments may make it more suitable for use in a variety of settings and more sensitive. GeneXpert Omni, a smaller and more rugged single-cartridge version of the test that is dustproof and runs on batteries could be a point-of-care test for TB. The test device's anticipated cost is $2,895.[32] Cepheid claims that another new product, the GeneXpert Ultra cartridge, is more sensitive than the MTB/RIF, approximating the sensitivity of culture, and has a shorter processing time.[33] FIND is currently validating both the Ultra cartridge and Omni platform: Ultra results are expected at the end of 2016; Omni results have been further delayed. If studies show them to indeed be as promising as the company claims, the WHO will issue recommendations and formulate guidance accordingly. Data on the use of Ultra in smear-negative specimens are expected in 2017, which could inform recommendations on whether Ultra can be used to replace culture. Cartridge prices are expected to remain consistently high at $9.99, as even though MTB/RIF sales volumes have increased,[34] those profits are said (by Cepheid) to have been reinvested in R&D. In 2017, Cepheid plans to release the XDR assay, designed to genotype resistance to isoniazid, fluoroquinolones, and second-line injectables when MTB/RIF (or Ultra) indicates rifampin-resistant TB, though no peer-reviewed data yet exist on this product.[35] A FIND evaluation is expected in 2018.

Molbio's TrueNAT, an Indian GeneXpert competitor that has been on the market since 2013, is finally being validated by outside parties (FIND and the Indian Council on Medical Research).[36] A recent study compared TrueNAT to Xpert MTB/RIF on 274 patient specimens, using culture as the reference standard. The assays had similar sensitivity on sputum-smear-positive samples: TrueNAT had 99% sensitivity (95% CI: 94.2%–99.95%) versus MTB/RIF's 100% (95% CI: 96.5–100.0%, respectively). With sputum-smear-negative, culture-positive samples, the sensitivity of the TrueNAT was 86.2% (95% CI: 74.1%–93.4%) as compared with 90.1% (95% CI: 88.7%–94.35%) for Xpert MTB/RIF.[37] The cartridge-based sample preparation extraction tool, TruePrep—which is rugged and portable—costs $7,000, and each assay costs $14; the public sector will receive a further discount.[38]

Other products without the data to back them up continue to be marketed by unscrupulous manufacturers. Epistem's Genedrive performed dismally in a recent clinical study of 336 participants: sensitivity was 45.4% (95%CI: 35.2%–55.8%) versus 91.8% (95% CI: 84.4%–96.4%) for Xpert MTB/RIF and 77.3% (95% CI: 67.7%–85.2%) for smear microscopy. In smear-negative cases, sensitivity of GeneDrive was 0% (95% CI: 0, 15.4) versus 68.2% (95% CI: 45.1%–86.1%) for Xpert.[39] Yet just after those data were published, Epistem announced full commercial launch of Genedrive TB tests in India, claiming it "enables early detection of TB and antibiotic resistance without need for central laboratory facilities."[40] The regulatory authority in India should ban the marketing of this test, and private providers should be extremely wary and not waste patients' time, money, and effort by subjecting them to it (see box).

Extending Quality and Affordability to the Private Sector

Many countries, including 12 of the 22 countries with the highest TB burdens (India, Pakistan, the Philippines, Bangladesh, Afghanistan, Kenya, Uganda, Vietnam, Indonesia, Myanmar, Nigeria, and Cambodia) have large private-sector markets for TB diagnosis and care.[41] Ensuring access to affordable, quality diagnosis is both critical and challenging. The use of unvalidated tests, or using tests off-label, can endanger patients and their communities and, at best, wastes their money and time. Important tests, such as GeneXpert, are not commercially available in the private sector in Burma, Cambodia, Indonesia, Nigeria, Uganda, or Vietnam.[42] But even when good tests are available in the private sector, patients pay dearly, as concessional prices are normally available only to the public sector, and some private practitioners are aiming to maximize profit. For example, in Afghanistan, Bangladesh, India, Kenya, Pakistan, and the Philippines, GeneXpert is available, but the average price charged by private laboratories is $68.73 (range $30.26–$155.44).[43] Private diagnosis without case notification to the public program also impedes getting a true picture of local, national, and global TB epidemiology.

In India, where about half of patients seek TB diagnosis and care in the private sector, the Indian government and other actors have taken steps to mitigate the inappropriate use of TB diagnostics, such as banning the use of serological tests and discouraging the use of Quantiferon TB Gold (a test for latent TB that was being inappropriately marketed and used in India to screen for active TB).[44,45] Efforts are underway to ensure best TB diagnostic practices among private-sector providers in India at an affordable price. The Initiative for Promoting Affordable and Quality TB Tests (IPAQT) offers WHO-recommended TB diagnostics to laboratories who agree to pass on these price reductions to patients by agreeing to a maximum ceiling price, participating in quality assurance programs, and notifying cases to the public program.[46]

To date, IPAQT has involved 116 laboratories across India, with over 250,000 presumptive TB cases tested, and volumes climbing. IPAQT has notified 23,000 cases in five cities under a pilot program and plans to further involve more decentralized laboratories and to streamline notification, as well as to look into expanding into cross-disease diagnostic support, such as including the HIV1 viral load GeneXpert cartridge in the IPAQT framework. Other countries with robust private-sector activity in TB should follow suit. The Clinton Health Access Initiative's Nigeria team recently conducted an analysis to determine feasibility there.

IN DEVELOPMENT

Back in the lab, a promising development came from a team at Stanford University that identified a three-gene set indicative of active TB (*GBP5*, *DUSP3*, and *KLF2*) in whole blood across eight data sets containing over 1,000 samples from both adult and pediatric patients in ten countries. This gene signature could accurately separate people with active TB from healthy controls, from people with latent TB, and from people with other diseases. HIV status, bacillus Calmette-Guérin (BCG) vaccination, and drug resistance did not confound expression of the three-gene set. The gene set may be of use in monitoring treatment, as its expression increases with disease severity and decreases with time of treatment, though this must be validated prospectively. Further validation and development are required.[47]

Researchers from the University of Washington and the University of Cape Town have received funding to further study a simple oral swab to test for TB DNA, and it detected TB well in 18 of 20 patients in a proof-of-concept study (90.0% sensitivity compared with GeneXpert MTB/RIF; 95% CI: 66.9%–98.2%).[48,49]

Several researchers are exploring the value of immune activation markers such as C-reactive protein (CRP) to indicate active TB disease or to identify good responses to TB therapy. One small study pre- and post-treatment in Gambia showed that CRP levels showed the most significant decrease by two months of treatment ($P < .0001$), whereas two other markers, beta2 microglobulin and neopterin, showed little change by two months but a significant decrease by six months of treatment ($P = .0002$ and $P < .0001$, respectively).[50] A larger prospective study identified a seven-marker biosignature including CRP as well as transthyretin, interferon-γ, complement factor H, apolipoprotein-A1, inducible protein 10, and serum amyloid A that identified TB disease in the test set ($N = 210$) with a sensitivity of 93.8% (95% CI: 84.0%–98.0%) and a specificity of 73.3% (95% CI: 65.2%–80.1%), regardless of HIV infection status.[51] CRP may be of particular interest for pediatric development (see "Tuberculosis Diagnostics Research for Children," page 7).

DST research saw some developments. Development of a rapid colorimetric method for detection of resistance to pyrazinamide—one of the most important drugs to treat TB, for which DST development remains challenging due to the enormous number of resistance-associated mutations in the *M. tuberculosis pncA* gene—using a dye called 5-cyano-2,3-ditolyl tetrazolium chloride (CTC) progressed when initial testing in a small test of 50 isolates showed DST results could be available in four to six days with 97.1% sensitivity

and 81.3% specificity, in comparison with liquid culture.[52] Unfortunately, research that could underpin DST development for bedaquiline has not yet been as successful—examining the 12 cases who had developed over fourfold increases in bedaquiline minimum inhibitory concentrations (MICs) in study C209 revealed that all had *M. tuberculosis* with mutations in the *Rv0678* gene, but there was no correlation between MIC change and treatment response, making it unclear what might be a clinically meaningful breakpoint.[53] Developing DST for bedaquiline will be important, as resistance to it has already started to develop.[54]

RECOMMENDATIONS

With new products moving forward and interesting new leads to pursue, we are pleased to report progress with the TB diagnostics pipeline. But the world is still far from ensuring all those with TB get appropriate diagnostics. Both R&D and access need dramatic infusions of funding and political will. In particular:

- **National governments and donors must substantially increase funding for TB programs to allow for best diagnostic practices.** This includes the widespread scale-up of NAAT to supplant microscopy, universal DST using liquid culture or LPAs, digital X-ray, and the rapid adoption of LAM testing in areas with high HIV burdens.
- **National governments, donors, and the private sector must invest far more in TB R&D to advance better tests, including those for children.** This should include a commitment to rapidly and rigorously evaluating new technologies and to publishing peer-reviewed results. Greater resources are necessary to achieve the requirements set out in Target Product Profiles (TPPs).[55]
- **National governments and donors should work closely with the nonprofit and private sectors to ensure only quality and affordable tests are used.** In countries with large proportions of care-seeking in the private sector, access to appropriate diagnostics is extremely limited and can be catastrophically expensive. Good programs such as IPAQT to address this exist and should be expanded and replicated.
- **Developers must commit to timely and rigorous validations of their tests prior to marketing, and health and regulatory authorities and private practitioners should hold them accountable for doing so.** Epistem and other companies who market ineffective or as-yet-unproven tests must cease doing so immediately. National governments should ban the import and use of inappropriate tests and enforce those bans. Those working in TB globally should call to task companies such as Epistem that inappropriately market them.

Tuberculosis Diagnostics Research for Children

By Lindsay McKenna

The ability to confirm the presence of tuberculosis (TB) bacteria in the body (microbiological diagnosis) underpins much of the existing technology and paradigm for diagnosing TB in adults, but this approach is problematic for children. An estimated 60 percent of children with TB go undiagnosed: in 2014, national TB programs reported 358,521 cases of TB among children to the World Health Organization (WHO),[56] yet credible models estimate that one million cases of incident TB occur among children each year.[57] TB is also likely a major unrecognized co-morbidity or cause of illness and death among children affected by pneumonia, meningitis, HIV, and malnutrition.[58] Children with the disease have fewer TB bacteria in their bodies (paucibacillary disease), difficulty producing sputum, and high rates of extrapulmonary TB. As a result, diagnosis is often empirical (presumed, rather than confirmed) and based on a combination of clinical and epidemiologic information.

The gold standard for diagnosing TB, microbiological confirmation using culture, is only obtained in 15–20% of children with clinically diagnosed TB disease.[59] Compared with culture, Xpert MTB/RIF has 62% pooled sensitivity when performed on induced or expectorated sputum (36% more sensitive than smear microscopy) and 66% pooled sensitivity when performed on gastric aspirate or lavage (44% more sensitive than smear microscopy).[60] Xpert MTB/RIF sensitivity in culture-negative children clinically diagnosed with TB is just 2% for induced or expectorated sputum.[61] The WHO recommends Xpert MTB/RIF as the initial diagnostic test in children suspected of having multidrug-resistant TB (MDR-TB) or HIV-associated TB or, where resources allow, as the initial diagnostic test in all children suspected of having TB.[62] These recommendations apply to both pulmonary and extrapulmonary specimens, with the exception of stool, urine, and blood, given the lack of data for the utility of Xpert MTB/RIF for these specimen types.[63] It is important to note that a majority of studies evaluating Xpert MTB/RIF's performance have been conducted at higher-level health facilities, where it is likely that sicker children with higher rates of smear-positive TB are present for evaluation. How Xpert MTB/RIF performs among children in an outpatient setting, and with different levels of TB disease severity, has not been well studied. That said, while Xpert MTB/RIF is superior to smear microscopy and helps provide rapid confirmation of disease, it should not be used as a rule-out test for TB in children: clinical evaluation remains important in diagnosing TB in children.

Research is ongoing to determine the most feasible and sensitive combinations of tests and specimen types (including urine and stool) for diagnosing TB in children[64]; to compare the performance of smear, culture, and Xpert at baseline and during treatment; and to optimize specimen sample collection and processing to improve diagnostic yields in children. In addition to efforts to optimize existing tools, new technologies in the pipeline might also improve our ability to detect TB in children in the future. The WHO recently recommended molecular line probe assays (LPAs) for the rapid detection of resistance to second-line TB drugs, including fluoroquinolones and injectable agents in children with confirmed rifampin-resistant TB or MDR-TB, based on extrapolation from data in adults.[65] Xpert MTB/RIF Ultra, currently under evaluation in adults, is expected to have increased sensitivity and ability to detect paucibacillary TB disease, which is common in young children. Xpert XDR is expected to improve our ability to quickly diagnose resistance to first- and second-line TB drugs. These advances, though extremely important, are incremental. To radically improve diagnosis of all forms of pediatric TB, a rapid biomarker-based test that does not rely on sputum and can be used at the point of care is necessary.[66]

The discovery and validation of biomarkers for TB diagnosis and treatment monitoring in children is an urgent research priority. A blueprint for pediatric TB biomarker identification and development, resulting from a 2014 U.S. National Institutes of Health (NIH)-convened workshop, is a call to action. The blueprint identifies critical research needs, including enhancing the detection of pathogen biomarkers and identifying host biomarkers, and calls for collaboration to advance the field.[67] Efforts by an NIH-organized working group are underway to harmonize pediatric biorepositories (specimen collection methods and clinical data collection) to optimize their use for the future discovery and development of TB biomarkers in children.

Compared with adults, children have increased risk of progression from infection to active disease.[68] While it is possible to diagnose TB infection in children using biomarker-based tuberculin skin testing (TST) and interferon-gamma release assays (IGRAs), these tests have shortcomings, including their inability to differentiate between TB infection and disease, cross-reactivity with other mycobacteria, particularly for TST, and increased false-negative tests among immune-compromised children. The ability to differentiate between infection and disease and to identify children at increased risk of progression to active disease would improve feasibility and make more efficient the targeted provision of preventive therapy to child contacts of TB patients in high-burden settings.

Efforts to identify and validate biomarkers of TB disease and risk of progression in adults and children are ongoing and, if proven, will greatly improve the reliability and ease of TB diagnosis. However, drug-susceptibility tests rely on microbiological samples. Where a microbiological sample cannot be obtained, biomarkers that enable treatment monitoring in children could provide an interesting opportunity to improve access to appropriate treatment. Select pediatric biomarker research highlights are presented below.

PEDIATRIC BIOMARKER RESEARCH HIGHLIGHTS

LAM

Because both children and people with HIV tend to have higher rates of extrapulmonary TB, it was expected that the lateral flow urine LAM assay (currently recommended in HIV-positive adults who have low CD4 counts or are seriously ill) would work well in children, too. However, the LAM test demonstrated poor sensitivity (48.3%) and specificity (60.8%) compared with culture in HIV-positive and HIV-negative children with TB.[69] The WHO recommendation for LAM in people with CD4 counts <100 (or with advanced HIV disease) does extend to children, based on the generalization of data from adults, while acknowledging very limited data in children.

C-reactive protein

C-reactive protein (CRP), a nonspecific marker of inflammation detectable in blood and measurable with existing assays at the point of care, has shown potential for screening for TB disease and indicating response to TB treatment in adults (see "In Development" in this chapter, page 6). In one study, CRP demonstrated 98% sensitivity and 59% specificity for TB among South African adults with smear-negative, culture-positive TB with or without HIV.[70] A study to identify the expression patterns of biomarkers in the plasma of HIV-negative children in India with pulmonary and extrapulmonary TB compared with healthy controls found that children with active TB showed significantly elevated levels of CRP. These findings are not surprising, as a detectable difference in inflammation can be expected when comparing healthy and sick children. As such, CRP should be evaluated as a marker of active TB and for use in TB diagnostic algorithms in larger pediatric cohorts, inclusive of children with latent TB and other pulmonary infections and HIV.[71]

TAM-TB

Encouragingly, a novel T-cell activation marker-tuberculosis assay (TAM-TB) demonstrated 83.3% sensitivity and 96.8% specificity among children with TB symptoms compared with culture. The pediatric cohort (N = 113) in this prospective proof-of-concept study included HIV-positive and HIV-negative children 6 months to16 years old. The combined use of the TAM-TB assay and Xpert MTB/RIF demonstrated 94% sensitivity compared with culture. TAM-TB is a rapid blood-based test with the potential to improve the detection of active TB in children; further refinement and testing, especially in HIV-positive children with low CD4 cell counts, are necessary.[72]

RNA expression signatures

A genome-wide analysis of RNA expression in blood among children undergoing evaluation for TB, including those with HIV, identified a 51-transcript signature capable of distinguishing TB from other diseases and from latent TB infection. The 51-transcript signature demonstrated 82.9% sensitivity and 83.6% specificity for culture-confirmed TB (Xpert MTB/RIF sensitivity was 54.3%). For culture-negative TB where children are deemed to have highly probable, probable, or possible TB, the 51-transcript signature had an estimated sensitivity of 62.5–82.3%, 42.1–80.8%, and 35.3–79.6%, respectively (estimated

sensitivity for Xpert MTB/RIF was 25%–35.7%, 5.3%–13.3%, and 0%, respectively). The 51-transcript signature distinguished TB from latent infection with a sensitivity of 94% and a specificity of 100%. The 51-transcript signature identified higher proportions of culture-confirmed and culture-negative cases of TB than Xpert MTB/RIF; however, innovation is needed to translate transcriptional signatures into diagnostic tools for resource-poor settings—current methods used to detect RNA transcripts are complex and costly.[73]

Gene expression signatures

A multicohort analysis of data sets available in two public gene expression microarray repositories identified a three-gene signature (*GBP5, DUSP3*, and *KLF2*) capable of diagnosing active TB in adults and children, irrespective of bacillus Calmette-Guérin (BCG) vaccination or HIV status. The TB score derived from the three-gene signature demonstrated 85 percent sensitivity and 93% specificity in a cohort made up of both healthy people and those with active TB, 80% sensitivity and 86% specificity in a cohort made up of people with latent or active TB, and 81% sensitivity and 74% specificity in a cohort made up of people with other diseases or active TB. The TB score showed a significant decreasing trend with progression of treatment, suggesting its potential as a biomarker of clinical response to treatment. However, TB scores in children with culture-negative TB were significantly lower than those in children with culture-positive TB. The TB score demonstrated 86% sensitivity and specificity for latent TB versus culture-positive active TB in children.[74] A blood-based test offers much advantage over what currently exists, but the ability to detect TB in culture-negative children is extremely important, limiting the potential utility of this three-gene signature for children with culture-negative TB, who account for 80% of children with TB.

RECOMMENDATIONS FOR PEDIATRIC TB DIAGNOSTICS

Much work remains to develop novel diagnostic technologies to accurately detect TB infection and disease; to predict disease progression in healthy, infected children; and to monitor treatment in children. The few tests that have been validated and recommended for use in children, including Xpert MTB/RIF, are sub-optimal and underutilized, partly due to difficulties with specimen collection. At the same time, efforts to identify children at risk for TB—especially within maternal and child health programs, where sick children often first present for care—and referral systems and decentralized capacity to diagnose childhood TB, clinically or with available tools, are urgently needed. We also need:

- To validate tests in adults and children in parallel to expedite access to improved diagnostic technologies for children. These evaluations should include a variety of sample types in children with and without HIV and should assess age-related performance;
- Increased investments in research to discover and validate biomarkers and innovation to translate these biomarkers into simple and affordable tests that can rapidly and accurately diagnose TB, monitor treatment, and predict disease progression in children. In 2014, less than $2.3 million and $2.8 million was spent globally on research and development for pediatric TB diagnostics and basic science, respectively;[75]
- To establish and support harmonized and collaborative pediatric biorepositories important for biomarker discovery and development;
- To support and create networks of sites that support field evaluation of new diagnostics and can pool data to more rapidly demonstrate the impact of new tools;
- To scale up and decentralize the use of existing technologies and strategies to diagnose pediatric TB infection and disease, especially within maternal and child health programs; and
- To train health care workers to improve their ability and confidence to clinically diagnose children with TB when tests are unavailable or come back negative.

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The Tuberculosis Prevention Pipeline

By Mike Frick

After decades of receiving short shrift from most national TB programs and international organizations, tuberculosis (TB) prevention is finally coming into the mainstream. In 2015, the World Health Organization (WHO) published its first-ever *Guidelines on the Management of Latent Tuberculosis Infection*.[1] The launch of these guidelines has awakened countries and donors to the idea that TB prevention is an area ripe for intervention—and for intensified research. In March 2016, the executive board of the global health financing mechanism UNITAID endorsed TB prevention as one of three "areas for intervention" that should be prioritized for targeted investments in its TB portfolio.[2] This support will likely include funding for research projects seeking to shorten and simplify preventive therapy for the groups that are most at risk of developing active TB disease: children and people with HIV. On the other side of the Atlantic, the U.S. White House's *National Action Plan for Combatting Multidrug-Resistant Tuberculosis* lists TB prevention—specifically, "increasing options for preventing active TB, latent TB infection, and TB transmission"—as the first objective toward its goal of accelerating basic and applied research to overcome the threat of drug resistance.[3]

As exemplified by these new guidelines and plans, a more focused TB prevention research agenda is beginning to take shape. This agenda involves tackling TB infection from two angles. First, preventive therapy is used to keep asymptomatic infection with *Mycobacterium tuberculosis* (MTB) from progressing to active, symptomatic TB disease. Second, vaccination is administered either pre-exposure to prevent infection with MTB altogether, or post-exposure to prevent infection from developing into disease. To date, research and development (R&D) on TB preventive therapies and vaccines have progressed with little interaction, despite the common goal of using new preventive therapies and vaccines to greatly hasten the decline in TB incidence by reducing the number of people with MTB infection who may one day develop transmissible disease. Indeed, mathematical modeling shows that the dramatic reductions in TB incidence required to meet the TB elimination targets of the WHO's End TB Strategy will require addressing TB infection—first through preventive therapy and then through vaccination.[4]

To acknowledge the momentum building behind TB prevention as a unified field of research, this year's *Pipeline Report* jointly reviews progress in the clinical development of TB preventive therapy and TB vaccines. (Advances in infection control—the administrative, environmental, and personal protective measures that reduce the risk of TB transmission in the built environment—fall outside of the biomedical focus of this chapter.) There is much to be gained from breaking the habitual thinking that has placed TB drug development in one camp and vaccines in another. For one, a joint discussion reveals that initiatives to develop new TB preventive therapies and vaccines face a shared thicket of thorny scientific issues, whose lack of resolution has snarled progress toward both ends. Approaching TB preventive therapy and vaccines as related endeavors may also jumpstart an advocacy movement for TB prevention that is more forceful than disjointed efforts to hold public and political attention on separate technological fixes (an approach that can sometimes be misinterpreted by politicians as an either/or choice between treatment and prevention). Finally, prevention research raises a number of unique ethical considerations, with corresponding implications for engaging communities in TB research that both drug and vaccine developers will need to address.

PROGRESS IN TB PREVENTION SCIENCE

Developing new tools to prevent TB will require an intensification of basic science research that can inform product development, so it is fitting that some of the most notable achievements over the past year have

come from the laboratory. Scientists are employing a range of tools to shine new light on how MTB interacts with its human host—sometimes literally, as with the application of positron emission tomography (PET) and X-ray computed tomography (CT) to visualize and map inflammation-based immune activity to MTB as it unfolds across the geography of the lung.[5] An array of studies—some in animals, others in humans; some observational, others experimental—are illuminating the hidden corners of genome, blood, and lung to improve our understanding of the dynamic nature of MTB infection, how it progresses over time, and why it sometimes spills over into active TB disease.

Predicting Disease Progression through Gene-based Signatures of Risk

The central challenge in TB prevention research is that scientists have yet to establish a firm link between the appearance of any specific biomarker in individuals with asymptomatic MTB infection and progression to active TB disease. Biomarkers are measurable characteristics, such as gene activity, biological processes, or clinical phenotypes, whose presence signifies either a particular disease state or the body's response to vaccination or drug therapy.[6] The quest to identify biomarkers that act as prospective signatures of risk for developing TB disease among individuals infected with MTB has animated much of TB prevention research.[7,8] Current methods for diagnosing MTB infection—the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)—cannot predict whether individuals with MTB infection will develop TB disease. (An estimated 10% of MTB-infected people will develop active TB at some point in their lifetimes.[9])

Once validated in late-stage clinical trials, a biomarker that could reliably predict disease progression or distinguish between individuals with high or low risk would be a powerful tool for guiding public health intervention efforts by identifying individuals most in need of preventive therapy, thereby creating opportunities to interrupt transmission by preempting disease progression. Biomarker-guided interventions might require fewer resources than less-targeted approaches by placing only those people most likely to progress to disease on treatment. More immediately, a biomarker of prospective risk could streamline the clinical development of new TB vaccines and preventive therapies by allowing clinical trials to enroll persons with the greatest risk of developing active TB disease. This targeted approach would reduce the costs of research by allowing investigators to conduct smaller, more quickly enrolling studies.[10]

Biomarker identification efforts took a significant step forward in 2016 with the publication of a prospective cohort study of over 6,000 South African adolescents with MTB infection.[11] Investigators reported discovering a blood-based RNA signature comprised of 16 genes that predicted the risk of TB disease progression over a two-year period. These 16 genes, collectively referred to as a gene signature, appeared to be more active in 46 adolescents who developed TB than in 107 matched controls who remained healthy. Notably, the gene signature's predictive power increased when measured at time points closer to TB diagnosis (sensitivity of 71.2% at 6 months before diagnosis compared with 62.9% at 6 to 12 months and 47.7% at 12 to 18 months, reported at a specificity of 80%).[12]

To validate these results, researchers tested the gene signature in two separate cohorts of HIV-negative adult household contacts of people with pulmonary TB: one from South Africa and the other from The Gambia. Successful validation in these cohorts led the investigators to ask two additional questions. First, given that sensitivity increased closer to diagnosis, could this signature of risk discriminate between MTB infection and active TB disease? When applied to published data from other adult cohorts in the United Kingdom, South Africa, and Malawi, the gene signature distinguished active TB from both MTB infection and other pulmonary diseases, including in people coinfected with TB and HIV (a population that usually presents more diagnostic challenges).[13] Second, could a risk signature found in adolescents perform well in younger children? Here, too, the researchers found that the signature could distinguish between MTB infection and culture-confirmed TB disease in children (but not culture-negative TB). Children with culture-positive TB have more bacteria in

their lungs than those with culture-negative disease; thus, the signature's discriminatory capability in this group suggests that activity in these 16 genes might be related to the number of replicating bacteria in the lung (i.e., bacterial load). Consistent with this idea, the gene signature gradually disappeared when researchers looked for it in patients receiving treatment for drug-sensitive TB.[14]

Discovery of this 16-gene risk signature was made possible by the kind of collaborative team science that requires time and sustained financial support. The cohort of South African adolescents that provided data for the primary analysis enrolled its first participant in 2005 and completed follow-up in 2009.[15] That means that the adolescents who participated in the study are now adults. No doubt many have since fallen sick from TB, and some may even have died from it. To build on the contribution of these then-teenagers, investigators should continue to follow them into adulthood to understand how risk of disease progression changes over the life cycle. Evaluating how well this risk signature performs in a larger number of participants drawn from a more general population with less exposure to TB is also important, as biomarker identification studies may have cohort biases that limit their generalizability across different populations.[16] This cohort drew adolescents from an area with an extraordinarily high TB incidence rate (1,400 per 100,000 people), where the lifetime risk of progressing from MTB infection to TB disease far exceeds the 10% risk observed in any given population.[17]

Failures of Translation between Markers in the Blood and Events in the Lung

One lingering question from this genetic risk signature study is the extent to which a signature identified from the blood reflects concurrent pathogenesis in the lung. Scientists are increasingly recognizing how the initial lung environment encountered by MTB is important for determining the outcome of infection, but these processes may not be well represented by immune cells circulating in peripheral blood.[18,19] Acknowledging this limitation, investigators countered that circulating white blood cells "can serve as sentinels of lung pathophysiology."[20] However, the fidelity with which measurements taken from peripheral blood mirror disease processes unfolding in the lung remains far from settled.[21] Long-held assumptions about the relationship between lung and blood in TB are being rethought on the basis of evidence from a range of studies (many in nonhuman primates) that is rewriting the script on the classic symbol of TB pathology, the granuloma, and its role in disease progression.

Granulomas (TB's signature pulmonary lesions) are organized collections of macrophages and other immune cells that flock to sites of MTB infection in the lung. Traditional thinking has likened granulomas to immune fortresses that serve an essential protective function by containing MTB in a quiescent state. In the canonical view, people who develop active TB mount a less-effective immune response than individuals who maintain MTB infection without falling ill. This implies that different granulomas in a given individual all behave similarly, and that differences in granuloma activity between individuals result in one of two divergent clinical outcomes: latent infection or active disease.[22]

Nothing seems so simple anymore. As one recent review put it, "the clinical hallmark of TB is the granuloma….[Yet] the field is even at a loss as to whether granuloma formation ultimately benefits host or bacterium, and which is the master of the situation."[23] Under certain conditions, granulomas appear to offer MTB a niche in which it can replicate and persist, whereas the granuloma at other times becomes the focal point at which immune cells marshal a coordinated response to control MTB.[24] Whether a granuloma becomes a site of vulnerability or protection appears to depend on the nature of the local CD4+ T-cell response, particularly the ratio of pro- and anti-inflammatory cytokines present in the granuloma.[25] CD4+ T cells are critical for immunity against TB, and TB vaccine research has focused on achieving protection through cell-mediated immunity by developing vaccines that trigger CD4+ T cells to release type 1 helper (TH1) cytokines such as interferon-gamma (IFNγ), tumor necrosis factor-alpha (TNFα), and

interleukin-2 (IL-2).[26] (Cytokines are small proteins that call and direct the behavior of other immune cells.) However, because immune responses to TB are usually measured in blood—which is easier to collect from humans than lung tissue—not much is known about the profile of local T-cell responses in the granuloma itself.[27]

A clearer picture is starting to form from a series of studies in cynomolgus macaques, which have become an important animal model for TB prevention research, as they can develop either clinically active TB disease or latent TB infection with granulomas similar to those seen in humans.[28] In addition, the MTB epitopes recognized by human CD4 T cells overlap substantially with those in macaques.[29] (Epitopes, or small cell-surface proteins, are the parts of antigens that are recognized by immune cells). Research summarized in last year's *Pipeline Report* shows that a spectrum of lesion activity exists in individual macaques with either active disease or latent infection. Animals with active TB disease can have sterilized lesions, but, critically, they also contain a number of granulomas in which infection is not controlled, resulting in disease progression.[30] This spectrum of activity in an individual suggests that the outcome of MTB infection is determined locally at the level of the granuloma and not systemically, where the immune response is more conveniently sampled from circulating blood. What controls infection at the granuloma level, and to what extent is this local response represented by immune readouts taken from the blood?

One recent study in MTB-infected macaques sought to answer this question by comparing the T cells and cytokines found in granulomas to those observed in circulating blood.[31] Investigators used PET/CT imaging to track granuloma formation in 28 cynomolgus macaques, 13 of which developed active TB disease and 15 of which remained latently infected. After macaques were necropsied (killed), granulomas identified by PET/CT underwent histological examination, quantification of bacterial burden, and immunological analysis to measure the presence of pro-inflammatory cytokines (IFNγ, IL-2, TNF, and IL-17) and the anti-inflammatory cytokine IL-10.[32] The results add several layers of complexity to our understanding of how cell-mediated immunity operates locally in TB. In a particular macaque, different granulomas exhibited highly variable cytokine profiles. Most T cells in granulomas produced a single type of cytokine (i.e., were monofunctional), but granulomas themselves contained a mix of T cells that produced different cytokines.[33] (This stands in contrast with the stated intention of many TB vaccine studies, which judged the immunogenicity of vaccine candidates by looking for polyfunctional T cells in blood.[34]) Granulomas in which T cells produced both pro- and anti-inflammatory cytokines were more likely to be sterile or have lower bacterial burdens.[35] This is consistent with an emerging consensus that stimulation of pro-inflammatory cytokines such as IFNγ is necessary, but not sufficient, for protection; there must be a counterpoint to inflammatory activity, as too much can damage the lung and impair protection.[36] Finally, in most of the macaques, T-cell responses measured in circulating blood (the systemic immune response) did not closely mirror T-cell responses observed in granulomas (the local immune response).[37]

A related study in macaques probed the differential fates of granulomas from the perspective of MTB itself.[38] Investigators added genetic barcodes to individual MTB isolates, tracked the formation of lesions using PET/CT, and, after necropsy, quantified the relative frequency of each MTB barcode in different lesions. They observed that most granulomas were founded by a single bacterium and that bacterial burden varied greatly across lesions, even in the same animal.[39] Differences in bacterial burden may reflect variability in the killing efficacy of the immune response at the level of the individual lesion, as animals with active disease also had sterilized granulomas. Given this heterogeneity, the investigators commented that "it is not surprising that relevant predictors of disease outcome have been hard to identify from peripheral measures of immune response."[40]

The combination of PET/CT, genetic barcoding, and histopathology has revealed that, so long as TB vaccine developers continue to measure success through blood-based immune assays, they risk overlooking important details of what effective immunity against MTB looks like at sites of infection in the lung.[41] Although it is now

possible to closely examine lung responses in nonhuman primates, investigators working in the clinic have few alternatives at hand. Some have predicted that PET/CT may one day be used in clinical trials to track biological signals of an effective vaccine. These signals might include observing fewer granulomas form early in infection, no dissemination of granulomas after infection, or lower levels of lung inflammation—as indicated by radiological markers picked up by PET/CT (e.g., 18-F fluorodeoxyglucose). However, due to concerns about exposing humans to repeated radiation without clear therapeutic necessity, PET/CT cannot be applied for routine monitoring in large clinical trials, and, even if the technique could, the composite vision of inflammation produced by PET/CT is not yet well enough defined to serve as a reliable surrogate of protection, much less a clinical trial endpoint. Other sampling methods, such as bronchoalveolar lavage (BAL)—a technique used to sample cells from the airway—yield closer approximations of the lung environment than blood, but there may be important differences between T cell responses in the airway and lung that make BAL an imperfect alternative.[42] In addition, given that BAL requires passing a bronchoscope through the mouth or nose into the lung, it may be too invasive to perform on the scale of a clinical trial. Although formidable, these limitations should not inspire a sense of futility among vaccine developers. Work to develop blood-based assays that provide indications of vaccine-induced immunity in the lung should be a priority for the field. Using assays that measure more than IFNγ and other TH1 cytokines may also yield a more complete picture of vaccine-driven immune responses for guiding clinical development.

Bacterial Individuality and Persistence

The ability to attach genetic barcodes to individual bacteria, as described above, has made it possible to speak of bacterial *individuality* and recognize that, just as not all granulomas behave identically, not all MTB cells are homogenous.[43] Most MTB cells are susceptible to the bactericidal effects of the immune response or antibiotic therapy, but in any given population of MTB, a few bacteria are able to survive these assaults. Sometimes referred to as *persisters*, these bacterial survivors are slow-growing, nonreplicating, and thought to develop noninheritable resistance to antibiotics and the body's adaptive immune response.[44] The recalcitrance of these persisters contributes to the lengthy duration of treatment for both TB disease and MTB infection, and likely gives rise to a range of observed phenomena in TB infection and disease, from latency to disease progression to posttreatment relapse.[45,46]

Understanding the biological mechanisms of persistence and how to overcome them is a major priority for TB drug developers working on prevention. Several TB drug research networks have formed scientific working groups to address the problem of persisters, and the topic has featured prominently in satellite meetings organized by the WHO at the 2014 and 2015 Conference on Retroviruses and Opportunistic Infections.[47,48] Of immediate concern for the development of new TB preventive therapies, some drugs may be more effective against persisters than others. For example, drugs with sterilizing activity such as rifapentine and pyrazinamide appear to be more capable of killing persistent organisms than bactericidal agents such as isoniazid, which is thought to be more active against replicating bacteria.[49] Research into MTB persistence has also raised more fundamental questions, leading many scientists to ask, "What is latency anyway?" The initial challenge has been to disentangle terminology that is often conflated in the drug development vernacular—for example, the terms *latency*, *persistence*, and *dormancy*, which likely point to related, yet distinct, concepts.[50]

PROGRESS IN TB VACCINE DEVELOPMENT

The past year has served as the opening chapter in the TB vaccine field's "shift to the left," a strategy in which major funders such as the Bill & Melinda Gates Foundation are moving resources to basic discovery, preclinical development, and phase I and II trials (events located on the left side of the clinical development pipeline).[51] No new vaccines have entered clinical testing since TAG's 2015 *Pipeline Report*, although many

of the 14 candidates in the pipeline have initiated new trials (see table 1). Thus far, the thrust of activity under this shift to the left has been directed toward two tactics: experimental medicine studies and novel clinical trial designs. Taken together, the intention behind deploying these tactics is to first generate a more diverse stable of vaccine concepts, and then to more efficiently triage these in early-stage trials so that only the most promising candidates advance to larger, costlier efficacy trials.[52] This strategy aims to correct a glaring weakness in the composition of the TB vaccine pipeline: the viral-vectored and adjuvanted subunit vaccines under development were all designed to play the same notes, just in slightly different combinations. For example, six of the eight subunit vaccines contain an Ag85 antigen (either Ag85A or Ag85B), and the majority of candidates were designed to provoke cell-mediated immunity driven by CD4 and CD8 T cells, resulting in vaccines with little immunologic diversity.[53]

Table 1. TB Vaccines in Development

Agent	Strategy	Type	Sponsor(s)	Status
M. vaccae	Immunotherapeutic	Whole-cell *M. vaccae*	AnHui Longcom	Phase III
M72/AS01	Prime-boost	Protein/adjuvant	GlaxoSmithKline, Aeras	Phase IIb
H4 + IC31	Prime-boost	Protein/adjuvant	Statens Serum Institut (SSI), Sanofi Pasteur, Valneva, Aeras	Phase IIa
H56 + IC31	Prime-boost	Protein/adjuvant	SSI, Valneva, Aeras	Phase IIa
MTBVAC	Prime	Live genetically attenuated *M. tuberculosis* (MTB)	University of Zaragoza, Biofabri, TuBerculosis Vaccine Initiative (TBVI)	Phase IIa
VPM1002	Prime	Live recombinant rBCG	Serum Institute of India, Vakzine Projekt Management, TBVI, Max Planck Institute for Infection Biology	Phase IIa
Dar-901	Prime-boost	Whole-cell *M. obuense*	Dartmouth University, Aeras	Phase IIa
ID93 + GLA-SE	Prime-boost	Protein/adjuvant	Infectious Disease Research Institute, Aeras	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
ChAdOx1.85A + MVA85A	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A (aerosol)	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A-IMX313	Prime-boost	Viral vector	Oxford University, Imaxio	Phase I
TB/FLU-04L	Prime-boost	Viral vector	Research Institute for Biological Safety Problems	Phase I

Experimental Medicine Studies

Experimental medicine refers to studies in humans—usually small and often nested into larger clinical trials—that are intended to ask and answer scientific questions that may inform vaccine discovery and product development.[54] These studies take advantage of opportunities to work in humans to further our understanding of the biological mechanisms underlying infection and disease. For the purposes of TB vaccine R&D, one major objective of experimental medicine studies is to develop new vaccine concepts by looking beyond immunity mediated through CD4 and CD8 T cells to consider other cell types (e.g., γδ T cells, mucosal-associated invariant T cells, CD1-restricted T cells, antibodies produced by B cells, etc.).[55] The overarching goal is to elevate the role of biological investigation in TB vaccine R&D and, in doing so, refashion product development from a strictly linear pathway to an iterative exchange between clinical work in humans, preclinical testing in their animal model counterparts, and basic research in vitro.[56]

Vaccine developers have already responded to the call to incorporate experimental medicine into clinical testing. For example, Aeras is working with the HIV Vaccine Trials Network of the U.S. National Institutes of Health (NIH) on an immunology study that aims to better understand the assays used to assess the immune responses generated by subunit vaccines that are currently in the pipeline.[57] In this study, South African adolescents will receive either the H4 + IC31 vaccine, the H56 + IC31 vaccine, or revaccination with bacillus Calmette–Guérin (BCG), the existing TB vaccine, which was first licensed in 1921 and used to prevent severe forms of TB in children. This is not a head-to-head trial between H4 + IC31, H56 + IC31, and BCG; rather, blood will be sampled at different time points and analyzed to generate a trove of immunological data on vaccine responses using validated and exploratory assays that may one day be evaluated as possible correlates of risk or protection.[58,59] There is interest in conducting similar experimental medicine studies involving whole-cell mycobacterial vaccines.[60] In such studies, the goal would be to refine assays to better distinguish the immune response provoked by whole-cell vaccines from that stimulated by BCG, or to develop assays to measure the activity of unconventional T cell subsets such as γδ T cells or CD1-restricted T cells. The field aspires to initiate one to two experimental medicine studies per year, and although each will have its own sharp focus, the overarching goal is to probe important scientific questions and increase our understanding of the biology of MTB infection in humans.[61]

Novel Clinical Trial Designs

In parallel with experimental medicine studies, vaccine developers are employing novel clinical trial designs in early stages of testing. This has mostly entailed getting creative with clinical trial endpoints by designing phase IIa trials around the primary outcome of prevention of MTB infection as opposed to prevention of TB disease.[62,63] As with any departure from convention, this strategy offers both risk and reward. Unlike TB disease, which can be microbiologically confirmed through diagnostic tests such as GeneXpert/MTB RIF or mycobacterial culture, MTB infection is difficult to reliably identify with extant tools. Prevention-of-infection trials define infection using blood-based IGRAs such as Qiagen's QuantiFERON Gold In-Tube (QFT-Gold), a test that converts from negative to positive when it detects cell-mediated immune responses (i.e., IFNγ) to MTB antigens.[64] However, the well-documented variability of IGRA results, and the potential of a positive IGRA to sometimes revert to negative after repeat testing, means that investigators must proceed cautiously.[65,66,67] Without a gold-standard diagnostic test for MTB infection, and without validated correlates of protective immunity, regulatory authorities are unlikely to license a new TB vaccine that is based on endpoints other than prevention of disease.[68]

As a result, prevention-of-infection is not being pursued as a licensable vaccine indication, but rather as a tool for winnowing vaccine concepts before mounting efficacy studies with traditional prevention of TB disease endpoints. Given that infection with MTB is a more common occurrence than TB disease, prevention-of-

infection trials promise to save money by enrolling fewer participants in less time.[69] The first results from this approach may be just around the corner. Aeras is conducting a three-arm phase IIa study of H4 + IC31 and BCG revaccination in 990 BCG-vaccinated, HIV-negative adolescents in South Africa's Western Cape province.[70] The H4 + IC31 candidate pairs MTB antigens Ag85B and TB10.4 with IC31, an adjuvant owned by Valneva. One-third of participants will receive two doses of H4 + IC31, one-third will be revaccinated with a single dose of BCG, and the final third will receive two doses of placebo.[71] The primary outcome is MTB infection, as defined by sustained IGRA conversion (in this case, QFT-Gold), and the primary analysis will occur when the study accrues 64 cases of MTB infection. Aeras reports that it is close to reaching this point and expects to release the results in 2017.[72]

The subunit vaccine H56 + IC31, developed by the Statens Serum Institut of Denmark (SSI), will soon be used in a prevention-of-infection trial in Tanzania. H56 + IC31 consists of three MTB antigens (Ag85B, ESAT-6, and Rv2660c) paired with Valneva's IC31 adjuvant. Given that the ESAT-6 antigen is present in both the H56 vaccine and the QFT-Gold test, the SSI first had to develop an IGRA without ESAT-6 before it could study H56 in a prevention-of-infection trial.[73] (Using QFT-Gold to measure MTB infection in participants vaccinated with H56 could result in false positives, as the ESAT-6 in H56 could prime the antigen-specific T cells that the test looks for as an indication of MTB infection). The resulting ESAT-6-free IGRA contains four antigens (CFP10, QTC6, QTC7, and QTC13) and has been evaluated in studies in Denmark, Egypt, Tanzania, and South Africa; its performance appears to be on par with that of QFT-Gold.[74] This ESAT-6-free IGRA was developed as a companion diagnostic for the H56 vaccine and is not intended to be a commercial alternative to QFT-Gold.[75] The trial in Tanzania will contain two arms—one with H56 and the other with placebo—and enroll 1,400 adolescents. Aside from the lack of a third arm looking at BCG revaccination, the major difference between this study and the H4 prevention-of-infection trial is that the incidence of MTB infection in this part of Tanzania is much lower than that in South Africa's Western Cape.[76]

In addition to prevention of infection, TB vaccine developers are designing trials to evaluate prevention of recurrence, defined as either reactivation of disease from latency (i.e., relapse) or reinfection with MTB after treatment completion.[77] Similar to MTB infection, the incidence of recurrent TB disease is higher in any given population than new cases of TB. Anywhere from 2–8% of treated TB patients will face recurrent disease, and the vast majority of these cases occur in the first 12 months after completing therapy.[78,79] Consequently, prevention-of-recurrence trials offer similar advantages as prevention-of-infection trials in terms of demonstrating the mettle of vaccine candidates before selecting which ones to move forward to efficacy trials looking at prevention of disease. Successful prevention-of-recurrence trials might also create a pathway for developing therapeutic vaccines to either shorten the duration of treatment or bolster chemotherapy.[80]

Several prevention-of-recurrence studies are under way. A phase IIa prevention-of-recurrence trial was recently begun for the subunit vaccine ID93 + GLA-SE in 60 South African adults who successfully completed therapy for drug-sensitive TB (DS-TB). Developed by the Infectious Disease Research Institute (Seattle, Washington), ID93 + GLA-SE combines the MTB antigens Rv2608, Rv3619, and Rv3620 with the GLA-SE adjuvant. The trial contains four arms and is testing two intramuscular injections of vaccine—given at three different doses—against placebo (saline solution). This safety and dose-ranging study will inform planning for a phase IIb prevention-of-recurrence trial of ID93 + GLA-SE that will enroll up to 450 adults per arm.[81] In addition to ID93 + GLA-SE, H56 recently completed enrollment in a phase I safety, immunogenicity, and dose-escalation study among 24 HIV-negative adults that were previously treated for DS-TB; results are forthcoming.[82] H56 + IC31 is being studied as an adjunct to TB therapy when paired with COX-2-selective inhibitors (a type of nonsteroidal anti-inflammatory drug).[83] The idea is that COX-2 inhibitors will strengthen the vaccine response to H56, and that the two together will shorten the duration of chemotherapy for multidrug-resistant TB. This initial study is recruiting participants in Oslo, Norway and is supported by the Norwegian Research Council.[84] Despite these interesting applications of H56 during and after TB drug therapy, the SSI has indicated that future development efforts will focus on prevention-of-infection trials rather than prevention-of-recurrence trials.[85]

Other Approaches and Developments

The TB vaccine field's only ongoing phase IIb efficacy trial is evaluating whether two intramuscular doses of M72 + AS01, a subunit vaccine developed by GlaxoSmithKline (GSK) that pairs MTB antigens 32A and 29A with GSK's AS01 adjuvant, protects MTB-infected, HIV-negative adults from TB disease progression compared with placebo.[86] The trial, which opened in 2014 and is being conducted in South Africa, Kenya, and Zambia, reached its targeted enrollment of 3,500 participants in 2015 and is now in follow-up for the primary outcome analysis, which will be case driven. The analysis will be conducted after investigators detect 21 cases of pulmonary TB; results are expected in late 2018.[87]

Activity also continues on the development of two vaccines designed to replace BCG and be administered to infants soon after birth: VPM1002 and MTBVAC. VPM1002, a live, recombinant form of BCG developed by Vakzine Projekt Management in Germany and licensed to the Serum Institute of India (SII), recently began a phase IIa trial in over 400 South African newborns. The study will compare the safety and immunogenicity of VPM1002 versus BCG in both HIV-exposed and unexposed infants.[88] The SII is currently in discussions with regulatory authorities in India to take VPM1002 into two larger studies: a phase IIb BCG-replacement trial in newborns (pending a favorable outcome from the South African study), and a phase III prevention-of-recurrence trial in adults.[89] Work also continues on MTBVAC, a live, genetically attenuated form of MTB that was made less virulent by the deletion of two genes (*phoP* and *fadD26*). A phase IIa safety, dose-escalation, and immunogenicity study of MTBVAC in South Africa is currently recruiting participants in two phases. The first will randomize MTB-negative, BCG-vaccinated adults to receive either MTBVAC or BCG. If safety is demonstrated in this group, the trial will progress to the second stage and randomize infants to receive either BCG or MTBVAC at one of three doses.[90] A phase IIa study among South African adults is also planned.[91]

Efforts to replace BCG will likely receive less financial and intellectual attention in the coming years. In contrast with earlier phase IIa and IIb trials, many of which were conducted in either adults with HIV or infants,[92,93] vaccine developers are now focusing on HIV-negative adolescents and adults, who account for the majority of MTB transmission globally. (This may be one reason why VPM1002 and MTBVAC—each designed as BCG-replacement vaccines—are also being tested in adult prevention-of-recurrence and prevention-of-infection trials). By conducting fewer clinical trials in children and people with HIV, TB vaccine developers are effectively making the decision to direct research away from the two groups most vulnerable to TB. If focusing testing on adults without comorbidities shortens the clinical development timeline, and if the resulting vaccine averts cases of TB in children and people with HIV through a herd immunity effect by interrupting TB transmission among the adult contacts around them (as modeling suggests could occur),[94] then this may prove to be a prescient move. But that string of assumptions contains many uncertainties, and developers should acknowledge that the current strategy risks leaving behind two key TB-affected populations with greatly enhanced risks of disease and death that rightly draw significant attention from global health actors.

PROGRESS IN TB PREVENTIVE THERAPY DEVELOPMENT

Although they are no longer the focus of TB vaccine development, children and people with HIV still occupy the center of efforts to develop new or improved TB preventive therapies (see table 2). Research into preventive TB treatment is pursuing answers to two primary questions. First, what are the most effective regimens for treating MTB infection, particularly in high-risk groups, including children, people with HIV, and pregnant women? And second, how should physicians treat probable infection with drug-resistant TB (DR-TB)?

As with the overall TB drug pipeline (see "Tuberculosis Treatment Pipeline," page 35, for a detailed overview), there are few new drug candidates available for investigators to study. Consequently, much of the activity has focused on optimizing existing drugs for TB prevention (e.g., rifapentine, a rifamycin that is closely related to rifampin and is off-patent and marketed by the French pharmaceutical company Sanofi) or studying the

chemoprophylactic potential of new drugs (e.g., delamanid, a nitroimidazole developed by the Japanese company Otsuka and approved for the treatment of DR-TB). Despite the limited armamentarium, the field is poised to make major strides in coming years with planned or ongoing phase III trials that, if successful, could dramatically refashion treatment guidelines.

Table 2. Clinical Trials to Prevent Tuberculosis Disease

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine + isoniazid for 1 month (vs. isoniazid daily for 9 months) NCT01404312*	Fully enrolled	People with HIV either living in high-TB prevalence regions or with a positive TST or IGRA (QFT or T-SPOT TB test)	ACTG
A5300/PHOENIx 6 months daily delamanid (vs. isoniazid)	Beginning enrollment Q4 2016	High-risk (HIV+, TST/IGRA+, or ≤5 years old) household contacts (adults, adolescents, and children 0–5 years old) of individuals with MDR-TB	ACTG, IMPAACT
WHIPP TB 6H versus 3HP (given once) versus p3HP (given once a year for two years)	Beginning enrollment Q3 2016	People with HIV without active TB in high–TB prevalence regions	KNCV, USAID
TBTC Study 37 6 weeks of daily rifapentine (P) versus rifamycin-based standard of care regimens (3HP, 4R, 3HR)	Protocol development	Household contacts, people with HIV, individuals with recent TST or IGRA conversion	TBTC, TBESC, UK MRC, University College London
4R versus 9H 4 months daily rifampin (self-administered) NCT00931736*	Fully enrolled	Adults with positive skin test or QuantiFERON-TB blood test, including people with HIV who are not on ARVs whose efficacy is reduced by rifampin	McGill University, CIHR
V-QUIN 6 months daily levofloxacin (vs. placebo) ACTRN12616000215426**	Protocol development	Household contacts (adults, adolescents, and children ≥3 kg) of individuals with MDR-TB	NHMRC, VNTP
P2001 12 weeks of supervised 3HP NCT02651259*	Protocol development	HIV-positive and HIV-negative pregnant and postpartum women with MTB infection	IMPAACT
CORTIS 3HP versus no intervention and active surveillance for TB NCT02735590*	Beginning enrollment Q3 2016	HIV-negative adults with MTB infection in high-risk individuals identified by a gene-based signature of risk	University of Cape Town, Bill & Melinda Gates Foundation

* Clinicaltrials.gov identifier; for more details, see http://www.clinicaltrials.gov

** Australian New Zealand Clinical Trials Registry identifier; for more details, see http://www.anzctr.org.au

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases (NIAID)
ARVs: antiretrovirals
CIHR: Canadian Institutes of Health Research
IGRA: interferon gamma release assay (QuantiFERON-TB Gold In-Tube (QFT) or T-SPOT TB test)
IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group, NIAID
NHMRC: National Health and Medical Research Council (Australia)
NIAID: National Institute of Allergy and Infectious Diseases (U.S.)
TBESC: Tuberculosis Epidemiologic Studies Consortium, U.S. Centers for Disease Control and Prevention
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
UK MRC: Medical Research Council, United Kingdom
VNTP: Vietnam National Treatment Program

Treating MTB Infection in Household Contacts of People with DR-TB

The question of how to treat MTB infection among individuals exposed to DR-TB is one of the most vexing, and least studied, in TB prevention. To date, no randomized controlled trials have been conducted to guide prophylactic treatment of people exposed to DR-TB, who are often people living in the same household as someone with multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). For household contacts of DR-TB patients, MTB infection is an experience fraught with uncertainty, as progression to active disease could entail an MDR-TB or XDR-TB diagnosis. The lack of research on this topic has resulted in wildly divergent guidelines. On one end of the spectrum, the U.S. Centers for Disease Control and Prevention (CDC) outlines a range of treatment options—typically 6–12 months in duration—based on the idea that physicians should treat probable DR-TB infection with two or more drugs to which the infecting organism is believed susceptible.[95] On the other end, the WHO contends "strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment."[96]

To help fill this evidence gap, the AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) are collaborating on the PHOENIx study, which will enroll HIV-infected and uninfected child, adolescent, and adult household contacts of adults newly diagnosed with MDR-TB, pre-XDR-TB, and XDR-TB.[97] Since being described in last year's *Pipeline Report*, the study has undergone an important modification to the composition of the experimental arm and will now compare the safety and efficacy of delamanid, rather than levofloxacin, to isoniazid—each given daily for six months—for preventing active TB among individuals exposed to DR-TB. Eligible household contacts include people with HIV of any age, children ages 0–5, and anyone older than 5 years who reacts positively to TST or IGRA.[98] Delamanid has several qualities that make it an attractive potential treatment for probable DR-TB infection. Most importantly, it is effective at treating DR-TB, at least according to the phase IIb data that underpinned its approval by the European Medicines Agency in 2015.[99] It also appears to be generally safe and well tolerated; has few drug-drug interactions with antiretrovirals that might limit its use among people with HIV; can be given as a single daily dose (thereby promoting adherence); and can be administered safely to children (a safety study of delamanid in children at all age groups is nearing completion).[100,101]

Given that PHOENIx is the first large MDR-TB household study undertaken by ACTG and IMPAACT, the two networks have been conducting an observational feasibility study to prepare for the larger trial. Clinical trial sites participating in this preparatory study hit the targeted enrollment of 300 adult MDR-TB index cases and over 800 household contacts much faster than investigators had anticipated, suggesting that TB prevention trials among DR-TB patients and their close contacts are feasible despite a lack of experience in this area.[102] In addition to PHOENIx, two other randomized controlled trials are investigating approaches to treating probable DR-TB infection. In Vietnam, the V-QUIN study is testing six months of treatment with levofloxacin versus placebo in Vietnamese adult, adolescent, and child household contacts of MDR-TB patients.[103] In South Africa, the TB CHAMP study will compare levofloxacin versus placebo in children ages five years and younger (see "Pediatric Tuberculosis Treatment Pipeline," page 52, for a detailed discussion of pediatric TB drug research).

Treating MTB Infection in People with HIV

Work to develop better TB prevention options for people with HIV is also progressing, and most of this work is revolving around rifapentine. The notion of using rifapentine to prevent TB has amassed considerable interest in the wake of the landmark phase III trial by the Tuberculosis Trials Consortium (TBTC), which demonstrated the safety and efficacy of 12 once-weekly doses of rifapentine and isoniazid (the 3HP regimen).[104] However, most participants in this trial were HIV-negative, raising questions about the effectiveness of the 3HP regimen

in people with HIV. The TBTC recently published the results of a 403-person substudy conducted with the ACTG and IMPAACT under the larger trial that showed 3HP is as safe and effective at preventing TB among people with HIV as nine months of daily isoniazid (9H) and is better tolerated.[105] These findings complement a study among nearly 1,150 adults with HIV and MTB infection in Soweto, South Africa, in which 3HP treatment had similar (although not superior) efficacy in preventing TB disease, fewer side effects, and better treatment completion rates than six months of isoniazid treatment.[106]

New research is investigating whether administering multiple courses of 3HP over several years offers people with HIV more durable and long-lasting protection against TB compared with a single round of 3HP in high-TB-burden countries. (Previous *Pipeline Reports* have summarized related work investigating the durability of daily isoniazid preventive therapy, or IPT). The proposed Weekly High-dose Isoniazid and Rifapentine [P] to Protect against TB (WHIPP TB) study will investigate this question using a two-part approach.[107] Part A is an observational, randomized comparison of 3HP versus six months of daily isoniazid (6H) treatment among people with HIV. The primary objective is to compare treatment completion between the two regimens; secondary objectives will compare 3HP to 6H with respect to TB incidence, all-cause mortality, and discontinuation of therapy as a result of adverse events.[108] If 3HP performs favorably in part A, the results could lead the WHO to recommend the provision of 3HP to prevent TB among people with HIV in TB and HIV high-burden countries, offering an alternative to IPT. Part B is a randomized, controlled trial with three arms and will enroll concurrently to part A. Participants in the first arm will receive one course of 6H; those in the second will receive one round of 3HP; and those in the third will receive two rounds of 3HP, one given each year for two years (referred to as pulsing 3HP, or p3HP). The trial will enroll 4,000 participants at 12–14 sites in Ethiopia, Malawi, South Africa, and Mozambique. After two years of follow-up, the primary outcome analysis will compare the effectiveness of a single round of 3HP versus p3HP in preventing TB disease among people with HIV.[109] The study is sponsored by the KNCV Tuberculosis Foundation and funded by the U.S. Agency for International Development (USAID); Sanofi is donating drugs for the study. Investigators have received ethics approval and are awaiting final regulatory go-ahead from the South African Medicines Control Council. They expect to begin enrollment in June 2016.[110]

The ACTG is also investigating the potential of daily rifapentine and isoniazid (HP) to prevent TB in people with HIV in study A5279. This phase III clinical trial is comparing the effectiveness of daily HP given for 4 weeks to daily isoniazid given for 36 weeks (9H) among 3,000 people with HIV 13 years of age and older who either have MTB infection or live in high-transmission areas. The study reached its targeted enrollment at the end of 2014 and will complete follow-up in November 2017.[111] Building on this effort, the TBTC, together with the U.S. CDC's Tuberculosis Epidemiological Studies Consortium (TBESC), the U.K. Medical Research Council (MRC), and University College London (UCL), is developing a study of daily rifapentine in settings of low-to-medium TB incidence. The study is still in the early stages of protocol development, but the current plan is to study the safety, tolerability, and efficacy of six weeks of daily rifapentine (P), primarily among HIV-negative individuals.[112] As written, the control arm in the study will be a composite of the three rifamycin-based standard-of-care regimens included in the WHO *Guidelines on the Management of Latent Tuberculosis Infection*: 3HP, three months of daily rifampin plus isoniazid (3HR), or four months of daily rifampin (4R).

The considerable potential of rifapentine to improve TB preventive therapy can only be unlocked if the drug becomes more widely available. Currently, rifapentine is approved for the treatment of MTB infection in just a single country, the United States, despite being studied through a series of public-private partnerships in at least a dozen more.[113] Sanofi has made some progress over the past year in broadening access to rifapentine, most notably through its decision to list rifapentine in the catalogue of the Global Drug Facility (GDF).[114] This means that, for the first time, TB programs outside of the U.S. will have a direct route for purchasing rifapentine and may even be able to start using the drug while registration is pending by exercising import waivers and other pre-approval access mechanisms.[115] Sanofi has also taken steps to register rifapentine in a wide swath of countries, with the most progress seen in East Asia (Taiwan and Hong Kong).[116] Still, access to

rifapentine remains far too constrained given its central role in the TB prevention research agenda. For their part, investigators should be asking more of Sanofi in terms of securing commitments to making rifapentine available swiftly and without undue delay after the conclusion of efficacy trials. This is all the more justifiable considering that the lion's share of investment in rifapentine has come from the public sector. In the United States alone, three public agencies (CDC, NIH, and USAID) are footing the bill for trials that may expand the use of rifapentine to a broader array of countries and patient populations.

PROGRESS IN PUBLIC ENGAGEMENT IN TB PREVENTION RESEARCH

The strategies being pursued by developers of TB vaccines and preventive therapies carry a mixture of risk and reward. For clinical trial participants, the decision about whether to enroll in a study involves a more personal risk/benefit calculus. Progress in the clinical research efforts described above will depend on the willingness of people at risk of TB to participate in experiments with uncertain outcomes. A similar bargain is struck by preventive interventions given that, as the writer Eula Biss reminds us, "it is through us, literally through our bodies, that certain public health measures are enacted."[117] For prevention, especially, it is important that these measures be safe, effective, and acceptable for the healthy individuals who will be asked to take therapy or undergo vaccination to ward off an event whose occurrence is probabilistic and may never come to pass. Cutting-edge science alone is not enough to guarantee that new TB prevention methods will be acceptable to their intended users—a group that at its largest could include all 2 billion people estimated to be infected with MTB globally. TB prevention science must progress in lockstep with the meaningful engagement of the communities that will be asked to embrace any resulting new technologies and that will be called, time and again, to participate in the research to develop them.

Thoughtful community engagement is an important element of any TB R&D endeavor, but its presence or absence invokes unique considerations for prevention research. The science underlying prevention carries profound implications, not only for its potential to avert suffering resulting from disease, but also for its ability to reshape how individuals imagine themselves as either sick or healthy in relation to new conceptions of risk and susceptibility.[118] If validated in clinical trials, correlates of risk, such as the gene signature identified from the South African adolescent cohort study, could create whole new clinical categories of people—the pre-symptomatically ill—that are subject to interventions ranging from treatment to vaccination to repeat testing. It is unclear whether signatures of risk will end up expanding the proportion of people with MTB infection in need of intervention, or whether they will narrow the eligibility for TB preventive services by assigning MTB-infected individuals to a spectrum of risk with interventions reserved for those at the high end. In either case, TB prevention science promises to open many people who consider themselves healthy to new forms of medical action. Engaging communities in TB prevention research, from the laboratory to the clinic, will help to ensure that the development of new TB vaccines and preventive therapies moves forward in parallel with the knowledge, values, concerns, and needs of the communities around the world at risk for TB.

Given these potentially transformative considerations, moves by Aeras in the last year to form a community engagement program come not a moment too soon. As designed, the program contains many of the best practices developed by earlier community engagement initiatives supported by TB drug developers such as the TB Alliance and the TBTC. Community engagement in TB vaccine trials sponsored by Aeras will occur on multiple levels: individual trial sites (e.g., through local initiatives led by community advisory boards), sponsors (e.g., through community reviews of clinical trials protocols), and regional (e.g., through the formation of an Africa TB vaccine advocates network).[119] Among the proposed activities, the most important is Aeras's plan to involve community representatives in reviewing clinical trials protocols—a key step for building scientific literacy and for incorporating community feedback into the research agenda. Funders of TB vaccine R&D should commit to funding the Aeras community engagement program and acknowledge this work as the ethical complement to other standards of clinical research, such as Good Clinical Practice.

RECOMMENDATIONS

For funders: Ensure financing mechanisms are sufficiently flexible and durable to support the multi-year, collaborative research endeavors that will be required to make progress against a challenge as complex and intractable as MTB infection.

For example, nearly ten years passed between when the South African adolescent cohort enrolled its first participant in 2005 and when it published results announcing the discovery of a risk signature of disease progression in the *Lancet* in 2016. This was not time wasted, and the cohort will likely yield publications and results for years to come. Further advancing our knowledge of MTB infection and TB disease may require larger cohorts with even longer periods of follow-up. In addition, funding agencies should support translational work to bridge advancements in basic science with clinical development and maintain openness to a wide range of approaches that probe the nature of MTB infection from the perspective of both host and pathogen, and through the application of new assays and imaging technologies in both humans and animal models.

For vaccine researchers and developers: Continue to explore a greater diversity of approaches to TB vaccine development through the use of experimental medicine studies and trials designed around novel endpoints.

Ultimately, this will likely require developers to introduce wholly new vaccine candidates whose designs look beyond the narrow focus on cell-mediated immunity that has dominated past efforts. The development and introduction of new assays that are able to translate signals of immunogenicity between lung and blood (or capable of safely measuring vaccine responses directly in the lung itself) should also be a priority. Developers and their sponsors should not foreclose on clinical trials among infants and people with HIV, two of the groups most in need of a new TB vaccine. Although previous trials in these two populations have fallen short of expectations, there is much that can be learned from past failures. Rather than wholly abandon vaccine concepts and constructs that did not work, vaccine researchers and developers should more forthrightly interrogate the reasons behind disappointing results.

For drug researchers and developers: Accelerate research to understand MTB persistence and the nature of latency to develop new drugs targeting latent infection.

Efforts to understand MTB persistence would benefit from initiating a dialogue with researchers involved in vaccine development about differences in how the TB drug and vaccine fields approach preclinical testing. Each field is confronting challenges related to MTB persistence and the nature of latency, but vaccine and drug developers do not always measure the same pathology or immunological events using relatable endpoints or definitions of scale in the animal models in which much of this work will be conducted. Closer collaboration with their vaccine counterparts might also open the door for drug developers to use vaccines as adjuncts to shorten therapy or reduce the risk of relapse. In the meantime, ongoing efforts to shorten and simplify TB preventive therapy for children, people with HIV, pregnant women, and household contacts of people with DR-TB should continue. The advanced stage of many of TB prevention trials obligates pharmaceutical companies involved in this research—namely, Sanofi and Otsuka—to take steps to register their products more widely and facilitate equitable access through measures such as affordable pricing.

For all researchers and developers: Recognize community engagement in research as the ethical complement to good clinical practice and take steps to involve representatives from TB-affected communities in all stages of R&D.

The potential of ongoing or planned TB preventive therapy and vaccine studies to refashion clinical practice in ways that could render many more people with asymptomatic MTB infection eligible for medical intervention makes it imperative that developers create meaningful spaces for community voices, concerns, and priorities to enter the research process. Communities must become true partners in TB prevention research, and not merely its silent beneficiaries.

For activists: Take up TB prevention as a unified cause and break with the habit of advocating for vaccines, preventive therapy, and infection control as separate and unrelated technological fixes.

With the exception of TB PROOF—a South African advocacy group founded by doctors who contracted TB that is dedicated to preventing MTB infection among healthcare workers—activist voices in TB prevention have been few in number and modest in volume. This absence does not reflect a lack of need. A global shortage of BCG continues into its third year, needlessly endangering the lives of millions of infants.[120] Rifapentine, the cornerstone of TB preventive therapy research, is registered for the treatment of MTB infection in just one country, despite being studied in at least a dozen more. Individuals exposed to MDR-TB have few evidence-based options to treat probable drug-resistant infection. And countries remain slow to rollout proven interventions such as IPT to people with HIV, 400,000 of whom died from TB in 2014.[121] We are one year closer to 2025, the year WHO says new prevention tools must be introduced to reach the End TB Strategy's goal of eliminating TB by 2035, and there is no new vaccine or transformative preventive drug regimen on the immediate horizon. The clock is ticking.

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The Tuberculosis Treatment Pipeline: Activity, but No Answers

By Erica Lessem

In the past year, the development of new tuberculosis (TB) drug candidates experienced some setbacks as well as some wise pruning, with the unexpected suspension of enrollment in STAND (a phase III combination trial that includes the new drug pretomanid), the discontinuation of candidate TBA-354 (due to signs of toxicity), and the official end of development of AZD5847 (due to lack of anti-TB activity). In a bright spot, Qurient's Q203 entered phase I, representing a new drug class and a new sponsor in TB clinical trials. But overall, the new TB drug development landscape remains parched, with just five candidates from four classes in development—including bedaquiline and delamanid, which already have conditional marketing approval in some countries. Most of these drugs have been stalled for years. Delays across the board, from sponsors, from regulators, and from funders, are preventing nascent progress from flourishing. The phase III trial for bedaquiline has finally started enrolling—some five years after the phase IIb trial concluded. Sutezolid is still awaiting entry into phase IIb, nearly five years after showing promise in phase IIa. Delamanid's phase III trial is chugging along dutifully, but, due to the lengthy standard-of-care background treatment and follow-up time required in TB clinical studies, won't give results till 2018.

More activity is ongoing among trials testing combinations of drugs already on the market, often called repurposed drugs. But again, most will not bear fruit for several years. These various trials to optimize therapies point to creativity among researchers but also to the poor existing evidence base for use that has left the TB field reliant upon lengthy, poorly tolerated—and, for drug-resistant TB, marginally effective—regimens. Some exciting advances are being made in preventive therapy for TB—these are now reported in the TB prevention chapter (see page 15)—but this chapter will focus exclusively on the development of treatments for active TB disease.

New guidelines from the World Health Organization (WHO) may help improve the treatment of multidrug-resistant TB (MDR-TB) by updating options for stronger treatments in combination regimens, though the newly recommended putative treatment-shortening approach has yet to be validated in randomized controlled trials. However, the updated WHO guidelines will help increase the use and availability of drugs of greater potency such as delamanid, bedaquiline, clofazimine, and linezolid.[1] MDR-TB treatment is still inadequate, with fewer than 10% of those with the disease successfully treated worldwide, and less than 2% of those who may benefit from new drugs receiving them.[2,3] Investment in new alternatives is also scandalously low; in 2014, just US$243 million out of the needed US$740 million were available for TB drug research and development (R&D).[4] Recent global and national strategic plans to address antimicrobial resistance and TB, such as those from the Netherlands, the United States, and the United Kingdom, must go beyond lip service and be met with financial commitments to increase support for TB R&D.[5,6,7,8] Countries with high TB burdens and large economies, such as Brazil, China, India, Indonesia, Russia, and South Africa, must contribute far more to R&D as well as to service scale-up.

UPDATES ON NEW COMPOUNDS IN DEVELOPMENT

Table 1. Drugs in Development for Tuberculosis

Drug	Class	Sponsor(s)	Phase
bedaquiline	diarylquinoline	Janssen (Johnson & Johnson), TB Alliance, NIAID, SAMRC, the Union, UNITAID, USAID	III
delamanid	nitroimidazole	Otsuka, NIAID, UNITAID	III
pretomanid	nitroimidazole	TB Alliance	III
sutezolid	oxazolidinone	Sequella, NIAID	IIa
Q203	imidazopyridine	Qurient, Infectex	I

NIAID: National Institute of Allergy and Infectious Diseases (United States)
SAMRC: South African Medical Research Council
The Union: International Union Against Tuberculosis and Lung Disease
USAID: The U.S. Agency for International Development

Q203

A new compound, Q203, developed by Qurient, entered clinical testing in late 2015.[9] Q203's phase I, single-dose, dose-escalating study has completed enrollment. Results will be shared in 2017, and phase II trials will likely start then.[10] A member of the imidazopyridine class, Q203 targets the respiratory cytochrome bc1 complex, inhibiting the synthesis and homeostasis of adenosine triphosphate (ATP), thereby crippling the energy conversion system in both replicating and nonreplicating TB bacteria.[11] Q203 brings much-needed diversity to the pipeline and is an important addition to early-stage development as TBA-354 drops out of the running. Qurient is developing Q203 with support from the Korea Drug Development Fund and is partnering with Infectex to develop the drug for Russia and the other Commonwealth of Independent States (CIS) markets.

TBA-354

TBA-354, in the same class of drugs as delamanid and pretomanid (the nitroimidazole class), was the first candidate to enter phase I TB trials in six years, but regrettably, this rising star burned out quickly. After a phase I dose-escalating trial showed an association with mild signs of neurotoxicity (repetitive uncontrolled eye movements and overactive reflexes, from which all affected study participants recovered), the TB Alliance voluntarily placed TBA-354 on hold in January 2016 and announced the discontinuation of its development in March 2016.[12,13] This unfortunate event nonetheless represents responsible stewardship and communication of results, and it reinforces the need for more investment in TB R&D since—as in all disease areas—the majority of early-stage drug candidates will fail, necessitating a variety of compounds in development at a given time.

Pretomanid

The development of another nitroimidazole, pretomanid, has also been hampered—this time by unexpected fatalities that led to a partial clinical hold on pretomanid and a complete hold for the STAND study.[14] This phase III trial was testing the combination of pretomanid (at different doses) along with moxifloxacin and pyrazinamide (PaMZ) in people with drug-sensitive TB (DS-TB) and some forms of MDR-TB; TAG has previously critiqued the design of this trial, particularly its uncontrolled MDR-TB arm and the regimen's expected vulnerability to resistance.[15] Unfortunately, the experimental regimen was associated with high levels of liver

toxicity, which caused the death of three participants, all in the drug-sensitive PaMZ arms of the study. The study's Data Safety Monitoring Committee (DSMC) promptly recommended a suspension in enrollment in September 2015 and, after further analysis, in November 2015 recommended restart of enrollment with the addition of safety procedures and, at least initially, the exclusion of people with HIV.[16] In May 2016, the DSMC completed its review and concluded that full enrollment could resume regardless of HIV status; in May 2016, the Alliance noted it was preparing all necessary regulatory submissions to prepare for resuming enrollment into the STAND trial.[17]

The NiX-TB trial, which is testing pretomanid, bedaquiline, and linezolid in participants with extensively drug-resistant TB (XDR-TB), is faring better—though there is no randomization or control arm in this open-label study. As of March 2016, 37 patients were enrolled, and 14 patients completed treatment. The TB Alliance reports—though data have not yet been peer reviewed or formally presented at a scientific meeting—that four patients have died early on in treatment due to underlying disease, and that all other patients are doing well and showing good clinical response, with the majority having converted their sputum cultures to negative in the first two months of treatment. Linezolid toxicity has been manageable, though some dose interruptions and dose reductions occurred, mainly after week 9. The first formal interim analysis will occur in the third quarter of 2016.[18]

NC-005, a phase IIb trial that is testing the efficacy and safety of two months of bedaquiline (in a simpler dosing scheme than the currently recommended one), pretomanid, and pyrazinamide in about 240 patients with either DS- or MDR-TB, completed enrollment at the end of 2015 and will have results at the end of 2016.[19] The PRACTECAL study, a multiarm, open-label, randomized controlled pragmatic trial from Médecins Sans Frontières (MSF) that will examine various combinations of pretomanid, bedaquiline, moxifloxacin, linezolid, and clofazimine given for six months to people with MDR-TB in comparison to the WHO standard of care, has received ethics and regulatory approval; MSF anticipates opening enrollment in the third quarter of 2016.[20]

Sutezolid

Readers will be dismayed to learn that sutezolid, an oxazolidinone hoped to be a safer alternative to linezolid, is still stuck in phase IIa some three years after Pfizer ended its anti-infectives program and licensed the promising candidate to the small pharmaceutical company Sequella. Sequella has recently called sutezolid a "companion drug" for its probably ineffective compound, SQ109.[21] Sutezolid is, in fact, a candidate in high demand on its own (unlike SQ109, see more in box "Foul Play in the Federation," page 41). Fortunately, the U.S. National Institutes of Health (NIH) will sponsor the manufacture of 15,000 doses of a 600 mg tablet, which should be ready within six months after a protocol for an AIDS Clinical Trials Group (ACTG) study is given the green light. ACTG study A5289 is under development and currently features sutezolid replacing ethambutol in the experimental arm of a two-stage, adaptive study design to evaluate the pharmacokinetics, safety, and initial efficacy of sutezolid over two and eight weeks in people with DS-TB. It would determine an ideal dose for sutezolid, as well as evaluate interactions between rifamycins and sutezolid and its main metabolite.

If the study is approved for implementation, A5289 will trigger sutezolid's long-awaited entry into phase IIb.[22] Sequella and Johns Hopkins (which owns the intellectual property rights for the development of sutezolid in combinations) should turn over intellectual property rights, and Sequella should also release the toxicity and clinical data on sutezolid to date to the Medicines Patent Pool (MPP). Fortunately, it appears Johns Hopkins has entered into negotiations to do so.[23] If Sequella refuses to turn over early data to facilitate collaboration, it will take other interested parties three to five years and several million dollars to reproduce data to move forward with development—wasted time and money that are simply not available given the scarce resources for TB R&D and the urgent need for new compounds.

Bedaquiline

Bedaquiline's use in programmatic settings is on the rise (see table 2), and data described below support the continued expansion of its use. Indeed, the new WHO MDR-TB guidelines better categorize bedaquiline (and delamanid) as agents that can be added on to an MDR-TB regimen to ensure incorporation of five effective drugs.[24]

Data from South Africa's incorporation of bedaquiline first into a clinical access program and then into routine programmatic use indicate the drug's safety, effectiveness, and importance in treating MDR-TB. The bedaquiline clinical access program, which started with just five sites while the Medicines Control Council (MCC) was reviewing bedaquiline's dossier for marketing approval, enrolled 221 patients for whom other treatment options had been exhausted. Data from the full cohort of 221 patients with follow-up will be available in 2017, but an interim analysis of the 91 patients with MDR- or XDR-TB enrolled by July 2014 (60 of whom had completed treatment) showed that 70 percent had culture converted or remained culture negative—an impressive result for these patients with intractable forms of TB, many of whom had HIV infection and low CD4 counts (as opposed to carefully screened clinical trial participants, who are generally healthier and have fewer complications). The South African experience showed that participants with HIV on appropriate antiretroviral therapy (ART) did quite well on bedaquiline, and participants could easily be switched to nevirapine- or lopinavir/ritonavir-based regimens for the duration of their treatment with bedaquiline and then be placed back on the preferred efavirenz-based fixed-dose ART (whose use is contraindicated with bedaquiline due to drug-drug interactions).[25] Notably, lopinavir/ritonavir does increase bedaquiline exposure compared with no ART (median area under the curve 67,002 vs. 34,730 ng·h/mL, P = .003; median time of highest concentration [Tmax] of 6 vs. 4 hours, P = .003; and terminal half-life of 55 vs. 31 hours P = .004), though clinical implications are unknown.[26]

Based on this positive experience, and with the MCC's approval of bedaquiline, the South African Department of Health launched a framework for routine programmatic use of bedaquiline in June 2015.[27] Under this framework, bedaquiline can be used in the public sector without review by the national or provincial program in anyone 18 years or older with pre-XDR-TB (TB that is resistant to either a fluoroquinolone or an injectable, as well as isoniazid and rifampin) or XDR-TB, whose TB shows *InhA* and *KatG* mutations (indicating resistance to isoniazid), who has intolerance to second-line drugs (such as drug-induced hearing loss or psychosis), or who has a history of surgery, as long as he or she has no personal or family history of QT prolongation (a potentially dangerous disturbance in the heart's electrical activity, for which bedaquiline increases the risk). The South African treatment program does allow for people who are under 18, who are pregnant, or who have MDR-TB treatment failure without proven second-line drug resistance to receive bedaquiline per individual case review and approval.

Over 1,000 patients from all but one (Mpumalanga) of South Africa's provinces have now received bedaquiline. The vast majority have XDR-TB (39%) or pre-XDR-TB (40%); 12% received bedaquiline due to intolerance of other drugs, 8% due to *InhA* and *KatG* mutations, and 1% because they were surgical candidates. For the first time, a new TB drug has been added to routine management for MDR-TB, and it is going very well.[28,29] In a separate analysis of the 598 patients who started bedaquiline between March and end of September 2015, the most common reason for denying bedaquiline initiation was having too few potentially effective drugs in the proposed background regimen, pointing to the urgent need for companion drugs such as linezolid and delamanid. Indeed, provinces that quickly scaled up bedaquiline use were those that had linezolid access, as well as those that had tools to detect need for bedaquiline (genotypic second-line drug resistance testing and capacity to detect high-frequency hearing loss).[30]

More data to inform the optimal use of bedaquiline come from a French cohort of patients started on bedaquiline between 2011 and 2013. In this cohort of 45 patients, 33 patients received bedaquiline for longer than six months (the duration that was studied in phase IIb clinical trials and hence the recommended

duration of treatment under conditional approvals and in WHO guidance);[31] some patients received bedaquiline for up to 768 days, with a median of 360 days. Patients receiving courses of bedaquiline for more than six months were more likely to have hepatitis C (58% vs. 17%, $P = .020$), to have been previously treated for TB (94% vs. 25%, $P < .001$), and to have sputum culture-positive TB (97% vs. 75%, $P = .048$). In those who received a standard six-month course of bedaquiline, 75% achieved cure, versus 82% of those receiving a longer course. There were no significant differences in adverse events in the two groups. These findings indicate that prolonged bedaquiline use is well tolerated, at least in this small cohort, and that good outcomes may be partially explained by the decision to extend bedaquiline treatment in select challenging cases. The clinicians from the French program therefore recommend extension of bedaquiline in cases that would have fewer than four effective drugs if bedaquiline were stopped, that have delayed microbiological response (i.e., culture positivity after four months of treatment), and risk factors for poor outcomes (e.g., extensive lung disease, low body mass index, high acid-fast bacilli [AFB] positivity, or HIV), as long as prerequisites such as pharmacovigilance, close monitoring, patient consent, treatment tolerability, and expert opinion are in place.

All countries with MDR-TB burdens should follow France's and South Africa's examples and safely incorporate bedaquiline into their treatment programs. Ministries of health in countries such as India and the Philippines have been negligent in making this drug available to their citizens who so desperately need it: despite registration and availability of the drug and guidelines for its use in country, as of May 31, 2016, neither has started a single patient on treatment under routine programmatic conditions.

Indeed, further research supports the increased use of bedaquiline. A new analysis of the phase II, randomized, double-blind C208 stage 2 study of bedaquiline showed that only two out of ten participants receiving bedaquiline who had either converted or relapsed acquired resistance to companion drugs, versus 16 out of 30 in the background regimen plus placebo arm. No participant developed pre-XDR-TB or XDR-TB in the bedaquiline arm, versus six and two participants, respectively, in the placebo arm. Though the number of participants in this analysis is very small, these data point to bedaquiline's potential ability to protect against the amplification of resistance to other drugs. Notably, one out of ten participants in the bedaquiline arm showed a greater than fourfold increase in the minimum inhibitory concentration of bedaquiline, indicating potential acquired resistance to the new drug, though this does not necessarily correlate with clinically observed lack of drug efficacy.[32] Some clinical cases of resistance to bedaquiline have been reported.[33]

A recent analysis of C209, the phase II single-arm open-label trial of bedaquiline plus background regimen in 233 adults with MDR-TB (including XDR-TB and pre-XDR-TB), showed high rates of culture conversion and good outcomes with bedaquiline, regardless of type of MDR-TB. Of 205 participants included in the modified intention to treat analysis, 40% had pre-XDR-TB or XDR-TB, and 66% had extensive cavitation. Yet outcomes were still good: using a conservative measure of cure (the old WHO definition of five consecutive negative cultures), 61% of participants were cured, and only 16% failed, 7 percent died, and 15% transferred out or were lost to follow-up at 120 weeks after treatment initiation. Of 37 patients with XDR-TB, 23 (62%) culture converted, and all remained culture negative during the trial—though follow-up data were only available for 16 of 23 participants for a median of 5.4 months. In multivariate analysis, cure was associated with newly diagnosed MDR-TB (82% versus 71% cured in previously treated participants, $P < .05$), and with lower AFB score (90% of sputum smear-negative cases had negative cultures by week 120 versus only 52% for participants who had an AFB score of 3, $P < .05$).[34]

The STREAM-II study, which will test bedaquiline in a nine-month injectable-free regimen, as well as a six-month combination, finally started enrolling in March 2016[35]—more than three years since the drug's approval from the U.S. Food and Drug Administration (FDA), which was conditional upon the timely conduct of a phase III trial. Mongolia is the first country to start enrollment; significant MDR-TB clinical trial capacity development for STREAM-II should benefit the field of TB R&D overall. The Union, the study's sponsor,

attributes the delay in the study's start to the greater burden required for a registrational trial (versus the pragmatic design of STREAM-I, described in the next section), including the requirement for export permits and couriering study samples when trial host countries do not have registered laboratories.

Despite these challenges, Janssen—bedaquiline's sponsor—could certainly have committed more resources to speed bedaquiline's entry into phase III, as required by the FDA. The gap between bedaquiline finishing phase IIb and entering phase III spans nearly five years; meanwhile, the paucity of data has contributed to the limited use of bedaquiline. Janssen's legal department has been delaying support for another important and long-awaited study, ACTG study A5343, which will test delamanid and bedaquiline in combination to determine if together they cause unsafe levels of QT prolongation, for which each drug individually increases the risk. Some patients have already been treated with a combination of bedaquiline and delamanid without adverse events; one patient from the Democratic Republic of the Congo experienced no QT prolongation, but a Tibetan patient from living in India did experience asymptomatic increases in QTc from <450 to 486 ms after eight doses of the new drugs. This observed increase was manageable, and no harm to the patient occurred, but it does reinforce the need for more information on the impact of the two drugs together.[36,37] Janssen's lack of urgency on A5343, coupled with its deplorable delays on initiating pediatric research even after receiving public contributions to expedite it (see "Pediatric Tuberculosis Treatment Pipeline," page 52), clearly point to Janssen's plummeting contributions to TB R&D since bedaquiline's approval—for which Janssen received a handsome reward of a priority review voucher as well as substantial tax credits. Janssen is looking into determining a breakpoint for resistance to guide drug susceptibility testing in line with the terms of its conditional FDA approval, though this appears to be scientifically challenging to determine.[38]

Public resources are furthering bedaquiline's research. The NExT study in South Africa, which is testing the drug in a six-month injectable-free regimen, has started enrolling in Cape Town, but bureaucratic delays from the South African Medical Research Council have meant that only one study site is open.[39] Bedaquiline and delamanid will also be tested together and separately as part of nine-month injectable-free regimens in the UNITAID-funded endTB trial, which sponsors MSF and Partners In Health anticipate to begin enrollment in late June or early July 2016.[40]

Delamanid

Delamanid's phase III trial, which started in a much timelier fashion than bedaquiline's (although it was arguably also more urgent, given the poor design of delamanid's phase IIb trial), is in follow-up, with results expected in 2018. These results, though eagerly anticipated for the information they will give about delamanid's safety and efficacy, will not inform the drug's optimal use in combinations, as the study design just adds it to the old WHO-recommended background regimen. The above-noted publicly funded endTB and A5343 trials should provide important information about delamanid's use, as will studies MDR-end (sponsored by the Korean Center for Disease Control to test an injectable-free regimen of delamanid, linezolid, levofloxacin, and pyrazinamide against the current standard of care in people with fluoroquinolone-susceptible MDR-TB, which is currently enrolling[41]), A5356 (the ACTG's study of linezolid and delamanid for MDR-TB), and VTEU (sponsored by the NIH Division of Microbiology and Infectious Diseases to test a delamanid-containing, injectable-free MDR-TB regimen against the standard of care).[42] Otsuka, delamanid's sponsor, which has been the lead private-sector investor in TB R&D for years, is much more advanced than Janssen in terms of its pediatric (see "Pediatric Tuberculosis Treatment Pipeline," page 52) and prevention (see "Tuberculosis Prevention Pipeline," page 15) research.

However, given Otsuka's limited-access strategy (if one can even call it a strategy), only a few hundred people have received delamanid outside of clinical trials, despite the fact that up to two-thirds of people with MDR-TB may benefit from it, according to WHO guidance.[43] Otsuka has finally made some much-needed and long-called-for changes, including allowing for the co-administration of bedaquiline and delamanid

under compassionate use, ending a formal blanket exclusion of pregnant women in the compassionate use program, and including delamanid in the Global Drug Facility catalogue. But this is just the tip of the iceberg, with approvals for delamanid still only in low-TB-burden regions of the European Union, Japan, and South Korea. Submissions are in progress for delamanid in China, Hong Kong, Indonesia, the Philippines, and Turkey.[44] Otsuka has still not filed in the vast majority of high burden countries, including in trial-site countries of Moldova, Peru, and South Africa, and in other countries with large epidemics, such as India. Table 2 provides a direct comparison of how each of the new drugs in phase III is faring on important research and access milestones. Access to bedaquiline and delamanid is particularly important as research continues to highlight the importance of early treatment in interrupting MDR-TB and XDR-TB, given extensive ongoing transmission in households, communities, and hospitals.[45]

Foul Play in the Federation: Unvalidated TB Drugs in Russia

Perchlozone and SQ109—not included in table 1, as there are no peer-reviewed clinical trial data in English to support their efficacy—are bulldozing their way forward into the Russian market. Perchlozone, developed by JSC Pharmasyntez, was approved for the treatment of MDR-TB in Russia in 2012, at a different dose and duration than those studied in the two small trials off which approval was based (see the *2013 Pipeline Report* for more details). It has since been added to the List of Vital and Essential Medicines in Russia, and the Russian Association of Pulmonologists recommends it for empiric TB treatment.[46]

In addition to the uncertain safety and efficacy of perchlozone, its clinical value for the treatment of MDR-TB might be limited because of its mode of action. A recent study demonstrated that perchlozone is a prodrug activated by monooxygenase EthA. This same enzyme activates the second-line drugs ethionamide and prothionamide[47] and is frequently mutated in the dominant MDR clones in Russia, which therefore raises the possibility that significant rates of preexisting resistance to perchlozone might exist due to prior use of ethionamide or prothionamide.[48] Moreover, the recommendation by JSC Pharmasyntez to prescribe perchlozone in combination with prothionamide is questionable.[49] This underlines the importance of a recent call to require the elucidation of resistance mechanisms as part of the approval of new TB drugs, as is already the case for antivirals.[50]

SQ109 appears to be following an equally troubling path. Developed by Sequella, the same company that has been unable to move promising candidate sutezolid forward for the past three years, SQ109 was found to have no discernable antimicrobial or clinical activity when used in combination therapy for drug-susceptible TB.[51] Sequella licensed SQ109 to Russian company Infectex, which conducted a measly but putatively registrational trial of 80 patients.[52] Despite the lack of a proper and robust trial, and no generation of peer-reviewed data or plans to do so, Sequella announced that SQ109 will be registered in Russia this year.[53]

The use of unvalidated drugs carries great costs to the patient, society, and the economy. Perchlozone's safety is unclear, its efficacy is unvalidated and may be impeded by known preexisting drug resistance, and its price tag of US$1,458 for three months is hefty.[54] SQ109, though probably safe, has no evidence of efficacy, is likely to also add substantial costs to treatment, and could endanger lives if it is used instead of a more effective drug. The use of these drugs is not only unwarranted but dangerous. Pharmasyntez, Infectex, and Sequella are each acting unethically in pursuing marketing approval before clinical evidence supports doing so. Roszdravnadzor, the Russian regulatory authority, is failing to protect public health and urgently needs to change its policies to end, rather than encourage, poor science and indiscriminate marketing. On a troubling note, Qurient, sponsor of the above-mentioned Q203, has also arranged to partner with Infectex for Russia and the other CIS countries and should be extremely careful to ensure an ethical and scientifically rigorous approach to the development of this important new compound.

Table 2. Research and Access for Late-Stage New Compounds

	Bedaquiline	Delamanid	Pretomanid
RESEARCH			
Pediatrics (see Pediatric TB Treatment, page 52)	Enrollment started May 2016	Trial started June 2013; delamanid appears safe in children age 6 and up, with further results from younger age groups expected 2017	Trial not yet started (further toxicology work pending)
Phase III trial	Enrollment started March 2016	Enrollment completed November 2013; results expected 2018	Enrollment in STAND trial started February 2015; on hold since September 2015
Latent TB infection trial (see TB Prevention, page 15)	None	Feasibility study successful; PHOENIx trial expected to start later in 2016	n/a
ACCESS			
Number of patients receiving drug under programmatic conditions	6,000 treatments shipped (as of April 2016)	1,100 treatments shipped (as of May 2016)	None
Pre-approval access programs	Started Q1 2011, ended Q3 2015; >800 patients from 47 countries enrolled	Started Q1 2014; ongoing	None
Expanded access trials	Started 2011 in Lithuania, Russia (application in China denied)	None	None
Approvals	2012: United States 2013: Russia 2014: EU, Peru, Philippines, South Africa, South Korea 2015: Armenia, India, Turkmenistan, Uzbekistan, Macau (import license)	2014: EU, Japan, South Korea 2016: Hong Kong	None (not pursuing accelerated approval; waiting for phase III combination trial completion)
Additional registrations pending	Azerbaijan, Bangladesh, Belarus, Brazil, Burundi, Cameroon, China, Colombia, Ethiopia, Ghana, Hong Kong, Indonesia, Kazakhstan, Kenya, Mexico, Moldova, New Zealand, Rwanda, Switzerland, Taiwan, Tanzania, Thailand, Uganda, Vietnam Note: Kyrgyzstan rejected due to lack of phase III data	Turkey (submissions in progress for China, Philippines, Vietnam)	None
WHO Essential Medicines List inclusion	Included (April 2015)	Included (April 2015)	n/a
Pricing	Tiered pricing by country income level plus donation program (treatment course price: high US$26,000; middle US$3,000; low US$900); 30,000 treatment courses donated to Global Fund–eligible countries	US$28,000–$33,000 in Europe; US$1,700 in Global Fund–eligible countries	n/a (note: nonprofit TB Alliance has affordability commitment)

EU: European Union; WHO: World Health Organization
n/a: not applicable as has not yet received marketing approval

OPTIMIZING THE USE OF APPROVED AND REPURPOSED DRUGS

Rifamycins

The quest for optimizing the use of rifampin, one of the most potent TB drugs and a backbone of DS-TB treatment, continues with several studies planned and underway to test much higher doses than the current standard 10 mg/kg. A two-month study to increase the dose to 15 or 20 mg/kg showed no significant increase in adverse events (no grade 4 liver enzyme increases; rates of grade 3 increases in liver enzymes were 1% in 10 mg/kg arm vs. 2% in the 15 mg/kg arm vs. 4% in the 20 mg/kg arm, P = .15).[55] Increasing the dose of rifampin to correct what is likely current underdosing may help reduce the pervasive resistance to this important drug. A recent interesting, if unvalidated, artificial model has shown rifampin is excellent at penetrating TB lesions, a breeding ground for bugs in people with cavitary TB disease.[56] If the model and the hypothesis that drug penetration improves outcomes are accurate, this may also help explain the widespread emergence of rifampin resistance, as the lack of penetration of other drugs means rifampin is effectively given as monotherapy.

Rifapentine, also in the rifamycin class, is the linchpin of shortened treatment for latent TB infection (see "TB Prevention Pipeline," page 15), and is now being studied by the Tuberculosis Trials Consortium (TBTC) and ACTG in Study 31/A5349 for its potential—with or without moxifloxacin—to shorten DS-TB treatment to four months.[57] Study 31 has started enrollment in Fort Worth, Hanoi, Hong Kong, Kampala, Port-au-Prince, and Soweto, but is behind schedule due to bureaucratic and regulatory delays. Additional funding for the TBTC, whose budget has either been cut or flatlined for the past several years, is critical to allow for timely enrollment and important additional activities such as biobanking at TBTC sites to gather as much useful data as possible from the study. In the meantime, additional funding for Study 31/A5349 from the NIH via the ACTG will support enrollment and allow for biobanking at ACTG sites.

One notable study, TRUNCATE-TB, aims to reduce treatment for most people with DS-TB to two months, using combinations of new and repurposed drugs, including the rifamycins. The approach taken in this trial is to allow larger proportions of patients to fail initial therapy than would otherwise be tolerated in conventional trials but treat again those who are not cured. The primary endpoint is the proportion cured at two years, whether or not they required additional treatment following relapse. By definition, this will result in a greater degree of illness in a number of participants but will benefit those who are cured quickly with shorter treatment durations. This is a philosophical shift from historical TB trials, which have aimed to cure as many patients as possible and do not tolerate relapses, which usually require longer treatment durations. The randomized controlled TRUNCATE-TB trial will examine four two-month regimens, compared with the standard DS-TB treatment. Experimental regimens involve an arm with high-dose rifampin (35 mg/kg), linezolid, isoniazid, pyrazinamide, and ethambutol; a second arm that is the same but substituting clofazimine for linezolid; a third arm that uses rifapentine, levofloxacin, linezolid, and pyrazinamide; and a fourth arm that has bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol. TRUNCATE-TB has complete protocol and ethics committee approvals in the United Kingdom and Singapore and should begin enrollment by the end of 2016. Planned trial site countries include Indonesia, the Philippines, Thailand, Vietnam, and China (if regulators allow it).[58]

Fluoroquinolones

Fluoroquinolones are arguably the most important element in MDR-TB treatment; resistance to fluoroquinolones greatly increases the likelihood of a poor outcome.[59] As such, several studies for MDR-TB continue to use fluoroquinolones. A recent randomized controlled trial in Korea compared treatment outcomes from levofloxacin or moxifloxacin and found they had similar treatment success rates (84.4% vs.

79.7%, P = .53 [a nonsignificant difference]), though rates of musculoskeletal adverse events were higher in those receiving levofloxacin (37.7% vs. 14.9%, P = .001).[60] Because moxifloxacin causes higher QT prolongation than levofloxacin, knowing levofloxacin has comparable efficacy is very useful in designing regimens with other QT-prolonging drugs, such as bedaquiline and delamanid. The Opti-Q study, sponsored by Boston University and the U.S. National Institute of Allergy and Infectious Diseases, is exploring the best dose for levofloxacin and should have results in 2018.[61,62]

Moxifloxacin is being used in the STREAM-I trial, a nine-month regimen for MDR-TB based on the modified Bangladesh regimen of multiple existing drugs (described in previous *Pipeline Reports*), including an injectable and clofazimine. Follow-up is ongoing; in the meantime, this regimen has received WHO endorsement for use in previously untreated patients with rifampicin-resistant TB or MDR-TB.[63] The recommendation is based on observational cohort data, with very low certainty in the evidence, calling into question the rationale for and the objectivity of recommending this regimen. Randomized controlled clinical trial data are essential for understanding how well this regimen truly works in the indicated population, and scale-up of drug susceptibility testing (see "TB diagnostics pipeline," page 1) must accompany shortened regimen rollout. However, given that the brutal 18–24-month standard of care for MDR-TB has also not been validated in randomized controlled clinical trials and is very difficult for patients, many may be eager for access to a shortened regimen.

Also controversially, gatifloxacin, used in the original Bangladesh regimen and then abandoned due to safety concerns, recently received endorsement in the new WHO MDR-TB treatment guidelines. [64] Like levofloxacin, gatifloxacin has less risk of QT prolongation than moxifloxacin, and observational studies and the OFLOTUB trial did not indicate safety issues (though in the trial the drug was only given for four months).[65] While more drugs in the arsenal to treat TB are helpful, re-adding gatifloxacin is confusing for countries and further fragments the challenging market for MDR-TB drugs, especially because there is no current quality-assured source of gatifloxacin due to its withdrawal from the market over safety concerns and because supporting evidence is of very low quality.

Because of the fluoroquinolones' good activity against TB, they continue to be examined for shortening treatment for DS-TB, for example in the above-mentioned TBTC Study 31 and as part of TRUNCATE-TB.

Of note, the FDA has recently recommended against the routine use of fluoroquinolones for more minor infections such as acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections when other treatment options exist, noting that because of serious side effects, the harms outweigh the benefits, so for these conditions, fluoroquinolones should be reserved for those without alternative treatment options.[66] This does not apply to MDR-TB and DS-TB, which are certainly more serious conditions, but does again point to the need for safer, better treatment options more generally for TB.

Clofazimine

Clofazimine, a riminophenazine long used for the treatment of leprosy and off-label for MDR-TB, is finally moving toward formal evaluation for TB in randomized controlled trials. Novartis has planned study CLAM320B2202, a phase IIb/III randomized, open-label trial to evaluate the efficacy and safety of clofazimine (at 200 mg once daily for six months followed by 100 mg once daily for the remaining 12 to 18 months of treatment) plus background regimen compared with background regimen alone in people with MDR-TB. Enrollment was anticipated to start in March 2016 but is now projected to start in April 2017.[67] The ACTG is planning a phase IIc study of clofazimine, added to standard therapy with a treatment duration of four months, for DS-TB. Clofazimine also plays an important role in the above-mentioned ongoing and planned PRACTECAL, STREAM-I, STREAM-II, and endTB studies.

The new WHO MDR-TB treatment guidelines recognize clofazimine's and linezolid's importance, elevating them as "core second-line agents" on par with cycloserine/terizidone and ethionamide/prothionamide and preferable to para-aminosalicylic acid for constructing a regimen.[68]

Linezolid

Linezolid, of increasing importance for MDR- and XDR-TB, has manageable but nonetheless challenging side effects, including painful nerve damage. The TB Alliance examined the early bactericidal activity (EBA) of linezolid over two weeks as part of its efforts to determine an ideal dose and dosing schedule for linezolid to support the above-mentioned NiX-TB trial. The study found that all daily doses, from 300 mg to 1,200 mg, given as either once-daily or twice-daily doses, demonstrated EBA, and there was a statistically significant dose response from 300 mg to 1,200 mg daily, indicating that higher doses provided greater activity, with no difference between once- and twice-daily dosing for the same total daily dose. As a result, the TB Alliance has changed the NiX study dosing of linezolid from 600 mg twice to 1,200 mg once a day.[69] Mouse model data suggest that linezolid may only be needed for one to two months, which might also be worth exploring in clinical trials.

As noted previously, linezolid availability is critical to the successful rollout of bedaquiline. One-year posttreatment outcome data from a small clinical trial of linezolid in South Korea whose four-month sputum-culture conversion data were previously reported further indicate that linezolid is an important drug for treating XDR-TB. Of 38 patients receiving linezolid, 27 had negative results on sputum culture one year after treatment end, 3 were lost to follow-up, and 8 withdrew from the study (including 4 who failed on linezolid treatment, as previously reported). Of the 27 participants completing the study, 4 had a dose reduction from 600 to 300 mg. Among 13 participants assigned to continue receiving 600 mg, 9 had to reduce the dose to 300 mg due to adverse effects. All serious adverse events resolved after the discontinuation of linezolid. Though the study design was questionable, as linezolid was effectively given as monotherapy, only 4 out of 38 participants, or 11% of those receiving linezolid, developed resistance to linezolid. In total, 27 of 38 patients (71%) with chronic XDR-TB were cured at one year after termination of treatment.[70]

To inform the use of linezolid for people with HIV on ART, a retrospective study of linezolid use for the treatment of pre-XDR-TB and XDR-TB in people with HIV in Khayelitsha, South Africa, and Mumbai, India, showed that the rate of culture conversion in patients treated with linezolid is better than previously reported among XDR-TB cohorts and that people with HIV on ART were able to tolerate prolonged linezolid exposure, adding to the body of evidence supporting linezolid's use in challenging cases.[71] Recent efforts to increase generic competition and bring down prices for linezolid in South Africa have been successful thanks to strong advocacy.[72] The Global Drug Facility has announced a 70% decrease in the price of linezolid.[73]

Carbapenems

Carbapenems such as meropenem and imipenem are beta-lactams—antibiotics with a good safety profile and low potential for interaction with antiretrovirals. Historically, they have received little attention for TB because of the high intrinsic resistance of mycobacteria to these drugs, although this can be overcome with the addition of amoxicillin/clavulanate.[74] Carbapenems have been used more frequently due to the need for companion drugs for bedaquiline. A recent proof-of-concept randomized controlled study gave two kinds of carbapenems—orally available faropenem (at 600 mg three times a day) or intravenous meropenem (at 2 g three times a day)—or the standard of care for 14 days to people (15 in each arm) with untreated, DS-TB. This study found that faropenem had no detectable EBA: estimated fall in $\log_{10}$ colony-forming units was 0.00 (95% confidence interval [CI]: −0.002 to 0.002, P value vs. control < .001), likely due to the very low exposures to the drug measured in in blood during the trial. In contrast, meropenem had good EBA, with a

fall in $\log_{10}$ colony-forming units of 0.11 (95% CI: 0.009 to 0.13) versus the control's 0.17 (95% CI: 0.15 to 0.19), though the control was still significantly better ($P < .001$).[75] Meropenem use was not associated with any grade 3 or 4 events (compared with four in the control arm and three in the faropenem arm). Diarrhea was observed frequently in both the meropemen and faropenem arms, likely from the amoxicillin/clavulanate. The study's findings indicate the need for further optimization of the use of this class for TB, including determining whether amoxicillin/clavulanate is necessary, reducing dosing to once or twice daily, prioritizing the development of orally bioavailable carbapenems, and testing faropenem medoxomil (an unapproved formulation that may have higher exposures and EBA against TB than faropenem alone) for use against TB.

Ertapenem, another carbapenem, may merit further study. A recent retrospective study in the Netherlands of 12 patients who received ertapenem as part of their treatment between 2010 and 2013 and in whom drug exposure was evaluated showed that ertapenem was well tolerated and had a favorable pharmacokinetics/pharmacodynamics profile in people with MDR-TB. Though not orally available, ertapenem requires only once-daily dosing, in contrast to meropenem's thrice-daily dosing.[76]

RECOMMENDATIONS

1. **Government agencies, pharmaceutical companies, and foundations must dramatically scale up funding for TB R&D.** In line with the third pillar of the WHO's End TB strategy, which calls for R&D, countries must commit more resources to TB drug development.[77] The U.S. government, which is the leading funder of TB R&D, should increase funding levels to $300 million by 2018 to keep its critical investments at pace with inflation. TAG suggests that this should entail an additional $17 million from the NIH, $15 million from USAID, $16 million from the U.S. Centers for Disease Control and Prevention, and $5 million from the FDA for TB R&D.[78] European Union countries, particularly Germany, should double their TB R&D funding, and Brazil, China, India, Russia, and South Africa should each triple their funding for TB R&D.[79] Activists in other countries should call for commensurate increases in their own settings.

   Companies such as Otsuka and Sanofi should maintain strong levels of investment, and Janssen needs to recommit to further developing bedaquiline, as significant work remains despite bedaquiline's conditional approval, and to moving the most promising of its pipeline of bedaquiline analogues further toward clinical study. Other pharmaceutical companies and philanthropic organizations should also begin to invest in TB R&D.

2. **Donor and high-TB-burden governments should create and invest in mechanisms that build access to TB drug development, and drug developers should participate in them.** The inability to access data hampers collaborative TB drug development, which is essential because TB must be treated with a combination of drugs to prevent the development of resistance. The inability to access drugs hampers TB treatment and cure and threatens to render the limited R&D that is occurring less useful. Fortunately, members of the TB community have proposed feasible and appealing solutions that should be actively pursued. These include remedying loopholes in the FDA's priority review voucher system to ensure innovation and drug availability and fair pricing[80] and should also entail product developers licensing their compounds to and sharing data with the MPP, which recently received a mandate to work on TB drug development and could possibly play a key role in brokering combination drug development.[81] MSF's proposed 3P ("Push, Pull, Pool") project may also provide an interesting, innovative, and potentially transformative approach to spur the development of regimens and ensure their availability post-approval, though the devil here will lie in the details of how it is actually executed.[82]

3. **Drug and trial sponsors must expedite the development of preclinical and clinical candidates.** Delays in TB research and development are widespread and atrocious. The TB drug development pipeline remains frighteningly sparse, pointing to the urgent need to advance preclinical work to allow viable candidates into clinical studies. Clinical development for the few products in the pipeline has been unacceptably slow, with drugs taking over five years to advance from one stage to the next. In particular, Janssen's and Sequella's failures to rapidly move bedaquiline and sutezolid, respectively, through important studies are deplorable.

4. **Ministries of health, regulatory authorities, and ministries of finance should prioritize the timely introduction of evidence-based TB treatment, and donors and providers of technical assistance should ensure they are supporting rather than hindering scale-up.** Drug development will not affect the TB epidemic and improve the lives of people affected by TB unless new interventions are available to communities and people who need them. Unfortunately, country-level demand for important new products such as delamanid and bedaquiline has been weak, and implementation slow. USAID, which has partnered with Janssen to make bedaquiline available via a donation program, literally cannot give the drug away for free to enough people. Poor advice from technical assistance providers has worsened the situation and excused complacency. All parties, national and global, must be much more ambitious and supportive of new ways to find and treat TB.

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The Pediatric Tuberculosis Treatment Pipeline: Beyond Pharmacokinetics and Safety Data

By Lindsay McKenna

INTRODUCTION

The roster of enrolling and planned pediatric tuberculosis (TB) treatment studies is growing. Emerging results from pharmacokinetics (PK) and safety studies continue to inform optimal dosing strategies in children and to highlight areas in need of further investigation. New pediatric formulations continue to advance to market, and consensus has begun to form around the need for efficacy studies of simplified multidrug-resistant TB (MDR-TB) treatment regimens in children.

PEDIATRIC PIPELINE OVERVIEW

Studies that are under way or starting soon will evaluate preventive therapy for children exposed to MDR-TB and treatment shortening for less severe forms of drug-sensitive TB (DS-TB) in children, as well as fill gaps in PK and safety data that are necessary to optimize treatment, including in HIV-positive children and children with MDR-TB. Table 1 provides an overview of ongoing and planned pediatric TB prevention and treatment studies.

Table 1. Ongoing and Planned TB Prevention and Treatment Studies in Children

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
P4v9 4 months of self-administered daily rifampin for prevention of TB NCT00170209*	Enrollment complete; results expected 2016	HIV-positive and HIV-negative infants, children, and adolescents 0–17 years old with LTBI	CIHR, McGill University
TBTC 35 PK and safety of rifapentine/isoniazid FDC for prevention of TB	Planned; opening 2017	HIV-positive and HIV-negative infants, children, and adolescents 0–12 years old with LTBI	TBTC, Sanofi
TB-CHAMP 6 months of levofloxacin vs. placebo for prevention of MDR-TB (substudy planned using delamanid for child contacts of FQ-R TB patients)	Planned; opening 2016	HIV-positive or HIV-negative infant and child household contacts 0–5 years old; children ≤5 years old will get new pediatric formulation	BMRC, Wellcome Trust, DFID, SA MRC
ACTG A5300/IMPAACT P2003 (PHOENIx) 6 months of delamanid vs. isoniazid for prevention of MDR-TB	Planned; opening late 2016/early 2017	High-risk (HIV+, TST+, or ≤5 years) infant, child, adolescent, and adult household contacts of index patient with MDR-TB	NIAID
V-QUIN 6 months of levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2016	HIV-positive or HIV-negative adult household contacts; phased inclusion of infant, child, and adolescent contacts	NHMRC

Study/Regimen	Status	Population(s)	Sponsor(s)
TREATMENT – NEW DRUGS			
232 PK and safety of delamanid; OBR for treatment of MDR-TB NCT01856634*	Enrolling; final results expected 2018	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
233 6 months of delamanid; OBR for treatment of MDR-TB NCT01859923*	Enrolling; final results expected 2020	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
IMPAACT P2005 PK and safety of delamanid; all oral OBR for treatment of MDR-TB	Planned	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID
JANSSEN C211 PK and safety of bedaquiline; OBR for treatment of MDR-TB NCT02354014*	Enrolling	HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤12 years old will get pediatric formulation	Janssen, UNITAID/TB Alliance (STEP-TB Project)
IMPAACT P1108 PK and safety of bedaquiline; OBR for treatment of MDR-TB	Planned; opening 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID
TREATMENT – EXISTING DRUGS			
Treat Infant TB PK and safety of FLDs using 2010 WHO dosing guidelines for treatment of TB	Enrollment complete; results presented 2015	HIV-positive or HIV-negative infants <12 months old with TB	UNITAID/TB Alliance (STEP-TB Project)
PK-PTBHIV01 PK of FLDs using 2010 WHO dosing guidelines for treatment of TB NCT01687504*	Enrollment complete; interim results presented 2015; final results expected 2016	HIV-positive or HIV-negative children 3 months to 14 years old with TB	NICHD
OptiRif Kids PK, safety, and dose optimization of rifampin for treatment of TB	Planned; opening 2016	HIV-positive or HIV-negative infants and children ≤5 years old with TB	TB Alliance
SHINE 4 vs. 6 months using 2010 WHO dosing guideline–adjusted FLD FDCs for treatment of minimal TB	Planned; opening 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–16 years old with minimal TB	BMRC, DFID, Wellcome Trust, UCL
TBM-KIDS Safety and efficacy of high-dose rifampin 3 levofloxacin for treatment of TBM	Planned; opening 2016	HIV-positive or HIV-negative infants and children with TBM	NICHD
MDR-PK 1 PK and safety of SLDs for treatment of MDR-TB	Enrollment complete; interim results presented; final results expected 2016	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB or LTBI	NICHD
MDR-PK 2 PK, safety, and dose optimization of SLDs for treatment of MDR-TB	Enrolling; results expected 2020	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB	NICHD, SA MRC

Study/Regimen	Status	Population(s)	Sponsor(s)
COTREATMENT WITH ARVS			
DATiC PK of FLDs using 2010 WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine NCT01637558*	Enrolling; results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB	NICHD
IMPAACT P1106 PK of rifampin and isoniazid with nevirapine or lopinavir/ritonavir NCT02383849*	Enrolling; results expected 2018	HIV-positive or HIV-negative low-birth-weight/ premature infants	NIAID, NICHD
PK and safety of nevirapine with rifampin-containing TB treatment NCT01699633*	Enrolling; results expected 2017	HIV-positive children 3 months to 3 years old with TB	NICHD
IMPAACT P1070 PK and safety of efavirenz with rifampin-containing TB treatment NCT00802802*	Enrollment complete; results presented 2016	HIV-positive children 3 months to <3 years old with TB	NIAID, NICHD
PK and safety of efavirenz with rifampin-containing TB treatment NCT01704144*	Enrolling; results expected 2017	HIV-positive children and adolescents 3–14 years old with TB	NICHD
HIVPED001 PK and safety of superboosted lopinavir/ritonavir (1:1) with rifampin-containing TB treatment NCT02348177*	Enrolling; interim results presented 2015; final results expected 2016	HIV-positive infants and children with TB weighing 3–15 kg; DNDi developing stand-alone ritonavir booster formulation	DNDi, AFD, UBS Optimus Foundation, MSF
IMPAACT P1101 PK and safety of raltegravir with rifampin-containing TB treatment NCT01751568*	Enrolling; results expected 2018	ARV-naive, HIV-positive children and adolescents 2–12 years old with TB	NIAID
*U.S. National Institutes of Health (NIH) clinical trial identifiers; for more information, go to ClinicalTrials.gov.			

AFD: French Development Agency
ART: antiretroviral therapy
ARV: antiretroviral
BMRC: British Medical Research Council
CIHR: Canadian Institutes of Health Research
DFID: Department for International Development (United Kingdom)
DNDi: Drugs for Neglected Diseases
FDC: fixed-dose combination
FLD: first-line drug
FQ-R: fluoroquinolone-resistant
IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, NIH
LTBI: latent tuberculosis infection
MDR-TB: Multidrug-resistant tuberculosis
MSF: Médecins Sans Frontières
NHMRC: National Health and Medical Research Council (Australia)
NIAID: National Institute of Allergy and Infectious Diseases, NIH
NICHD: National Institute of Child Health and Human Development, NIH
OBR: optimized background regimen
PK: pharmacokinetics
SA MRC: South African Medical Research Council
SLD: second-line drug
TB: tuberculosis
TBM: tuberculous meningitis
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
TST: tuberculin skin test
UBS: Union Bank of Switzerland
UCL: University College London
WHO: World Health Organization

TB drugs and regimens with proven efficacy in adults have long been assumed to work at least equally as well in children. Typically, PK and safety studies are conducted in children only to inform appropriate dosing and to confirm safety and tolerability; efficacy studies are therefore not usually considered to be necessary.

However, given the paucibacillary nature of TB disease in children (characterized by fewer TB bacteria in the body), it might be possible to achieve a cure using shorter, milder regimens than those that are necessary in adults. This logic underpins **SHINE**, a study to evaluate whether it is possible to shorten standard first-line treatment from six to four months for less severe forms of pulmonary and extrapulmonary TB in children. There is an urgent need to conduct a similar evaluation to shorten treatment for children with less severe MDR-TB; conversations about what this regimen and study might look like are ongoing. Regimens for children with more severe forms of TB with higher bacterial loads, such as disseminated or HIV-associated TB, should also be studied.

RESEARCH UPDATES

Data from ongoing pediatric PK and safety studies continue to contribute findings that are important for optimizing TB treatment for children. Here we present recent research updates and discuss remaining research needs for first-line, second-line, and new TB drugs in children. For a comprehensive discussion of available evidence and recommended doses for TB drugs in children, see the review *Antituberculosis Drugs in Children*, from Schaaf, Garcia-Prats, and Donald.[1]

First-Line Drugs

A study of first-line treatment in infants in Cape Town, South Africa (**Treat Infant TB**; N = 39), using doses recommended by the WHO, found that 35 mg/kg (recommended range: 30–40 mg/kg) of pyrazinamide and 15 mg/kg (recommended range: 10–20 mg/kg) of isoniazid achieved drug exposures in infants that are comparable to those in adults. Exposures following 15 mg/kg (recommended range: 10–20 mg/kg) of rifampin and 20 mg/kg (recommended range: 15–25 mg/kg) of ethambutol were lower than those achieved in adults. HIV-positive infants taking ARVs (abacavir, lamivudine, and lopinavir/ritonavir) achieved lower pyrazinamide and ethambutol exposures than did HIV-negative infants.[2,3]

Another study of first-line treatment using WHO-recommended doses in Durban, South Africa, in children 10 years old or younger found exposures for rifampin, isoniazid, and pyrazinamide below those associated with optimal microbiological and clinical outcomes in adults.[4]

A study of first-line treatment in infants and children in Ghana (**PK-PTBHIV01**; N = 62; 47% of children less than five years old), again using WHO-recommended doses, found that 59% of children had low exposures to rifampin and 52% of children had low exposures to ethambutol.[5,6]

A recent study in Vietnamese children 15 years of age or younger found rifampin concentrations in cerebrospinal fluid below the minimum inhibitory concentration (minimum drug concentration required to inhibit mycobacterial growth) for almost all children treated for TB meningitis using pre-2010 WHO-recommended doses.[7] These findings support planned work to investigate the use of higher doses of rifampin for TB meningitis (**TBM-KIDS**). Further research is urgently needed to establish optimal drug combinations and doses for the treatment of pediatric TB meningitis.

Despite good treatment outcomes, investigators continue to find lower drug exposures measured by Cmax (peak drug exposure) and area under the curve (AUC, or total drug exposure) in children compared with adults. It is important to note a recently demonstrated association between low TB drug levels and poor outcomes in children. A study in India comparing PK for rifampin, isoniazid, and pyrazinamide in HIV-

positive and HIV-negative children receiving thrice-weekly TB treatment found that the Cmax of rifampin and pyrazinamide significantly affected TB treatment outcomes.[8] These findings support the higher and daily doses recommended by the WHO and underscore the need to identify PK targets that correlate with good outcomes in children and the drug doses that are necessary to achieve them. Low rifampin exposures in children are of special concern for the treatment of more severe forms of TB and in light of plans to evaluate shorter regimens.

Children experience a broad spectrum of TB disease, ranging from severe TB (e.g., TB meningitis) in young children to limited pulmonary disease to cavitary disease in adolescents. Optimal drug doses and treatment durations likely differ by disease type (extent and location). It is critical to determine which PK values correlate most precisely with efficacy for TB drugs in children. This information is necessary to optimize pediatric dosing, which is especially important in the context of simplified and shortened regimens for DS-TB and drug-resistant TB (DR-TB) and in treating more severe forms of TB.

Findings from these studies point to the need for investigations to determine PK targets for children, especially considering differences in bacterial burden and severity and location of disease; to elucidate optimal age- and weight-based dosing schedules in infants and young children; and to optimize dosing for first-line TB drugs in children younger than five years. In addition, as investigators continue to study higher doses of rifampin in adults without finding toxicity (see "Tuberculosis Treatment Pipeline," page 35), higher doses should be considered in children and evaluated in future PK and safety studies. Some work is already under way or being planned, including a study to evaluate the PK and safety of higher doses of rifampin in children 0–12 years old with severe and nonsevere forms of TB (**OptiRif Kids**). This dose-finding and safety study will explore the drug doses in children necessary to achieve the PK exposures shown to be safe, well tolerated, and associated with improved TB killing activity in recent adult studies.[9]

Cotreatment with ARVs

Rifampin (a rifamycin) induces drug metabolism by increasing the amount of drug-metabolizing enzymes in the liver.[10] As a result, rifampin interacts with many other drugs, including anti-HIV compounds such as the non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine and the protease inhibitors lopinavir and ritonavir. Studies are necessary to characterize these drug-drug interactions and to determine whether dose adjustments are necessary or contraindications exist.

Efavirenz, which has minimal interactions with rifampin, is an important treatment option for people coinfected with TB and HIV, but PK variability and formulation issues have precluded its use in children younger than three years. A PK study using higher doses of efavirenz (65 mg/kg) in TB/HIV-coinfected children 3–36 months old (**P1070**) found therapeutic efavirenz concentrations in children with fast metabolism of drugs processed by the cytochrome P450 2B6 enzyme (encoded by the *CYP2B6* gene). The investigators concluded that a lower dose is likely to be necessary for TB/HIV-coinfected children with slow CYP2B6 metabolism.[11] This study demonstrates that optimal exposure to efavirenz can be achieved in coinfected children younger than three years but requires pretreatment genotyping with pharmacogenomic assays that are expensive and not widely available.

A study of rifabutin, an alternative to rifampin that is more forgiving in adults on protease inhibitor–based antitretroviral therapy (ART), in HIV-positive children younger than five years receiving lopinavir/ritonavir closed early due to safety concerns. In the six children who completed the study prior to closure, rifabutin dosed at 5 mg/kg three times a week resulted in lower AUC and Cmax values for rifabutin and its metabolite compared with those in adults receiving the recommended dose of 150 mg rifabutin daily. In addition, high rates of severe transient neutropenia (characterized by low concentrations of white blood cells that are important for fighting infections) were observed.[12] It is unclear whether a safe and effective rifabutin dose exists for TB/HIV-coinfected children on protease inhibitor–based ART.

Interim results from a study evaluating superboosted lopinavir/ritonavir administered in a ratio of 1:1 (standard lopinavir/ritonavir is administered in a ratio of 4:1) with rifampin-containing TB treatment to infants and young children (**HIVPED001**) found that exposures to lopinavir/ritonavir (1:1) with rifampin were not inferior to exposures to lopinavir/ritonavir (4:1) without rifampin. Virological efficacy and safety were also comparable. However, problems with existing lopinavir/ritonavir formulations and tolerability remain.[13]

Given the challenges presented by interactions between protease inhibitors and rifamycins, integrase inhibitors may provide a good alternative for young TB/HIV-coinfected children. PK and safety studies for integrase inhibitors, notably dolutegravir and raltegravir, are under way for children and infants[14] (see "Pediatric Antiretroviral Pipline," in *2016 Pipeline Report*), and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network is planning to evaluate the PK and safety of raltegravir administered with rifampin-containing anti-TB treatment to children 2–12 years old (**P1101**).

Second-Line Drugs

In addition to the preliminary PK and safety data covered by previous reports,[15,16] further analyses from **MDR-PK 1**, which completed enrollment in 2015, are presented here for ofloxacin, levofloxacin, and amikacin. More data will be disseminated throughout 2016, including those on moxifloxacin and linezolid.

Children given ofloxacin at 15–20 mg/kg as whole or crushed tablets for treatment (N = 55) or prevention (N = 30) of MDR-TB had peak exposures slightly lower than, but comparable to, those achieved in adults. Total exposures were far below the targets achieved in adults—likely because of more rapid drug clearance in children. Higher Cmax values were observed in children receiving crushed versus whole tablets (statistically insignificant), but AUCs remained unaffected. Peak exposures were higher among younger children, but increased with total exposure and weight. No difference was observed in children coinfected with HIV. Ofloxacin appeared to be safe, with no grade 3 or 4 adverse events in 46 children followed for a median of 150 days.[17,18] Of the fluoroquinolones, moxifloxacin and levofloxacin are generally considered to be superior to ofloxacin, but given cost, availability, and formulation constraints, ofloxacin is still used in children in some settings.

Previously published data on levofloxacin dosed at 15 mg/kg in children show low drug exposures compared with those achieved in adults.[19] Using additional PK data from children given levofloxacin at 15 mg/kg and 20 mg/kg (N = 109) and pharmacometric modeling, researchers have determined that the 20 mg/kg dose more closely approximates adult exposures.[20] However, there is room to further optimize levofloxacin exposures in children, and studies are under way (**MDR-PK 2**).

Age influenced the AUC, but not the Cmax, when amikacin was given to children (N = 96) at 15–20 mg/kg (recommended range: 15–30 mg/kg). There was no effect on exposure by HIV status. Based on these and earlier data, to achieve exposures similar to those in adults, the investigators suggest that amikacin be given to children at a dose of 18–20 mg/kg.[21] Hearing loss (associated with cumulative amikacin exposure) has not yet been analyzed in this cohort, but has been previously reported in up to 24% of children in this setting.[22]

Further analyses of the data collected in MDR-PK 1 are planned for high-dose isoniazid, ethionamide, para-aminosalicylic acid, and linezolid. **MDR-PK 2**, which opened in October 2015, will build on the evidence collected in MDR-PK 1 to further optimize the use of key second-line drugs in children, including moxifloxacin, levofloxacin, and linezolid. MDR-PK 2 incorporates a crossover design to allow for the collection of PK data on moxifloxacin and levofloxacin in children across all ages; children younger than eight years are typically only given levofloxacin due to the limitations of the existing formulation of moxifloxacin, a large unscored tablet that is bitter when crushed. MDR-PK 2 will look more closely at bioavailability when moxifloxacin and levofloxacin are administered as whole tablets versus crushed tablets or extemporaneously prepared solutions.[23]

The PK and safety data presented here and still being collected are critical to informing dosing for first- and second-line TB drugs in children. However, several ongoing or planned treatment-shortening studies in adults use higher doses of key first- and second-line drugs (see "Tuberculosis Treatment Pipeline," page 35). It is imperative that these treatment-shortening studies collect data on ideal PK values in adults, as this information is necessary to inform appropriate, evidence-based dosing in children.

In May 2016, the WHO issued an update to its guidelines for treating MDR-TB. Based on data in adults, the guidelines recommend that children with confirmed rifampin-resistant or MDR-TB be given the same consideration for treatment with a shorter MDR-TB treatment regimen as adults.[24] However, this recommendation is likely to have limited reach given the challenges of obtaining viable samples for microbiologically confirmed diagnosis of TB in children (see "Tuberculosis Diagnostics Pipeline," page 1). Another pediatric recommendation that was included in the WHO's 2016 update to the MDR-TB treatment guidelines and is likely to have much broader implications is for the exclusion of injectable agents from regimens for children with nonsevere disease.[25] This recommendation was based on consideration of the potential harms associated with the injectable agents, namely hearing loss and pain with administration, and meta-analysis of individual patient data, which points to insignificant differences in rates of treatment success among children with clinically diagnosed and nonsevere disease treated with or without an injectable agent.[26]

New Drugs

After one year of follow-up for the first age cohort (12–17 year olds) enrolled in **C232/C233** (a pediatric PK and safety study of delamanid in HIV-negative children), Otsuka found six months of twice-daily delamanid administered at 100 mg to be safe and well tolerated. Delamanid exposures in the adolescent cohort were slightly higher than but comparable to, those achieved in adults, suggesting that the standard adult dose for delamanid is adequate for adolescents.[27]

Follow-up for the second age cohort (6–11 year olds), who received 50 mg of delamanid twice daily, is ongoing, and enrollment for the third cohort (3–5 year olds), using the pediatric formulation, is half completed. A modification to Otsuka's Pediatric Investigation Plan, agreed to by the European Medicines Agency (EMA), will allow for the final cohort (0–2 year olds) to enroll in parallel. This sets an important precedent for the parallel enrollment of pediatric cohorts, which is expected to help expedite access to new drugs for younger children.[28] Despite the encouraging pace at which Otsuka's pediatric investigations are progressing and the recent inclusion of delamanid in the Global Drug Facility (GDF) catalogue, delamanid has been registered only in the European Union, Japan, and South Korea. Routine access is likely to be an issue for years to come (see "Tuberculosis Treatment Pipeline," page 35).

The WHO is planning an update to its guidance on the programmatic use of delamanid before the end of 2016 and will consider the available PK and safety data in children as young as six years.[29] Rapid release of its guidelines will be necessary to ensure that policy is not a barrier to access for children. In the meantime, the Sentinel Project on Pediatric Drug-Resistant Tuberculosis has released rapid clinical advice on the use of delamanid and bedaquiline in children.[30] Country programs shouldn't wait, but many programs will not procure or use delamanid for children without formal recommendation from the WHO in the form of updated treatment guidelines. This underscores the importance of WHO processes that allow for more rapid review and incorporation of emerging data into guidelines for children.

In contrast, bedaquiline is much more widely available to adults under programmatic conditions, but children have virtually no access to it due to lack of data. Janssen's PK and safety study of bedaquiline in HIV-negative children (**C211**), which has been in development for over five years, finally opened to enrollment in May 2016.[31] Janssen's lack of experience setting up pediatric MDR-TB studies, the paucity of adequately prepared trial sites independent of those participating in established pediatric research networks like the IMPAACT

Network, and apparent pushback from regulators were among the reported causes of the study's severely delayed start.[32] In an effort to expedite the study, Janssen is now exploring additional trial sites in Ethiopia, India, and the Philippines.[33]

To further hasten the investigation of bedaquiline in children, Janssen should make its pediatric formulation available free of charge for complementary studies, including **P1108**, a pediatric PK and safety study of bedaquiline that will include HIV-positive and HIV-negative children with MDR-TB.[34]

Box 1. Inclusion of Pregnant Women in TB Research

An estimated 3.2 million women develop TB each year; conservative models estimate that 216,500 of them are also pregnant, but these data are not collected.[35] TB is one of the leading non-obstetric causes of death among pregnant women, accounting for 28% of maternal deaths globally.[36] Currently, treatment of TB during pregnancy is done with minimal specific guidance and with a lack of information on the effects of physiological and metabolic changes that occur during pregnancy on drug metabolism and achieved drug exposures. Pregnant women are systematically excluded from TB research, and, as a result, clinicians are forced to use old and sometimes new TB drug regimens in pregnant women with TB without any guidance on safety, efficacy, or dose adjustments—or, even worse, to deny them treatment for lack of options.

An expert panel convened by the NIH recently published a consensus statement advocating for the earlier inclusion of pregnant and postpartum women in TB drug trials and outlining priority research needs.[37] The few ongoing or planned TB prevention and treatment studies in pregnant women are presented in table 2.

In line with a 1994 report by the Institute of Medicine, which recommends that pregnant women be "presumed eligible for participation in clinical studies,"[38] TB researchers should assume inclusion, and then, on an individual trial basis, think carefully about safety and whether the balance of risks and benefits warrants the exclusion of pregnant women from TB drug trials. In fact, expert consensus statements, regulatory frameworks, and guidance documents already exist to facilitate the appropriate and earlier inclusion of pregnant women in research.

Additionally, a registry, similar to the Antiretroviral Pregnancy Registry, should be established for pregnant women with TB to prospectively monitor birth defects in infants exposed to TB drugs in utero, provide early warning of major teratogenicity (ability to induce congenital malformations), and help estimate risk of birth defects. In the absence of clinical trials data, a TB registry is critical for informing the safe treatment and prevention of TB in pregnant women and their children.[39]

Table 2. Ongoing and Planned TB Prevention and Treatment Studies in Pregnant Women

Trial	Phase	TB type	Study purpose
PREVENTION			
IMPAACT P1078 (TB APPRISE) NCT01494038*	IV	DS-TBI	To evaluate antepartum vs. postpartum isoniazid preventive therapy in HIV-positive women
IMPAACT P2001 NCT02651259*	I/II	DS-TBI	To evaluate the pharmacokinetics and safety of once-weekly rifapentine and isoniazid in pregnant and postpartum women with and without HIV
TREATMENT			
IMPAACT P1026s NCT00042289*	IV	DS-/DR-TB	To evaluate the pharmacokinetics of first- and second-line TB drugs with and without ARVs in pregnant women
ACTG A5338 NCT02412436*	IV	DS-TB	To evaluate the pharmacokinetic interactions among depo-medroxyprogesterone acetate, rifampin, and efavirenz in women co-infected with HIV and TB
TB pregnancy registry	IV	DS-/DR-TB	To evaluate maternal and infant treatment and safety outcomes from clinical research databases (planned)
*NIH clinical trial identifiers; for more information, go to ClinicalTrials.gov.			

DR-TB: drug-resistant tuberculosis DS-TB: drug-sensitive tuberculosis DS-TBI: drug-sensitive tuberculosis infection

PEDIATRIC FORMULATIONS IN THE PIPELINE

In dose or form, preexisting pediatric formulations and preparations of TB drugs have been inadequate.[40] However, new pediatric fixed-dose combinations (FDCs) provide a rare occasion for celebration. Anticipated additional advances in pediatric formulation development should be approached with tempered optimism, as much remains to be done. Table 3, presented at the end of this section, provides an overview of the pediatric formulations new to market and in development.

First-Line Drugs

Five years after the WHO increased the recommended doses for first-line TB drugs in children, and following significant investments by UNITAID and work by the TB Alliance and partners under the STEP-TB project grant, Macleods has introduced new pediatric FDCs.

Macleods's FDCs of HRZ (isoniazid, rifampin, and pyrazinamide) and HR (isoniazid and rifampin) are now available through the GDF and have been successfully registered in Côte d'Ivoire and India. Registrations are pending in Botswana, Burkina Faso, Cambodia, Cameroon, Congo, Ethiopia, Ghana, Kenya, Mozambique, Nigeria, the Philippines, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe.[41] Registration is stalled in South Africa, as the Medicines Control Council requires bioequivalence work to be conducted in-country.[42] Rollout of the new pediatric FDCs is anticipated in Kenya and the Philippines before the end of 2016 and as part of a 100-site pilot program in India.[43] Macleods has also received orders from Papua New Guinea and Kiribati and an inquiry from Zimbabwe.[44]

Other companies, including Lupin, Sanofi, Sandoz, and Svizera, are working on developing and introducing their own versions, albeit at varying paces and at the mercy of review and approval times of country regulatory authorities and WHO prequalification—a mechanism put in place to ensure and monitor the quality of

medications procured in bulk—and in the absence of approval by a Stringent Regulatory Authority, a requirement of manufacturers to sell medications through the GDF.

Work to increase awareness and facilitate uptake of the new pediatric FDCs is being led by the TB Alliance, the WHO Global TB Program, and the WHO Department of Essential Medicines and Health Products. The UNITAID-funded STEP-TB project will come to an end in 2016, but UNITAID will continue to promote scale-up of the new pediatric treatment options and to support a more sustainable market, and it has issued a call for relevant proposals.[45]

Sanofi, the sponsor of rifapentine (indicated in the United States, in combination with isoniazid, for latent TB infection in children as young as two years), will perform a bioavailability and safety study of the components of its mango-flavored, fixed-dose dispersible of rifapentine and isoniazid and of a rifapentine stand-alone dispersible to facilitate dose adjustments in young children before the end of 2016. The Tuberculosis Trials Consortium will use these formulations in its pediatric PK and safety study of three months of once-weekly rifapentine and isoniazid (3HP) to prevent TB in children. The study (**S35**) is expected to open in 2017, and HIV-positive children on select ARV regimens will be eligible for participation.[46,47] Unfortunately, rifapentine is still registered only in the United States; Sanofi has a long way to go to ensure wider access for adults and children (see "Tuberculosis Prevention Pipeline," page 15).

Second-Line TB Drugs

Encouragingly, in August 2015, the WHO Expert Review Panel (ERP) issued an invitation to manufacturers to submit an expression of interest (EOI) to the WHO prequalification team for pediatric formulations of several second-line TB drugs, including cycloserine, levofloxacin, moxifloxacin, linezolid, and ethionamide.[48] Macleods expects to register pediatric formulations of these second-line drugs before the end of 2016.[49] A pediatric formulation of clofazimine was not included in the invitation for EOI, but should be immediately added considering its increasingly important role as a component of MDR-TB treatment and trials of shortened regimens. A scored-dispersible or other novel pediatric formulation of clofazimine is urgently needed to facilitate dosing in small children; an invitation for an EOI from the WHO ERP for a pediatric formulation of clofazimine is a necessary first step. It is critical that these new formulations undergo palatability and acceptability evaluations in children and that their quality be assured.

Still, even with the invited EOI and continued investments by Macleods to bring pediatric formulations for second-line TB drugs to market, without updated WHO dosing guidelines, future uptake by country programs is likely to be severely limited. The first time the WHO recommended doses for second-line TB drugs in children was 2006. In 2010, the WHO issued *Rapid Advice: Treatment of Tuberculosis in Children*,[50] which recommended increased doses of first-line TB drugs in children; in 2014, it updated its *Guidance for National Tuberculosis Programs on the Management of Tuberculosis in Children*.[51] Yet neither of these updates considered data that have emerged for the use of second-line TB drugs in children since 2006. In fact, existing WHO guidelines do not include a recommended pediatric dose for clofazimine at all. The WHO should immediately take the steps necessary to issue updated, comprehensive, and evidence-based dosing guidelines for second-line TB drugs in children.

New Drugs

Otsuka is using 5 mg and 25 mg dispersible tablets of delamanid in strawberry and cherry flavors in its PK and safety study, which is now enrolling children under five years of age (**232; 233**).

The bioavailability study for Janssen's 20 mg dispersible tablet of bedaquiline has long been completed, and Janssen's pediatric study finally opened to enrollment in May 2016. A second bioavailability study to evaluate differences between crushed and whole tablets of the adult formulation of bedaquiline (**bedaquiline-crush**) is under regulatory review in South Africa.[52] Without access to Janssen's pediatric formulation, these data are necessary to inform IMPAACT's planned PK and safety study of bedaquiline in children, including those with HIV (**P1108**). Data from bedaquiline-crush will also be important to inform use of bedaquiline in children during the time between when evidence from pediatric PK and safety studies is available and when the pediatric formulation enters the market.

Table 3. Pediatric Formulations Newly Marketed and in Development

Drug	Dose	Formulation	Company
First-line drugs			
Fixed-dose combinations H: isoniazid R: rifampin Z: pyrazinamide P: rifapentine	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Macleods
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Lupin
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Sandoz
	HRZ: 50/75/150 mg HR: 50/75 mg HP: 150/150 mg	Dispersible tablets	Sanofi
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Svizera
Ethambutol	100 mg	Dispersible tablet	Macleods
Isoniazid	100 mg	Dispersible tablet	Macleods
Pyrazinamide	150 mg	Dispersible tablet	Macleods
Rifapentine	100 mg	Dispersible tablet	Sanofi
Second-line and new drugs			
Bedaquiline	20 mg	Dispersible tablet	Janssen
Cycloserine	125 mg	Mini capsule	Macleods
Delamanid	20 mg 5 mg	Dispersible tablets	Otsuka
Ethionamide	125 mg	Scored dispersible tablet	Macleods
Levofloxacin	100 mg	Scored dispersible tablet	Macleods
Linezolid	150 mg	Dispersible tablet	Macleods
Moxifloxacin	100 mg	Scored dispersible tablet	Macleods

RECOMMENDATIONS

In recent years, significant strides have been made in pediatric TB research and development (R&D). Yet much work remains to collect critically important data in children, to increase access to the new pediatric FDCs, and to expedite development of, and access to, pediatric formulations for new and second-line TB drugs.

For researchers

- Consider children when planning adult studies. Building PK investigations into studies that evaluate higher doses of TB drugs in adults is necessary to inform future PK targets in children.
- Determine which PK value(s) correlate best with efficacy for TB drugs in children and establish PK targets based on adult data, taking into consideration the variability in severity and type of TB disease among, and challenges defining efficacy in, children.
- Enroll children two years of age and younger in pediatric studies, as this is the period during which drug disposition changes the most for children, increasing risk for high or low drug exposures.
- Include HIV-positive children in studies of new TB drugs and regimens.
- Include pregnant women in studies of new TB drugs and regimens.

For policy makers

- Incorporate emerging data into guidelines for children more rapidly, especially those for new and second-line TB drugs in children.

For regulatory authorities

- Enforce more thoughtful requirements to ensure comprehensive and timely investigations of TB drugs in children. Mandatory and time-bound pediatric investigational plans that also require studies in HIV-positive children will help to shrink the persisting evidence and access gaps that exist between adults and children for new TB drugs.[53]
- Follow the important precedent set by the EMA and allow parallel enrollment of pediatric cohorts in PK and safety studies.
- Be transparent and clear about requirements to register pediatric formulations for both existing and new drugs.
- When possible and appropriate, consider waived requirements and registration fees to facilitate access.

For donors

- Maintain and adequately fund momentum in pediatric TB drug R&D, for which global investments totaled $11.6 million in 2014.[54] Recent attacks on the budget for and AIDS research priorities of the NIH are particularly concerning for pediatric TB R&D. Not only is the NIH the leading funder, but its investments support studies that are critical to improving treatment of pediatric TB and to filling both long-standing and new gaps in pediatric PK and safety data, especially for HIV-positive children taking ARVs.[55]
- Further attention to and investments in pediatric TB trial infrastructure and site capacity development are urgently needed to support the increasingly full research agenda for prevention and treatment of TB in children.
- UNITAID, whose investments have led to the market introduction of appropriately dosed FDCs of first-line TB drugs for children, and whose planned investments will ensure global uptake of these new formulations, should invest in a project modeled after STEP-TB that is focused on expediting development and market introduction of pediatric formulations of second-line TB drugs.

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