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Tuberculosis: Is the landscape changing?

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Robert Heinrich Herman Koch, a German physician and microbiologist, received Nobel Prize in 1905 for identifying the specific causative agent of tuberculosis (TB). During his time it was believed that TB was an inherited disease. However he was convinced that the disease was caused by a bacterium and was infectious, tested his postulates using guinea pigs, and found the causative agent to be slow growing mycobacterium tuberculosis. TB is the second most common cause of death from infectious diseases after HIV/AIDS. Drug-resistant TB poses serious challenge to effective management of TB worldwide. Multidrug-resistant TB accounted for about half a million new cases and over 200,000 deaths in 2013. Whole-genome sequencing (first done in 1998) technologies have provided new insight into the mechanism of drug resistance. For the first time in 50 y, new anti TB drugs have been developed. The World Health Organization (WHO) has recently revised their treatment guidelines based on 32 studies. In United States, latent TB affects between 10 and 15 million people, 10% of whom may develop active TB disease. QuantiFERON TB Gold and T-SPOT.TB test are used for diagnosis. Further research will look into the importance of newly discovered gene mutations in causing drug resistance.

Tuberculosis (TB) is a potentially curable disease yet so challenging. Historically, it is referred to as "Captain of death" (1). Tuberculosis is a global problem as such every nation is battling with new cases especially among immigrant populations. Although death related to tuberculosis has declined in the last decade, it remains a threat to mankind. Worldwide control measures are underway but progress is hindered by the HIV-1 epidemic, drug resistance and other factors like malnutrition, diabetes, overcrowding, and poor resources (2). Tuberculosis in children has additional challenges; is underreported; diagnosis is difficult, and those less than 2 y old are at higher risk of extra-pulmonary tuberculosis.

Mycobacterium tuberculosis is an acid-fast bacillus. Humans are the only reservoir. Its intrinsic nature and other epidemiologic factors make eradication difficult. Once inhaled by aerosol, a human's immune system can eradicate an infection (50–75%) or succumb to active tuberculosis disease (5–10%). The infection can remain dormant for many years as latent TB (90–95% of patients) or it can reactivate into active disease (3,4).

Mycobacterium has existed for thousands of years based on the evidence of disease found in Egyptian mummies more than 5,000 y ago and was considered an inherited disease until Hermann Heinrich Robert Koch, a German physician and microbiologist, identified it as the specific causative agent for tuberculosis in1882. TB was noted in East Africa over 70,000 y ago before the Europeans' arrival in the 19th century. Migration of humans carrying this disease was explained by the description of TB in other countries like India and China (5). Before Koch's discovery, Hippocrates recognized it as phthisis and consumption, Clarisssimus Galen wrote about it. Fransiscus de la Boë coined the term tubercle found in the lungs; scrofula was recognized in Europe during the Middle Ages and was cured by royal touch. Laennec described the pathology of TB, and an experimental animal study was first done on rabbits in 1865. Since then, there has been tremendous progress in tests, medications, and management (**Figure 1**) related to TB (6). Traditionally for diagnosis, AFB smear test has poor sensitivity and standard culture is limited by the long 6–8 wk needed for growth of Mycobacterium. New developments such as the interferon-γ Release Assay (IGRA) and Xpert MTB/RIF are revolutionizing the diagnosis of tuberculosis. Xpert MTB/RIF has shortened drug susceptibility testing results as well (7).

Whole-genome sequencing technologies first done in1998 have provided new insight into the mechanism of drug resistance. For the first time in 50 y, new anti-TB drugs have been developed. Enough new information based on 32 studies has become available that WHO has recently revised their treatment guidelines. Centers for Disease Control and Prevention now recommends 3-mo directly observed therapy using Isoniazid (INH) and Rifapentine (RPT) as an option for treating latent TB infection (LTBI) based on the results of randomized controlled studies (8). SHINE trial was launched in July 2016 which is a large-scale randomized pediatric TB trial over 4 y period to examine the effectiveness of 4 mo treatment course. This review article focuses on the changing landscape in the diagnosis of TB in children and the future diagnostics and therapeutics for multidrug-resistant tuberculosis (MDR-TB).

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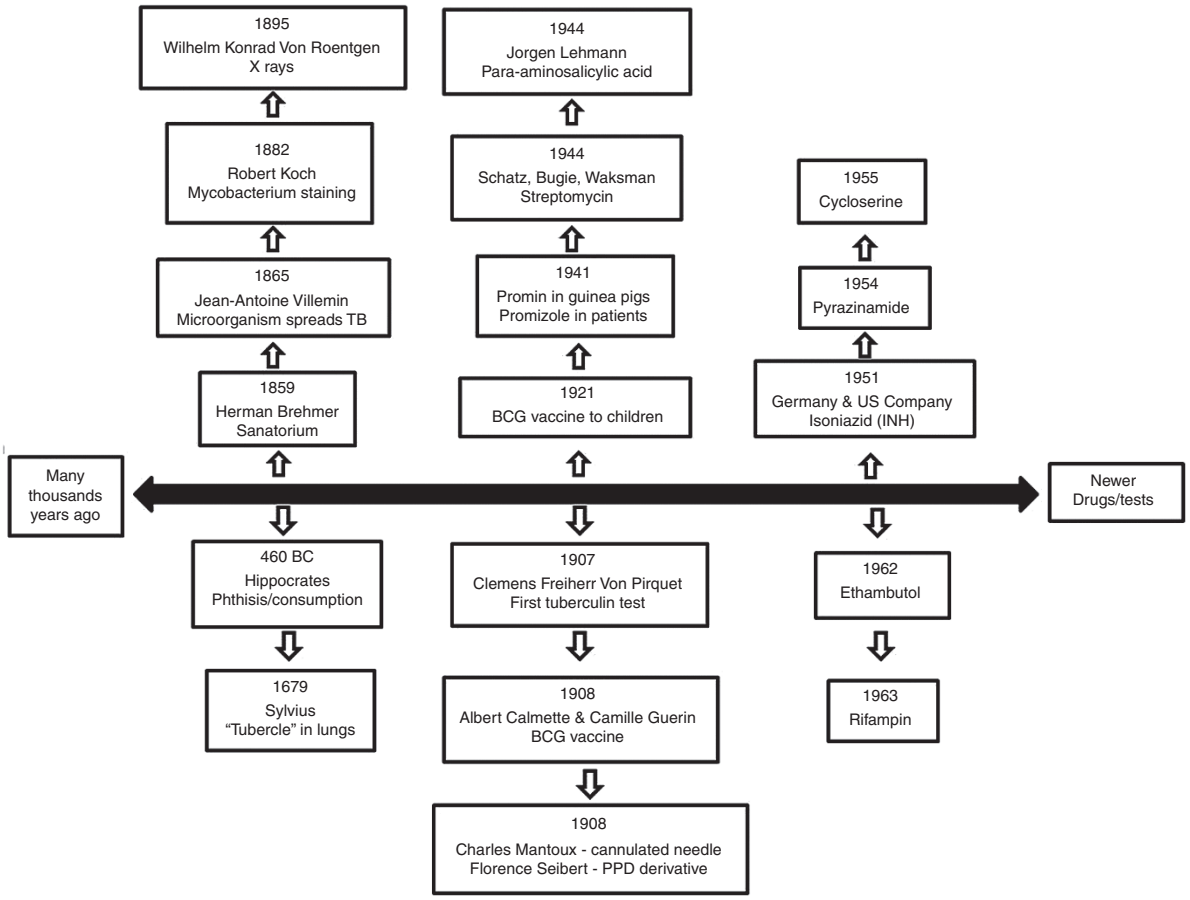

Figure 1. Timeline in tuberculosis associated with events and discoveries by notable people.

EPIDEMIOLOGY

Worldwide, TB and HIV dominate the world's biggest health threats. Around 9.6 million (6 million new cases were reported to the WHO) people were diagnosed with TB in 2014, of which 12% were in HIV positive patients. The death toll from TB in 2014 was 1.5 million people including 140,000 children, of whom 55,000 were coinfected with HIV. With a concerted global effort, TB mortality and prevalence has fallen by an estimated 47 and 42%, respectively, lower than in 1990; with the greatest improvement observed starting in year 2000. Demographics remain unchanged with the majority of cases in South-East Asia and the Western Pacific regions (58%). A large number of cases come from the African region (28%), India (23%), Indonesia (10%), and China (10%). These countries also hold the highest record for MDR-TB.

Among these 9.6 million reported cases, 5.4 million are men, 3.2 million are women and 1million are children. TB rates in US-born children are higher if one parent is foreign-born compared to if both parents are US-born (9). The WHO notes that estimating TB incidence among children poses a challenge due to rare bacteriological confirmation, under-reporting by pediatricians, lower likelihood of diagnosis in children when compared to adults cases in high-burden countries, and differing estimation methodologies (10).

LATENT TUBERCULOSIS INFECTION (LTBI) IN CHILDREN AND ADOLESCENTS

It is estimated that 1/3 of the world's population has LTBI but true incidence is limited since it is not required to be reported (6). Children represent a vulnerable group to TB and an important goal for the WHO in their 2015 END TB strategy is to identify children at risk for TB infection, test them for infection, and provide effective treatment for any with latent infection in order to prevent progression to disease (11). In particular, children under the age of 5 y are at increased risk of progression to disease shortly after infection occurs and are at risk for the most serious manifestations of TB disease such as meningitis, which still carries a high mortality even in developed countries (7). Therefore any child in close contact with a contagious source case of TB should undergo testing for evidence of infection. In countries that are upper middle-income to high-income and have a low TB incidence (<100 cases per 100,000 population), the WHO now recommends expanded testing. Targeted groups should include children immigrating from any country with a high burden of TB, or if the child has disease that may alter the immunity against TB, such as a transplant recipient, a requirement for hemodialysis or the need for anti-tumor necrosis factor therapy (12).

DIAGNOSIS OF TB INFECTION IN CHILDREN

The tuberculin skin test (TST) continues to be the mainstay in detecting tuberculosis infection in children, especially in those under age 5 (10,12). In use among children for the past 10 y, IGRAs are another diagnostic tool that can be used in certain clinical settings to improve specificity, such as in children who are BCG-immunized. These assays can also be used along with the TST to increase sensitivity in detecting infection in children who may be at higher risk for progression to disease and warrant treatment. A positive result can also be supportive evidence for TB disease in a child who has another symptom that may suggest the disease is present (13,14). The WHO has recommended the use of either TST or IGRA for screening at-risk children who reside in countries with a low burden of disease where there are ample resources for performing both tests (12). Other immunologic assays, such as interferon-inducible protein 10 (IP-10), continue to be explored for use in detecting TB infection in children. A recent prospective study investigated the correlation between the IP-10 levels in children who were household contacts to infectious TB cases with their later TST and (QuantiFERON) QFT results and identified value in its use for diagnosing TB infection. It maintains the limitation which TST and IGRAs possess but IP-10 levels cannot distinguish between LTBI and TB disease (6,15).

Once infection is established, the clinician must identify the status of the infection, specifically if it is latent or if there is disease. This evaluation requires three core components: patient history, physical exam, and radiography (10,12). Symptoms of TB disease can be nonspecific in children. Young children with TB disease have a lower bacterial load compared to adults which usually result in a different clinical presentation. Physical exam may also be normal in children with disease; so, radiography is necessary, which may show typical patterns associated with TB. Additionally, cultures in children can be difficult to obtain (hard to induce sputum and uncomfortable to intubate nasogastric tube for gastric aspirate) and may often be negative (paucibacillary disease). Sputum may be collected for acid-fast bacilli (AFB) smears but this is limited by the children who cannot produce sputum. At least 10^3 AFB per milliliter of sputum are needed in order to be detected on the smear. Recently, the use of Xpert MTB/RIF has now been endorsed by the WHO for use in detection of TB disease in children due to its improved sensitivity (20.6%, 95% CI: 13.7; 27.5) over the AFB smear method (9.2%, 95% CI: 4.2; 14.1) as well as offering the ability to identify Rifampin resistance simultaneously (3,16). The lower sensitivities can be explained by the fact young children with TB disease have a lower bacterial load compared to adults which usually results in a different clinical presentation. Hence, a negative test for TB does not rule out disease.

Biomarker research in children are promising but limited by sample size; which includes urine lipoarabinomannan with poor sensitivity (48.3%) and specificity (60.8%) (17), C-reactive protein (18), T-cell activation marker-tuberculosis assay (TAM-TB) with 83.3% sensitivity and 96.8% specificity (19), RNA expression signatures (51-transcript signature) with 82.9% sensitivity and 83.6% specificity, Gene expression signatures (LTBI—sensitivity and specificity 86%) (20).

TREATMENT OF LTBI IN CHILDREN AND ADOLESCENTS

A prospective study looked at children who were contacts to infectious household source cases and used symptoms, TST and CXR and followed for 1 y. Children with LTBI who were <5 y old were placed on Isoniazid (INH) while those >5 y old were not (in accordance with global guidelines). Among children who went on to develop disease, it was noted that they were all in the >5 y old group and therefore had not received INH (21). Treatment of LTBI in pediatrics has expanded from a single regimen to now include three options: Isoniazid, Rifampin, or Isoniazid combined with Rifapentine. Treatment duration depends on the selected agent: 6–9 mo for Isoniazid, 4 mo for Rifampin and 3 mo for Isoniazid combined with Rifapentine (22). If the child is intolerant of one agent or has a suspected mono-resistant strain, then an alternate antibiotic should be chosen for therapy. If the child could be infected with a multidrug-resistant strain, close clinical monitoring is needed but there is no consensus on the best treatment regimen. Two studies involving pediatric contacts to a source case with MDR-disease are ongoing. Simplified regimens and more pediatric-friendly formulations are also needed in order to promote adherence and completion of therapy (10,12).

MULTIDRUG-RESISTANT TB (MDR TB) AND EXTENSIVELY DRUG-RESISTANT TB (XDR TB)

MDR TB is resistant to at least Isoniazid and Rifampicin. XDR TB is defined as MDR with additional resistance to any fluoroquinolones and any of the three second-line injectable agents-kanamycin, amikacin, or capreomycin. XDR TB has been reported in 105 countries (10,23–25). Globally, an estimated 3.3% (95% CI: 2.2–4.4%) of new cases and 20% (95% CI: 14–27%) of previously treated cases have MDR-TB; similarly children with MDR-TB was estimated around 3% (26,27). On average, an estimated 9.7% (95% CI: 7.4–12%) of people with MDR-TB have XDR-TB; it is estimated that 0.15% of children are with XDR-TB (27). Globally, only 50% of patients on MDR-TB treatment were successfully treated, largely due to high rates of mortality and loss to follow-up (10).

MECHANISM OF INTRINSIC DRUG RESISTANCE OF M. TUBERCULOSIS

The bacterium has unusual structure of mycolic acid-containing cell wall which confers a low permeability and limits its drug uptake for many antibiotics and chemotherapeutic agents (23,28). The other known mechanisms for drug resistance are active efflux systems that extrudes the drug molecules that enter the cell (also responsible for resistance to other antimicrobials) (29), physiologic adaptations that occurs within the host (23,30), asymmetric growth and division which result in growth phase-dependent antibiotic survival (27), and intrinsic resistance which favors in a high level of drug resistance (23).

MECHANISM OF ACQUIRED DRUG RESISTANCE OF M. TUBERCULOSIS

Spontaneous mutations in chromosomal genes are mainly responsible for acquired drug resistance, producing the selection of resistant strains during suboptimal drug therapy (23,31). The most commonly used drugs; Isoniazid (*KatG/mabA-inhA*), Rifampicin (*rpoB*), Pyrazinamide (*pncA*), and Streptomycin (*rpsL/rrs*) develop resistance by mutation in gene and more mutations vary by geographic locations (23,32–35).

ADVANCES IN THE DIAGNOSIS OF DRUG-RESISTANT (DR) TB AND NEW DRUGS

The diagnosis of drug-resistant TB has been dependent on phenotypic, culture based methods for decades with a disadvantage of diagnostic delay. The lack of available globally-approved diagnostic tests capable of rapidly determining MDR and XDR TB remains a serious problem.

Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) was launched in 2004 and in 2010 WHO recommended its use. This assay rapidly (2 h) identifies MTB and resistance to rifampicin (36,37). WHO recommends Xpert MTB/RIF as a primary diagnostic test for adults with suspected DR-TB, children and adults with HIV with suspected TB in areas with high HIV prevalence, and detecting extra-pulmonary TB (10,36). It can detect smear negative TB in HIV-infected individuals (1). In children, where induced sputum or gastric aspirate is a challenge, this assay can diagnose TB from nasopharyngeal aspirate. This assay compared to culture in pediatric pulmonary TB showed that the pooled sensitivities and specificities of detection as 62% (95% CI: 51–73) and 98% (95% CI: 97–99), respectively. Similarly, sensitivity and specificity to detect rifampicin resistance was 86% (95% CI: 53–98) and 98% (95% CI: 94–100), respectively (38). This test may be used along with but does not replace conventional microscopy and culture diagnosis in children as Xpert MTB/RIF is not studied in outpatient settings or with different clinical or severity of TB disease. Since limited data, it is not recommended to test on urine, blood, or stool.

Line Probe Assays detecting INH and Rifampicin resistance (39), direct drug susceptibility (40), pyrosequencing (41), and microscopic observation drug susceptibility (41) are studied sparsely in children.

NEW DRUGS

Bedaquiline kills both dormant and actively multiplying mycobacteria by inhibiting mycobacterial ATP synthase, thus interfering with energy production and disrupting intracellular metabolism (**Table 1**). It is active against both drug-susceptible and DR-TB. Adding it to WHO recommended MDR-TB regimen reduced the time of sputum culture conversion in pulmonary MDR-TB (42). However, it is not recommended in children, not even for compassionate use (43).

Delamanid kills MTB by inhibition of mycolic acid biosynthesis. Two phase II trials are underway for pediatric treatment of MDR TB (clinicaltrials.gov; NCT01859923 and NCT01856634).

Sutezolid acts by binding to 23sRNA, blocking translation and thereby protein synthesis (5). It is not approved for children.

Fluoroquinolones are the key components of current MDR-TB treatment regimens. They accumulate in macrophages and granulocytes with intracellular drug concentration exceeding extracellular concentration by at least four- to five-fold. Several studies have shown their efficacy where first line drugs could not be used. Levofloxacin and Moxifloxacin have been shown to be superior to Ofloxacin (24).

CONCLUSION

Childhood TB accounts for 6–10% of all TB cases worldwide, resulting in significant morbidity and mortality (44). Children with TB can present with symptoms of common childhood illnesses, and not with typical cough, fever, weight loss as seen in adults. Up to 50% of children may be asymptomatic in the early stages of the disease (44). Once they are infected, they progress more quickly than adults to active disease, disseminated TB, and death, if untreated. Due to paucibacillary nature

Table 1. New Drugs

Study/regimen	Status	Population(s)	Sponsor(s)
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 y old with MDR-TB; children ≤5 y old will get pediatric formulation	Otsuka
233; 6 mo of delamanid; OBR for treatment of MDR-TB NCT01859923*	Enrolling; final results expected 2020	HIV-negative infants, children, and adolescents 0–17 y old with MDR-TB; children ≤5 y 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 y 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 y old with MDR-TB; children ≤12 y 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 y old with MDR-TB	NIAID

Courtesy: Lindsey McKenna. Pediatric Tuberculosis Treatment Pipeline: Beyond Pharmacokinetics and Safety Data. www.pipelinereport.org/2016/tb-pediatric-treatment.
NIAID,National Institute of Allergy and Infectious Disease, NIH ; OBR, Optimized background regimen.
*US National Institute of Health (NIH) clinical trial identifiers

of the disease in children, culture may be negative in children, even though they are infected. In many countries, one of the reasons for inadequate access to diagnosis and treatment of drug-resistant TB is that the management of drug-resistant TB (PMDT) is too centralized. Hospital-based models of care, which are still dominant in many countries, are a barrier to the expansion of PMDT because they depend on hospitals or referral centers. Greater use of ambulatory care is necessary to expand access.

Highly sensitive and more specific tests for the diagnosis of latent TB infection have been developed, both of the interferon-ϒ release assays showed high diagnostic value in bacteriologically confirmed childhood TB (45). Recent advances in diagnosis with Xpert MTB/RIF with a rapid turnaround time, with high positivity rates than smear microscopy, is important for early detection particularly in smear negative cases (44). It should be offered upfront in TB endemic areas, where rapid screening is of utmost importance. Advances in treatment include 4 mo of Rifampicin alone or 2 mo of Rifampicin and Pyrazinamide for latent TB (44). Efforts are under way to develop vaccines to control disease in latent TB patients (45). More than 10 vaccine candidates have entered clinical trials in the last few years (45,46). Future research should aim to find a noninvasive point of care TB test, new, shorter, safer regimen consisting of only oral medicines that are well tolerated in children, and those should be accessible to families living in poverty (47). MDR-TB in children will mainly be from transmission from an adult, so history of contact with MDR-TB case is very crucial, in order to achieve the goal of end TB strategy which aims to reduce TB deaths by 90% between 2015 and 2035.

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