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Review

Global Impact of Tuberculosis and HIV coinfection

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Abstract

Tuberculosis (TB) is ranked second among the casualties caused by infectious diseases and therefore has been a focus of research for decades. Multi Drug resistant (MDR) tuberculosis is a potential threat to eradicate TB globally. HIV coinfection further complicates the situation due to difficulty in the management of the dual disease, resulting in a high rate of mortality in cases of MDR-TB with HIV coinfection globally. In India, the HIV-TB coinfection incidence is at the rate of 3.8 per 100,000 people, which is at a significant standing in the world. Early and prompt diagnosis helps in designing an effective treatment regime which includes antiretroviral therapy for HIV and the use of the second line of drugs for the treatment of MDR-TB. Since the course of action is extensive, designing policies to provide a support system to the patient and the caregiver will ensure better management of the disease.

Keywords: Tuberculosis, HIV, Multidrug resistance, Extensively drug-resistant, Anti-retroviral Therapy

Introduction

With centuries of existence, tuberculosis (TB) is the second major cause of deaths among infectious diseases (earlier ranking first before COVID-19 pandemic), becoming more portentous than ever, tolling to around 10 million cases (Figure 1) and 1.5 million deaths (including 214,000 people with HIV) in 2020 [1]. In 1882, Robert Koch discovered *Mycobacterium tuberculosis*, the causative agent of tuberculosis [2] and since then, this organism has taken the centre stage for research. *M. tuberculosis* being an obligate aerobic Gram-positive pathogen causes infection primarily in the lungs in around 87% of the cases, where it damages lung tissue and causes necrosis [3].

The existence of *M. tuberculosis* has been traced back to 3 million years ago in East Africa [4], with its ancestry of current strains originating around 20,000 years ago [5,6]. Presently, *Mycobacterium tuberculosis* Complex (MTC) encompasses at least nine species belonging to genus *Mycobacterium*: *M. tuberculosis sensu stricto* (human), *M. africanum* (human), *M. canettii*, *M. bovis* (cattle, human), *M. caprae* (cattle), *M. microti* (rodents), *M. pinnipedii* (seals), *M. orygis* (antelope) and *M. mungi* (mongoose) [7]. Among the species pathogenic to humans, *M. tuberculosis sensu stricto* is accountable for majority of cases worldwide, followed by *M. africanum* which is endemic to West Africa [8]; infection by *M. canettii* is extremely rare and limited to the Horn of Eastern Africa [9], whereas infection by *M. bovis* is only caused through animal contact [6].

There are two types of tuberculosis: primary and secondary. Primary tuberculosis is when the individual develops the disease after being infected for the first time and the immune system is unable to eliminate the bacteria. This commonly occurs in immunocompromised patients, who, in turn, can infect other people. In other cases, *M. tuberculosis* remain in the immune system and is not eliminated. The bacteria form a protective biofilm in the necrotic tissue. In this case, it is termed latent tuberculosis and can later develop into a secondary infection in an event of immunosuppression [10]. Only 5-15% of individuals infected with *M. tuberculosis* progress towards active (primary) tuberculosis and the rest remain in constant danger of developing the disease later in life (secondary) [11].

Multi Drug resistant (MDR)-TB is considered as a public health predicament by WHO in which the patient doesn't respond to standard antibiotics which results in treatment failure and death. Incessant research over several decades unfortunately could not lead to successful cure of disease caused by MDR-TB strains. Due to incoherence to the complete antibiotic course by the TB patients, the MDR strains mutate, imitating geometric progression, while the development of new drugs appear much slower than arithmetic progression. It is seen that various resistant strains of *M. tuberculosis* have been developed in different regions of the world, mainly due to inappropriate use of drugs, improper prescription, meager quality drugs, or premature termination of treatment [1]. Still, the most commonly used drugs are isoniazid, rifampicin, [yrazinamide, and Ethambutol (categorized as first-line anti-tubercular drugs); and fluoroquinolones (levofloxacin, moxifloxacin, ofloxacin), aminoglycosides (amikacin, kanamycin), thioamides (ethionamide, prothionamide), capreomycin, cycloserine, and para-aminosalicylic acid (second-line anti-tubercular drugs) [12]. Isoniazid and rifampicin are the two most effective first-line anti-TB drugs and resistance developed by bacteria to these drugs leads to MDR-TB.

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Due to the steady rise in mutations and resilience to drugs shown by variants, TB has been categorized as mono-drug-resistant TB (mono-DR-TB) (showing resistance to any of the single first-line drugs); polydrug-resistant TB (poly-DR-TB) which shows resistance to one or more first-line drug; rifampicin-resistant TB (RR-TB) which shows resistance exclusively to Rifampicin; MDR-TB showing resistance to first-line drugs; and extensively drug-resistant TB (XDR-TB) which is impervious to at least one of the fluoroquinolones and injectable drugs respectively [13].

Affecting one third of the world's population latently, TB causes a threat to the immune system when associated with other communicable and non-communicable diseases [14]. The situation gets complicated with COVID-TB comorbidities, though the interaction between COVID-19 and TB is not established so far [15,16]. Among other communicable diseases, HIV and malaria are comorbid, amongst which TB poses a major threat to people suffering from HIV/AIDS, causing 25% of HIV-related deaths across the world [14]. TB-HIV coinfection is a matter of concern in resource-limited countries. Both pathogens act synergistically to potentiate each other, causing more damage to the immune system [17]. Hence, the present review focuses on the severity of tuberculosis, its global burden with emphasis on Indian scenario and comorbidies with respect to HIV/AIDS coinfection. The review also intends to highlight present diagnostics and treatment regimens, and the challenges posed to cure MDR and XDR strains.

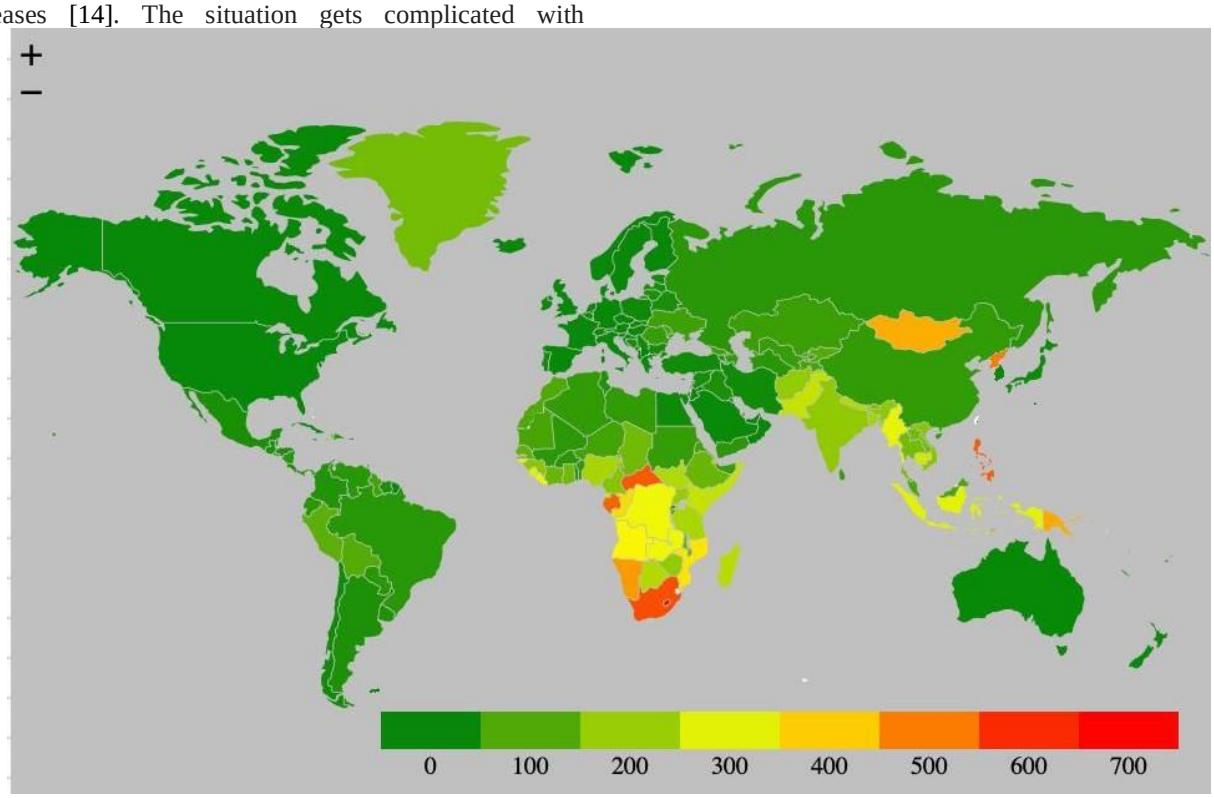

Figure 1: Global incidences of Tuberculosis per 100,00 people. The countries with the most cases are shown in red in the gradient - South America (554), Gabon (547), Central African Republic (540). And the countries shown in green have almost no cases, such as the United States (2), Australia (7), and Canada (6).Data taken from https://data.worldbank.org/indicator/SH.TBS.INCD?end=2020&start=2020 [18].

Pathophysiology of Tuberculosis

There are several steps to the infection and pathogenesis of tuberculosis (TB) [19,20]. *M. tuberculosis* is not very infectious (one individual can infect 3 to 10 people in a year) [21,22]. It also has a slow rate of transmission due to longer incubation time [23]. The first step of the disease is the infection which results from inhalation of aerosols which might contain 1-3 bacilli of *M. tuberculosis*. These infectious units are released by forceful expiration from an individual with active tuberculosis. Upon inhalation, these droplets reach the alveolar sac of the lungs which are the primary route of infection. The tubercle bacilli are then acted upon by alveolar macrophages as well as by some monocytes and dendritic cells which act in the first line of defence. The alveolar macrophages also known as the dust cells are the major immune cells in action; however the surfactant limits their bactericidal activity [11]. A resilient bacterium might escape the action of the macrophage and continue to reside in it which prevents the fusion of phagosome and lysosome. The macrophage and *M. tuberculosis* migrate from alveolar space into the lung parenchyma, where the immune system starts forming granuloma around the invader (also referred to as tuberculoma). The bacteria now enter the logarithmic phase of growth, where they proliferate and hence need to be prevented from spreading across the organ.

With the onset of caseous necrosis, the bacteria reach the stationary phase of their growth. The macrophages transport *M. tuberculosis* to the draining lymph nodes of the lung where the T lymphocytes are present [11]. The bacteria delay the initial T cell priming as well as the movement of activated T cells into the lung [21,22]. The $CD4^+$ helper T (T_H) cells respond three weeks post-infection during which period the bacteria have already spread to other organs. In tuberculosis, Th1 plays a major role in defense by producing Interferon γ which allows the maturation of phagolysosomes in macrophages and the production of nitric oxide (NO). The hypoxic environment created within the granuloma due to the presence of NO temporarily restricts the growth of the *M. tuberculosis* [11]. The macrophages expresses vascular endothelial growth factor which directs angiogenesis and blood flow into the granuloma.The blood vessel does bring more immune cells to the site of infection but also expidites the spread of bacteria to the other organs. The necrotic tissue further acts as the source of nutrition and a protective barrier for these growing invaders, encouraging their further growth. This disease gets particularly fatal in immunocompromised patients like those suffering from HIV.

Susceptibility of Tuberculosis in HIV patients

Tuberculosis and HIV form a lethal combination and pose a major burden, especially on the health system of the resource-limited countries. In 2020, there were 215,000 reported deaths of HIV related TB patients [24]. When the individual host has both the pathogens (*M. tuberculosis* and HIV*)*, it results in rapid deterioration of the immune system resulting in premature death, if untreated [25].

The route of HIV-1 infection is via genital mucosa and it can develop into a chronic disease despite the fact that the antigen evokes both innate and adaptive (cellular and humoral mediated) immunity. During the initial phase of acute infection, the $CD8^+$ T cells play an important role in reducing the proliferation of virus in the bloodstream. [25].

The hallmark of any HIV infection is the depletion of the T_H cells falling to 50–80 cells/mm^3/year [26]. During the primary infection HIV first depletes the memory effector T_H cells in gut mucosa and then targets the naïve population of T cells. This, along with continual persistence of the viral antigen, results in accelerated turnover of the dysfunctional population of exhausted T cells, which have lost their ability of cytokine production and cytotoxicity, resulting in progression of the disease [25].

The depleted population of the T_H cell in AIDS patients make them immunocompromised with increased risk of developing latent TB or becoming susceptible to primary infection from *M. tuberculosis* [27]. Some studies have shown that $CD8^+$ T cells play some role in controlling latent TB [28,29]. HIV infection, as discussed earlier, results in disruption of $CD8^+$ T-cells' function. Other factors that help in the entry of *M. tuberculosis* in HIV patients is increased number of entry receptors of the bacteria on macrophages, manipulation of the bactericidal pathway of the macrophages, deregulated chemotaxis, imbalance in Th1 and Th2 population, impaired tumor necrosis factor (TNF)-mediated apoptotic response to the bacteria and increased necrosis which helps the bacteria survive in the host [25]. All these factors contribute to making HIV patients more susceptible to infection by *M. tuberculosis*, worldwide.

Global Burden Of TB –HIV coinfection

As mentioned above, TB reigns as the number 1 reason for death among HIV infected people, globally (https://www.cdc.gov/tb/topic/basics/tbhivcoinfection.htm). This condition becomes particularly dangerous if a person has latent TB infection along with HIV-AIDS and is unaware about the coinfection. 66 million deaths have been averted between 2000 and 2020 due to the provision of Anti- Retroviral Therapy (ART) to HIV- positive people [1]. According to the WHO Global Tuberculosis Report, 2021, over 7 million people with HIV-TB coinfection have been treated in between 2018-2021. The situation, although improving, remains grim; from 423,000 deaths in 2017 to 214,000 patients with TB- HIV coinfection dying in 2021. Worldwide, 88% of the patients with the active TB were found to be coinfected with HIV [1]. This load of coinfection is so significant that WHO has released three updated lists of high burden countries for MDR- TB and TB associated with HIV. The countries with high burden of coinfection include Africa, South Asia and some parts of Central and South America. India bears 38% of the burden of global deaths due to TB and 34% share of the combined deaths due to TB and HIV positive people [1]. It must be noted that among HIV-TB coinfected deceased people, 50% were men, 40% were women and 9.8% were children [30]. It can be safely said that even though the death rates due to TB-HIV coinfection has seen a decline in the last 5 years, the numbers are subject to significant fluctuations. The most significant decline (19%) was observed in the WHO African region. Several countries of the African continent registered 4-10% reduction in TB-HIV coinfection cases after a peak in the HIV epidemic and the subsequent expansion of the program on TB and HIV prevention and care. The other regions as recognized by WHO have shown much less decline in the numbers. The reasons for the poor performance of the rest of the WHO regions are lack of awareness and public education, poor access to WHO approved rapid diagnostic tests, inaccessibility to medicines and monitoring and lack of congruence of the people to the treatment regime, along with other comorbidities.

It is a matter of serious concern that the success rate of treatment continues to remain low for TB-HIV coinfected people and it is expected that the COVID-19 pandemic might have further pushed down the success rate [1].

Status of TB-HIV Coinfection in India

Globally, India has the third highest HIV burden in the world with 0.22% infection rate in adults [1]. This situation turns grave because India shoulders 9% of the world's load of HIV associated TB and approximately 11,000 people in India die every year due to this.

15.6% of these patients are from Nagaland, 10% from Karnataka, 9.1% from Chandigarh and 8.9% from Manipur [31]. A lot of measures are being taken in India to detect HIV among presumptive TB patients. Such services are being provided through the antiretroviral therapy (ART) centres across the country where more than 96% of the patients with HIV are regularly screened for TB. Due to continual effort by the government, TB awareness among Indians has been created and 95% of the total TB patients in India knew about their HIV status in 2021. Acknowledging the high incidence rate of TB-HIV coinfection, the government of India has come up with a Strategic Plan for Elimination of Tuberculosis (National Strategic Plan, NSP 2017-2025) whose major focus is prevention of TB in vulnerable populations. This program is in congruence with The Guidelines for Programmatic Management of TB Preventive Treatment (PMTPT), India. This program is particularly active in 12 states of India namely, Andhra Pradesh, Telangana, Delhi. Gujarat, Himachal Pradesh, Karnataka, Kerala, Maharashtra, Meghalaya, Odisha, Punjab and Assam; and aims at gaining pragmatic evidence of the TB-HIV coinfection to further upholster the fight and bring down the number of incident cases.

Provider Initiated Testing and Counselling (PITC), an initiative by Government of India, is being implemented across the country for early detection of TB and aims at easing the diagnostic process for the patients by providing single window for TB and HIV services. Here the use of "4 symptoms screening tool" is very common. Apart from the above, several intensive measures are being taken across the country for rapid screening and assessment of TB and HIV. A few notable examples would be, 'Intensified TB Case Finding' at ICTC, use of molecular diagnostics such as CBNAAT/ Truenat for detection of MDR-TB and HIV coinfection, implementation of TB Preventive Therapy and Introduction of diagnostics like TB-LAM. The Supply Chain Management Strengthening (SCMS) project for TB and HIV-AIDS drugs has garnered several international collaborations [30]. This project is led by the Plan International (India Chapter) which is the principal recipient for the TB and HIV Supply Chain grant under the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). The above mentioned projects aim to strengthen the technical capacities of various state and central TB cells to help them better design, manage and monitor the supply chains for high quality TB drugs, diagnostics and other related commodities in India. There are several such outreach programs funded and collaborated internationally which aim at providing better public awareness and education. Though the progress made under these programs is slow, strengthening them especially by rapid diagnosis of the disease is the only promising path to increase awareness among people.

Diagnosis

The diagnosis of MDR-TB in HIV infected patients poses a problem since the symptoms (cough, fever, night sweats and weight loss) in these patients are similar to other systemic or pulmonary infections. Misdiagnosis or delay in diagnosis can increase the risk of mortality in patients with dual infection. Thus there is an emphasis on early detection and prompt initiation of effective treatment at the right time to reduce the rate of mortality.

Sputum smear is the most common and economical test done during the early phase of disease but it is usually negative at the advanced stage. The conventional solid Lowenstein–Jensen medium culture and DST remain the gold standard for diagnosis, but usually take 2–6 weeks for the results. Other tests like *Mycobacterium* growth-indicator tube, Bactec Radiometric 960, and microscopic observation broth drug-susceptibility assay are more sensitive and give rapid results, but are not cost effective and can be easily contaminated [32]. Radiology data can also be used for assistance in diagnosis. Middle- or lower-lobe infiltration, pleural effusion, mediastinal lymphadenopathy, or interstitial nodular opacities in radiological presentation, is usually observed in HIV patients at an advanced stage ($CD4^+T$ cell count $<200/cm^3$) (12.). All these patients are also recommended to be screened for drug resistance with culture and drug susceptibility test (DST). Cartridge based nucleic acid amplification test (CBNAAT) can be used for prompt diagnosis (within 2h) and shows higher sensitivity. Newer tests like XpertMTB/RIF, GeneXpert and Line probe assay (LPA) are also being used for rapid detection of drug resistant TB [33,34].

Treatment

As a preventive measure we have been administering Bacille Calmette-Guerin or BCG vaccine for close to a century. Though it has been found to be effective against severe forms of TB like TB-meningitis, but does not prevent primary infection or reactivation of latent pulmonary infection which is the main source of bacillary spread in the community [35,36]. Treatment of patients with HIV and MDR-TB involves the use of a second line of anti-TB drugs including the newer Bedaquiline and Delamanid for at least 18-20 months along with ART for HIV treatment. If the ART treatment is not given, relapse of MDR-TB has been found to be 2.4 times higher in patients who received 6 months of TB treatment (WHO guidelines 2019). The conventional system of classification divided the anti-TB drugs into first and second-line anti-TB drugs with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line anti-TB drugs. Revised guidelines of WHO 2019 put these drugs into groups A, B and C (Figure 2). The duration of treatment is decided by the treatment response and the

treatment should be continued 15-17 months post-recovery. The regimen for treatment can be standardized or invidualized depending on the resources available. A regimen should contain a minimum 5-6 drugs as each active drug increases the chance of cure by 65% [37]. During the intensive phase of treatment a standardized regimen contains five effective anti-TB drugs with pyrazinamide and four core second line anti-TB drugs one from each group A, B and two from group C. However conventional regimen is lengthy and expensive. WHO has recommended a shorter MDR-TB regimen for those patients in whom resistance to fluoroquinolones and second-line injectable agents has been excluded [13,38]. These include an intensive administration of gatifloxacin or moxifloxacin, clofazimine, prothionamide, kanamycin, isoniazid, pyrazinamide and ethambutol for a period of 9 to 12 months [39].

A support system must be ensured to the patients and their caretakers so that they complete the treatment regimen. They should be provided with a comprehensive package of prevention, diagnosis, treatment and care interventions, and integrated TB and HIV services. The civic bodies should ensure the participation of all the stakeholders for planning and monitoring the epidemic situation (WHO 2014).

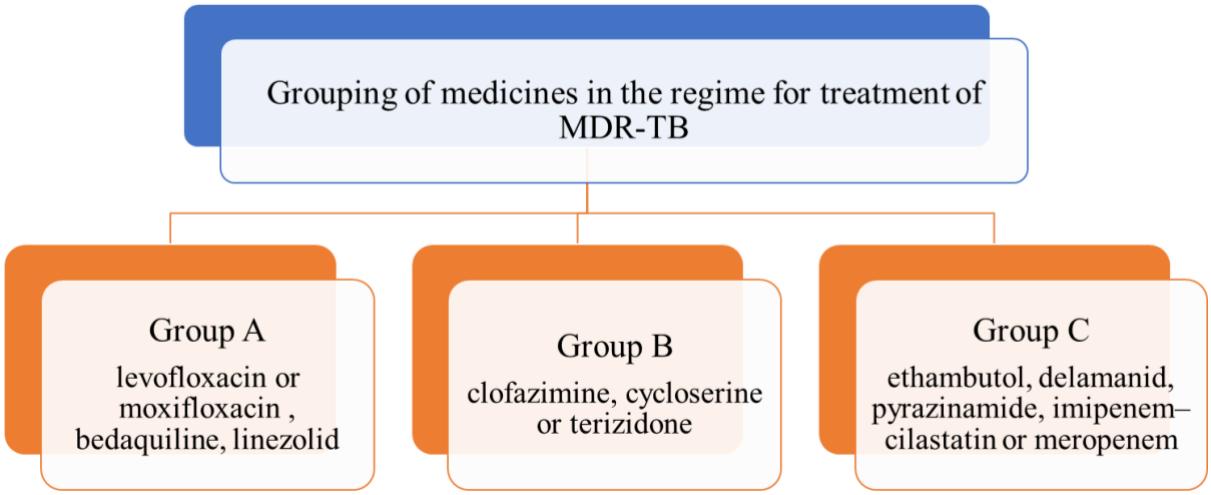

Figure 2: The figure shows the three groups into which the MDR-TB medicines have been categorised according to WHO guidelines on drug-resistant TB treatment, 2019. All three medicines from Group A, and one or both medicines from Group B should be added to the regime. In case medicines from Group A and Group B cannot be used add medicines from Group C to complete the regime.

An unusually exaggerated form of immune reaction to the viable or dead *M. tuberculosis* antigens is Immuno-reconstitution Inflammatory Syndrome (IRIS) which occurs in HIV-infected patients and is a complication of ART. In mild or moderate form it is relatively common in TB patients who have been started on ART therapy. Management of IRIS is tough. Usually, treatment modalities of IRIS include observation with the continuation of ART and anti-TB therapy. Nonsteroidal anti-inflammatory drugs can be used for treatment of mild while corticosteroid can be used for moderate form. In other cases ART therapy needs to be paused [13].

Conclusion

Tuberculosis is a global concern as it is the leading cause of deaths among infectious diseases, increasing health burden in economically weaker countries. The situation complicates further with emergence of MDR and XDR strains *M. tuberculosis*. Though the present drugs like delamanid and bedaquiline are effective against MDR strains of TB and have improved the situation, yet comorbidity with other diseases is still a matter of concern. HIV coinfection wreaks havoc by posing a greater challenge for global TB control in immunocompromised patients. Hence, WHO has revised its guidelines in 2019 for curing TB. But the government needs to focus on an efficient integrated system: diagnosis, treatment and management of dual infection to achieve the WHO's goals of 'End TB' by 2035, and patients need to get their act together to make it possible.

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Conflict of Interest

The authors report there are no competing interests to declare.

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