Immigrant Health and the Intersection of Type 2 Diabetes and Non-Endemic Infectious Diseases in the United States

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The current type 2 diabetes (T2D) pandemic is expected to afflict almost 500 million people over the next 15 years. Its global burden is well publicized, but less attention has been paid to how it interacts with other conditions, particularly infectious diseases like tuberculosis (TB). T2D is characterized by insulin insensitivity, along with chronic low-grade inflammation and subsequent immunocompromise; when comorbid with TB, T2D tends to increase symptom severity and heighten mortality rates. Recent immigrants (both documented and undocumented, especially those from Latin America) and persons of Hispanic or Latino descent in the United States are particularly vulnerable to this comorbidity due to factors such as lack of access to healthcare, poverty and acculturation, meaning the process by which immigrants adopt American behaviors. The goal of this investigation is to elucidate the interaction between T2D and TB, thereby highlighting a troubling disparity in healthcare availability that is likely to apply beyond immigrants and affect other marginalized populations as well.

Introduction

Despite being a noninfectious, lifestyle-related disease, type 2 diabetes (T2D) is emerging as a pandemic with shocking rapidity. 90% of all diabetes cases are type 2, and the current estimate of 340 million T2D sufferers worldwide is expected to balloon to 439 million over the next 15 years.[1,2] This increase in global T2D burden is not particularly surprising given how the high-calorie, low-nutrition American diet and largely sedentary lifestyle associated with the disease are spreading to developing and rapidly industrializing countries.[3] More specifically, the interaction between genetic predispositions, which differ among various ethnicities, and environmental factors such as rapid urbanization, a major shift in the production and consumption of food products and a growing dependence on nutrition-poor processed foods in countries all over the world have spurred and will continue to spur the sharp rise in T2D.[1] Over the next 15 years, the sharpest increases in T2D prevalence are predicted to occur in sub-Saharan Africa (98% increase), the Middle East (94% increase) and the Indian subcontinent (72% increase).[1]

It is no secret that T2D is a global problem, but little attention has been paid to the interaction between T2D and other diseases. T2D has been shown to interact negatively with other conditions from non-communicable diseases such as Alzheimer's to various infectious diseases including tuberculosis, Chagas disease and dengue fever.[4,5,6,7] It is also important to note that diabetes exacerbates a variety of US-endemic infectious diseases, such as influenza, pneumonia and other respiratory infections and urinary tract infections.[8,9] In one striking example, along the Texas-Mexico border near Matamoros, Mexico, 28% of TB cases were attributed to underlying T2D.5 T2D also accelerates the acquisition of drug resistance in TB patients, which creates not only a public health issue but also an economic burden.

Undocumented and documented immigrants, particularly Hispanics and people of Latin American origin, are especially at risk for the T2D/TB comorbidity. In addition to discrimination and poverty, immigrants of this background face deteriorating physical and mental health that counter intuitively worsen the longer they stay in the US.[10] As immigrants acculturate to American diets and exercise habits, they also become at risk for developing T2D.[11,12] Their susceptibility to T2D, along with increased likelihood of coming into contact with other immigrants from TB-endemic countries—often in Latin America, Asia and South America—puts immigrants especially at risk for this underappreciated comorbidity.[13] Improving disease surveillance, initiating focused research efforts and increasing healthcare access are important strategies for tackling this growing problem of T2D/TB interaction.[5] Understanding the interactions between these diseases will be crucial to everything from global economic development to disease eradication to poverty alleviation and beyond.

Type 2 Diabetes (T2D)

T2D is a chronic disease characterized by insulin insensitivity, which causes glucose to build up in the bloodstream, eventually leading to damage of blood vessels and nerves, heart disease and kidney failure.[14] Patients with T2D also tend to have chronic low-grade inflammation due to the production of excess cytokines, which are immune system signaling molecules. These cytokines are produced by the pancreas and adipose tissue and can disrupt proper adaptive immune responses. The inflammation causes tissue damage in the pancreas and elsewhere, leading to an immunocompromised state with both abnormal insulin production and general insulin insensitivity within the body.[15,16]

Tuberculosis

TB is an infectious disease caused by the bacterium Mycobacterium tuberculosis, which is highly transmissible through the respiratory droplets of patients with active TB. People with compromised immune systems, such as those with T2D, are more

likely to develop active TB; those with healthy immune systems are better able to fight the infection. Symptoms of active TB include fever, cough with bloody sputum, weight loss and weakness, which can ultimately lead to death.[17]

TB is considered one of the 'Big Three' diseases, along with HIV/AIDS and malaria, which kill millions worldwide and are difficult to control. Infecting one-third of the world's population, TB is the second most prolific infectious killer.18 With the introduction of the Millennium Development Goals by the United Nations, fighting the 'Big Three' has become a priority. As a result of worldwide drug programs and treatment efforts, the rates of new TB infection have been slowly but steadily declining.[17] In the United States, 9,241 TB cases were reported in 2014, indicating a decline of 2.2% from the previous year; however, 66% of TB cases in 2014 occurred in immigrants.[19] More specifically, 20.6% of those cases were in Mexican immigrants. Members of the Hispanic/Latino ethnic groups who are not necessarily immigrants have TB rates that are almost eight times higher than that of whites in the US.[20] Texas, California, New York and Florida all had TB incidence rates that were higher than the US average in 2014 ; these states are also home to large immigrant communities.[20,21]

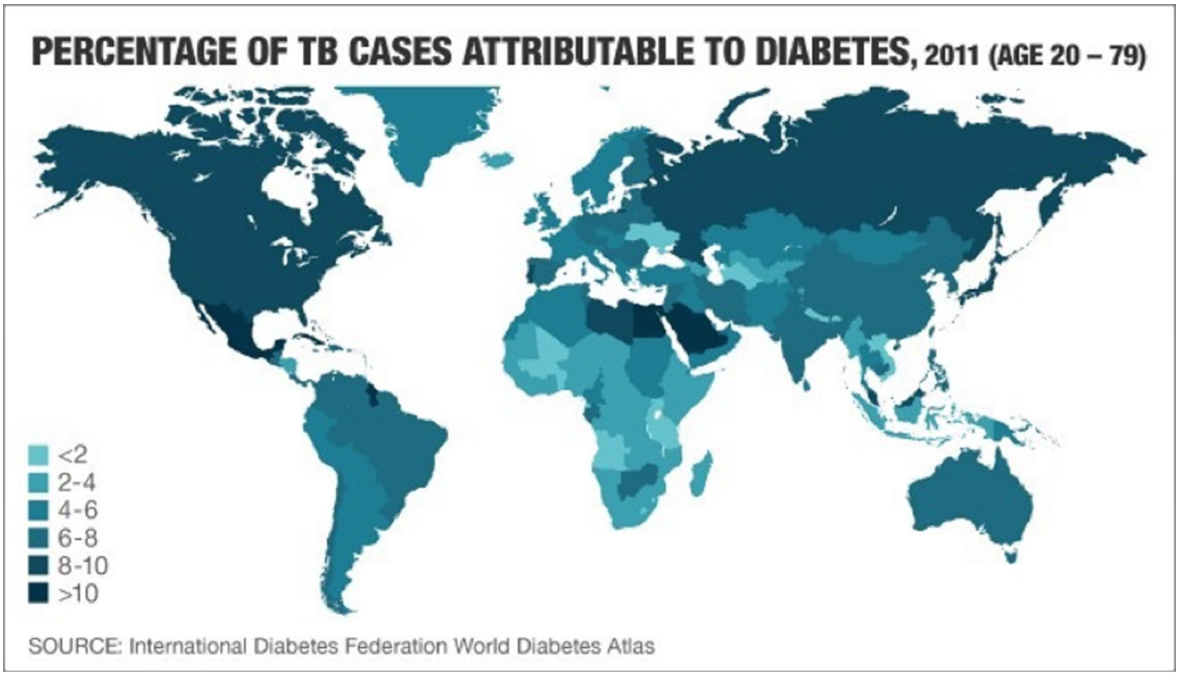

Figure 1. This map is almost a complete inversion of a traditional map of TB distribution alone, where TB rates are highest in developing countries. It is not TB, but T2D, that is the driving factor and the geographic determinant behind the rise and pattern, respectively, of the TB/T2D comorbidity. Figure reproduced with permission from the International Diabetes Federation.[23]

Intersection of T2D and TB

The existence of mutually negative interactions between T2D and TB is not a new discovery. However, only recently has the T2D/TB comorbidity become a problem as the ever-expanding T2D pandemic sweeps into areas where TB is endemic, such as developing countries in Central and South America and Africa (Figure 1).[22] A traditional map of TB distribution would show the highest TB prevalences in developing countries with almost no cases in the US. In sharp contrast, Figure 1 shows high TB prevalences in the US and other developed countries that are attributable to similarly high T2D prevalences in those areas. As T2D prevalence skyrockets in developing countries over the next 15 years, the T2D/TB comorbidity is likely to markedly increase as well.[1]

T2D affects the outcome and severity of TB in a variety of ways. Much still remains unknown about how these two diseases interact, but research has yielded several important insights: T2D heightens the likelihood of contracting TB, increases TB severity, encourages the development of drug resistant TB, disrupts the normal immune responses to TB and alters the profile of the at-risk TB population.[24]

A recent study looking at the Texas-Mexico border found that in this region, 28% of TB cases are due to underlying T2D.[5] The study concluded that the high prevalence of T2D around the border of southern Texas and northeastern Mexico and the increasing spread of the disease worldwide make T2D a substantial threat to TB control. In some areas, T2D is even more of a threat than HIV despite the latter's attendant immunocompromise and its ability to make those infected more susceptible to other infections.[5, 24]

Diabetic patients with TB exhibit severe symptoms and even resistance to standard TB treatment. Researchers have observed that diabetic patients suffering from TB are more likely to die than non-diabetic patients with TB.[5] Additionally, diabetic patients tend to have the more severe and infectious forms of TB, namely pulmonary and cavitary TB.[5] Pulmonary TB occurs when TB bacilli infect the lungs (as opposed to infecting other areas of the body), and in general, cavitary TB will appear in 40-87% of pulmonary TB cases. In cavitary TB, cavities form in the lungs and are colonized by high loads of TB bacilli, making this form of the disease especially contagious. Most drug-resistant forms of TB involve cavitation.[25]

One method of gauging TB severity is by examining bacterial loads in response to treatment. A study in Veracruz, Mexico, compared the responses of diabetic and non-diabetic TB patients to TB treatment over time. The researchers found that not only did the diabetic patients have higher initial loads of TB bacteria, but they also remained TB-positive for longer than non-diabetic individuals (Figure 2).[26] This result suggests that having T2D negatively impacts the effectiveness of TB treatment by delaying bacilli clearance, which can facilitate the spread of TB in vulnerable populations.[26] Another study by the same group in Veracruz found that diabetic patients are 2.8 times more likely to develop drug-resistant TB than non-diabetics.[27]

Researchers in Taiwan obtained similar results; their measures of severity included stage of infection, bacterial load, rates of treatment failure and duration of bacterial clearance. They found that diabetic patients scored higher on all markers of TB severity than did their non-diabetic counterparts. Additionally, they found that diabetics were more likely to develop multidrug-resistant TB (MDR-TB), which is non-responsive to the two most effective TB drugs. They suggest that higher bacterial loads in diabetic patients provide increased opportunity for mycobacteria to mutate and become drug-resistant.[28]

Generally, when external respiratory droplets from a person with an active TB infection enter the lungs of a non-diabetic patient, there are four possible outcomes. First, the TB bacilli in those droplets could be rapidly and effectively eliminated by the innate immune response. Second, the bacilli could replicate and initiate a primary TB infection. Third, the bacilli could establish a latent, non-contagious infection by becoming dormant. Fourth, the bacilli could revive the dormancy of a latent infection, result-

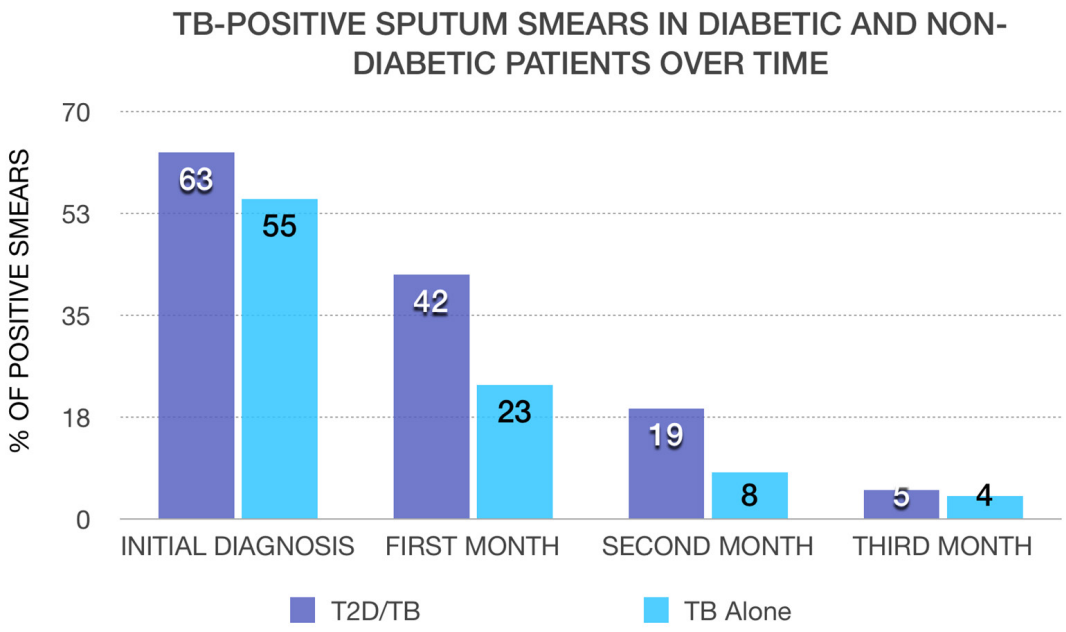

Figure 2. Diabetics remain TB-positive for longer than non-diabetics after initiating treatment. A longer period of infectiousness among diabetics could put contacts of those individuals at higher risk of contracting TB than contacts of non-diabetics. Adapted from Pérez-Navarro, et al. (2015).[26]

ing in reactivation TB.[29]

In vitro studies involving monocytes from diabetic patients challenged with TB bacilli have shown a reduced ability of these monocytes to phagocytose, or bind and engulf, the pathogens. The researchers suggest that this reduced binding is due to defects in complement or serum opsonins, which normally collect on the surface of a pathogen to mark it for phagocytosis.[5] These defects in phagocytosis often lead to unrestrained replication of TB.[5]

The defects in the innate immune response of diabetic patients to TB are compounded by the simultaneous alteration of the adaptive response. Studies have shown that diabetic patients tend to have a hyper-reactive adaptive response to TB, meaning T-cells proliferate at higher rates than usual in response to TB infection. This hyper-reaction may exist to compensate for the inadequate innate response and may be responsible for diabetics' higher susceptibility to TB, but the connection requires further study.[5] The failure of diabetic immune systems to properly eliminate TB infections helps account for the increased TB severity suffered by diabetics.

Interestingly, a study examining the Texas-Mexico border revealed that the at-risk population for the T2D/TB comorbidity is distinct from that for TB alone. In the United States, the populations most at risk for TB alone are young (<40 years old), HIV-positive homeless males with histories of drug or alcohol abuse, imprisonment and/or immigration. In stark contrast, the US groups at the Texas-Mexico border most at risk for the T2D/TB comorbidity are older (>40 years old), Hispanic females with none of the social risk factors (not including immigration) of the aforementioned TB-risk population. Importantly, the older age of the latter group corresponds with the typical age of onset of T2D.[24] T2D, like HIV, hinders the immune response and increases TB susceptibility. The typical TB at-risk population has immigration in common with the TB/T2D at-risk group, indicating that it is likely that TB is associated with the process of migration to America or possibly with contact with recent immigrants.

Immigration

Although immigrants to the US tend to have lower levels of obesity than those born in the US, the longer they reside in the US, the higher the likelihood of their developing T2D.[11] Recent immigrants from Mexico and Central America have a diabetes prevalence of about 8%, which is lower than the overall US prevalence of 9.3%.[30,31] However, later generation immigrants of Hispanic background in the US have a diabetes rate of 12.8%, suggesting that the risk of developing T2D increases over time and from generation to generation for Hispanic immigrants.[30] This increase in T2D development is a far-reaching problem, considering that the immigrant population in the US has more than quadrupled over the past forty years so that 13% of the US population was foreign-born in 2011. Of that 13%, the majority (53%) are from Latin America.[32] Interestingly, recent immigrants tend to have longer lifespans, lower disability rates and better overall health than their US-born counterparts. Researchers attribute this phenomenon to the 'healthy immigrant effect,' a term that describes how those who survive the journey into America are only those who are mentally and physically healthy enough to do so.[32] However, over time, immigrant health gradually declines to match or fall below the poor baseline of American health. Immigrants to the US face many challenges that interact to affect health outcomes, often negatively. Poverty, inadequate healthcare, poor education, discrimination and acculturation combine to cause mental and physical health deterioration.[10,32]

Lack of healthcare access among immigrants (both documented and undocumented) and their families as well as the process of acculturation are two major causes of declining health. For example, Hispanic immigrants live, on average, five years longer than the total US-born population. Strikingly, although the lifespan of US-born Hispanics is still higher than that of the total US-born population, it is approximately 2.9 years less than that of Hispanic immigrants, indicating a decline in lifespan.[32] Furthermore, in stark contrast to recent immigrants, later generation immigrant populations (i.e. those whose parents, grandparents, etc. were immigrants) exhibit sharp declines in both physical and mental health. For example, the rates of both chronic conditions, such as diabetes, asthma and obesity, and learning disabilities, such as ADHD, in children increase markedly in direct proportion to the mother's length of US residency.[12,32]

Undocumented immigrants or recent immigrants without health insurance especially suffer from a lack of access to healthcare, resulting in underutilization of healthcare services, which could result in an increased risk of disease. Poverty plays an important role in healthcare access; Hispanic immigrants have the highest poverty rates of all ethnic groups, with 26.9% of Hispanic immigrants extremely poor and an astonishing 57.2% in or near poverty, compared with a mere 13.5% of US natives extremely poor and 31.1% in or near poverty. Furthermore, 56% of Hispanic immigrants are uninsured and 51% are on welfare, indicating that this group is largely devoid of the finances essential to securing good health and procuring healthcare when necessary.[33] Although recent immigrants are in better health than their counterparts who immigrated less recently despite socioeconomic status, this difference quickly levels out. Acculturation puts immigrants at risk for a variety of health conditions. American habits such as poor diet, sedentary lifestyle and smoking contribute to the development of excessive weight and obesity and can eventually lead to more serious diseases such as type 2 diabetes (T2D).[12]

When these environmental and lifestyle-related risk factors are combined with a disparity in healthcare access between the US-born and the foreign-born, it is not surprising that immigrants are eventually worse off in terms of health outcomes than their US-born counterparts.

Immigrants provide an interesting case study for the diabetes/infectious disease intersection due to their susceptibility to T2D after American acculturation and their increased likelihood of contact with new immigrants from TB-endemic countries. Despite declining rates worldwide and low rates in general in the United States, immigrant populations in the US are especially vulnerable to developing TB. A recent study found that immigrant children have TB rates 32 times higher than their counterparts born in the US to parents born in the US. This elevation of TB rates extends to second-generation immigrant children as well; these US-born children with foreign-born parents have TB rates six times higher than their counterparts with US-born parents.[34] Hispanics made up the largest proportion of these second-generation immigrant children; additionally, two-thirds of TB exposures occurred in the US, underscoring the significant role of disease spread in immigrant populations coming from TB-endemic countries.[34] Immigrants, both undocumented and documented, enter into close-knit communities in the US, especially along the border in Texas. As immigrant communities develop, the US-born, later-generation population will inevitably mix with the recently arrived, foreign-born population. The US-born are more likely to exhibit a range of behaviors that put them at higher risk for chronic conditions such as T2D, which is a major risk factor for a variety of infectious diseases. For example, first generation Mexican immigrants have smoking rates of 8.5%, which, for later generation immigrants, jumps to equal the national average of 17.8%.[12,35] Therefore, as new immigrants or refugees from any countries endemic for diseases such as TB enter into communities in the US, they are potentially bringing deadly diseases to communities that are in a uniquely vulnerable position. [24,36]

T2D/TB Healthcare Requirements

As the T2D/TB comorbidity becomes more prevalent, especially in at-risk immigrant populations, interactions between T2D and TB medications must be considered. Diabetes care on its own is very complex and must be carefully managed; this kind of intricate treatment is difficult in low-resource or high-disparity settings, such as in immigrant populations in the US with inadequate access to healthcare.[37] When TB also becomes a problem, the healthcare requirements skyrocket to unsustainable levels for the populations most at risk for the T2D/TB comorbidity.

TB treatments do not work the same in all patients. Obese patients who receive TB drug dosages based on their total body weight could experience adverse effects due to drug toxicity.[38] Obesity can also inhibit treatment by altering the body's metabolism. In obese patients or those with poorly controlled T2D, the resultant hyperglycemia can lead to changes in how drugs are metabolized. This altered metabolism can negatively affect treatment for conditions such as TB by decreasing drug concentrations and reducing their efficacy, thereby making TB infections in diabetics more difficult to treat and eliminate.[26] More research is necessary to further elucidate how body weight influences the action and efficacy of drugs.

As TB/T2D comorbidity becomes more prevalent, interactions between TB and T2D drugs must be taken into account. The need for more integrated medical care with this comorbidity is highlighted by a recent study, which found that the standard TB drug rifampin could have negative effects in diabetic patients even if those patients are controlling their T2D. The study examined the interactions between rifampin and gliclazide, a common antidiabetic drug. They determined that rifampin increased clearance of gliclazide, therefore reducing the efficacy of the latter drug.[39] In this way, TB treatment can negatively impact the pharmacological control of T2D, thereby inducing hyperglycemia and making the TB drugs less effective, in a seemingly endless cycle of negative interactions.

Another standard TB drug, isoniazid, has been shown to be potentially harmful for immunocompromised patients in particular. A recent study found that isoniazid impairs adaptive immune responses to the TB bacterium through the apoptosis of Mycobacterium tuberculosis-specific CD4 T-cells.[40] Therefore, patients treated with isoniazid are more likely to suffer TB reinfection or reactivation.[40] In patients with already compromised immune systems, such as those with T2D, isoniazid treatment could further worsen their ability to fight infections. This view is complicated by the previously mentioned observance of a hyper-reactive T-cell adaptive response in diabetic patients; knocking down T-cell activity in these individuals may not be as devastating as it would for non-diabetic individuals with normal levels of activated T-cells.

Transmission and Infectivity

The US has a very low prevalence of TB and may therefore be more vulnerable to and less well equipped to handle a possible epidemic due to an influx of an immigrant source population.[41] The likelihood of such an epidemic depends on many factors, including contact between ill individuals (such as immigrants) and susceptible individuals (such as diabetic Americans). Given the 'othering' of Latin American immigrants in the US, immigrants tend to form tight, close-knit communities that separate them from Americans. Therefore, it is quite possible that immigrants entering the US with TB will inadvertently facilitate transmission within their communities. Immigrant populations in the US, although they do tend to cluster together, still interact on a daily basis with people outside of their communities. For example, children from immigrant populations go to school with children of a variety of ethnic groups, and adults have jobs that involve routinely interacting with unfamiliar individuals. Thus, the assumption that TB, once introduced to the US by an immigrant, would stay within that community is not realistic.[24]

It is possible that T2D will fuel a rebound in TB rates in the US, which have been steadily declining since 1992, in the same way that HIV/AIDS encouraged a TB epidemic in the late 1980s. The most recent TB crisis in the US occurred between 1985 and 1992, when the epidemic of HIV combined with increased immigration from TB-endemic countries encouraged high rates of TB transmission and subsequent infection.[41] If this past crisis is any indication, the US has been historically unprepared for TB epidemics. Additionally, the spread of TB beyond the population of those with HIV/AIDS highlights the relative ease with which TB can infect those outside of communities made vulnerable by chronic, immunosuppressive diseases. Furthermore, although the most recent rates of TB in the US show a decline from the previous year, this decline is the smallest in over a decade, indicating that other factors, such as the increase in T2D, may impede the success of TB control strategies.[19]

Many other factors complicate predictions about the potential for TB transmission in countries such as the US. These factors, in addition to prevalence of diabetes, include age structure of the population, population growth and urbanization. A recent study examined how these factors interact to affect TB rates in a high-incidence (India) versus low incidence (Korea) country. As for age structure, TB tends to affect the elderly more severely; it takes time to progress from infection to active TB with the median incubation period being within the first two years following infection; therefore, TB prevalence is higher in older populations.[42,43] Shifting age structure is related to population growth; an increase in elderly people could result in higher TB rates. Finally, urbanization has differing effects in a country like India versus a country like Korea.[42] In India, urbanization increases opportunities for TB transmission, thereby increasing prevalence rates in cities. Conversely, TB rates in urban Korea were lower than in rural Korea.[42] As a result of these various factors interacting, high-TB incidence India has an increasing T2D prevalence, while low-TB incidence Korea has a decreasing T2D prevalence.[42] As T2D becomes a pandemic and proliferates in areas that, like India, are undergoing an economic, structural and population-based transition, efforts to curb the rise of TB will likely be complicated.

As a country with a low TB burden but an increasing preva-

lence of T2D, the US seems to lie somewhere between India and Korea. The US has excessively high T2D rates, an aging population and immigration populations, such as those from Latin America, which could serve as TB vectors. Thus, there is a firm possibility that TB could take hold in the US unless, as the researchers suggest in relation to India and Korea, early TB drug treatment and surveillance are prioritized.[42]

Economic Burden

T2D encourages the development of drug resistant TB, which can be exorbitantly expensive to treat. In 2013, there were 9,582 newly reported TB cases in the US, with immigrants shouldering the majority of the case burden at 65%. After Asians, Hispanic populations have the highest rate of TB prevalence in the US at 28% of all US TB cases. Additionally, the majority (51%) of TB cases occurred in Texas, Florida, California and New York, all of which have large immigrant populations.[44] This TB burden represents an economic hardship for both those populations most at risk and the healthcare system that may or may not shoulder the cost of treatment.

The average cost of treating regular TB in the US is $17,000 per case. As drug resistance increases, treatment costs skyrocket. For comparison, the average cost of treating multidrug-resistant TB (MDR-TB) is $134,000 per case, and treating extensively drug-resistant TB (XDR-TB) costs, on average, $430,000, making MDR- and XDR-TB treatment often more expensive than the lifetime treatment of a patient with HIV or breast cancer.[45] Treatment for MDR- and XDR-TB involves expensive medications, lengthy hospital stays and extensive case management. Even though drug-resistant TB represents just 1-1.5% of all US TB cases, the enormous expense of treating these cases is a considerable problem, especially since public funding covers the majority of the expense. Between 2005 and 2007, treating these cases cost nearly $17.5 million and $2.1 million for 364 cases of MDR-TB and 9 cases of XDR-TB treatment, respectively.[45] Public funding covered 75% of MDR-TB costs and 100% of XDR-TB costs.[45]

As previously mentioned, T2D enhances the severity of TB and increases the likelihood of developing drug-resistant forms of TB.[27] It is possible that rates of drug-resistant TB among diabetics might rise in parallel to the rates of T2D and that the drug-resistant TB could spread rapidly and affect non-diabetics as well. Therefore, rising rates of T2D and MDR/XDR-TB would increase the US economic healthcare burden due to the exorbitant cost of treating drug-resistant TB. Improved access to healthcare among vulnerable populations, such as immigrants, would help to curb the development and spread of both diseases and could ultimately reduce current healthcare costs or prevent increasing future costs.

Conclusions

As has been discussed, the longer immigrants stay in the US, the more likely they are to experience a decline in health.[32] Immigrants may develop T2D and accompanying health deterioration as a part of the acculturation process, which could put them at risk for a variety of other diseases, such as tuberculosis.

Members of tight-knit communities, where new arrivals from Latin America and later-generation immigrants meet, may be uniquely at risk for infectious diseases. Recent immigrants from countries where diseases such as TB are endemic may bring the disease with them into these communities, thereby exposing later-generation immigrants experiencing the typical health decline to infections to which they are particularly susceptible.[24]

Given that T2D is a pandemic and not limited just to immigrants, the potential spread of infectious disease in immigrant communities is also dangerous for the greater US population. For example, the US does not traditionally vaccinate against TB, meaning the arrival of TB in the US in the midst of a diabetic, immunocompromised and unvaccinated American population could be an unprecedented public health crisis.

There is a host of potential measures to combat the looming threat of diabetes and infectious disease in immigrants and other populations, including both simple measures like better screening procedures and education and more complex measures like reformed immigration laws at the national level. Smaller scale measures to catch any infections before they even enter the US include better health surveillance, improved health screenings at borders and specific training of physicians to check for previously overlooked or misdiagnosed diseases, such as asymptomatic TB. Recently, Minnesota launched an initiative to screen for latent TB in immigrant and refugee populations. This initiative involves screening all foreign arrivals regardless of how long they have been in the US. Following screening, those with positive test results are more thoroughly tested with chest X-rays and physical exams, accompanied by an in-depth medical history. Physicians then counsel patients about what latent TB is and follow-up with appropriate treatment to avoid reactivation TB. This type of initiative is highly replicable within other states and would help reduce not only the burden of latent TB but also the possibility of reactivation TB among immigrants.[36]

The current surveillance in place for TB is the National TB Surveillance System, which relies on state and local health departments to report confirmed TB cases to the CDC.[46] However, the initial sources of TB reports are physicians. Because immigrants have poor healthcare access, it is unlikely that this surveillance system is capturing a highly at-risk population. Therefore, national TB reports may be underestimates of the true burden. To alleviate this problem, active instead of passive surveillance for TB may be necessary. Active surveillance could include calling households, sending out questionnaires, surveying doctors or other health professionals in immigrant-dense areas or even in-person canvassing of vulnerable immigrant communities. Active surveillance could not only identify undiagnosed TB cases but also provide encouragement to those afflicted to seek early treatment. Although active surveillance is expensive, the growing severity of the T2D/TB comorbidity warrants this increase in funding to limit this problem before it grows to be even more unwieldy. Another possibility to enhance surveillance is to adopt an entirely electronic reporting system, such as the Tuberculosis Information Management System (TBIMS) put in place in China beginning in 2005. TBIMS has proven to be remarkably effective, producing a vast amount of complete, real-time case data that can be accessed at all levels of TB healthcare and political organization.[47]

From a prevention standpoint, educational campaigns in immigrant communities about T2D risk factors such as smoking, poor diet and excessive weight/obesity could help improve health literacy and alter lifestyle behaviors that promote the development of T2D.[1] Furthermore, educational pamphlets or brochures handed out at the border could likewise disseminate actionable information about diabetes prevention to the persons most at-risk.

Larger scale measures include reformed immigration procedures that are able to better classify and handle immigrants escaping humanitarian crises, better access to healthcare for those most at risk of developing these comorbidities and research into how T2D and infectious diseases interact so as to be able to better treat comorbid patients and lessen disease severity and spread. Much of the research surrounding T2D/infectious disease comorbidities, particularly for Chagas disease, is limited to animal models, indicating how far away we are from really understanding this intersection in real populations. The larger scale measures suggested, with the exception of further research, would be the most difficult to implement. Immigration regulations are an incredibly controversial issue, which slows down the legislative process considerably. The complicated and therefore lengthy procedures of Congress present a time issue for those at-risk for T2D/TB because managing these comorbidities is an intricate process that requires access to significant amounts of healthcare as soon as possible. Given how poorly controlled T2D makes TB and other infectious diseases worsen, it is crucial that immigrants have improved healthcare access both for their own health and the health of their communities. Furthermore, increased access to healthcare would allow previously undiagnosed conditions in recent immigrants to be identified and treated before symptoms increase in severity and communities are exposed.[48] The skyrocketing cost of healthcare is a problem for all Americans, not just recent immigrants. Reining in these costs and making healthcare and health insurance more

affordable would greatly increase the likelihood of widespread access and coverage. Furthermore, prevention of TB through healthcare-provided screenings would save millions of dollars in TB treatment down the road.

Understanding the interactions between T2D and infectious diseases such as TB will become crucial as the comorbidities become more prevalent, especially in the US and developing countries. Immigrants to the US provide an interesting case study for T2D comorbidities as they experience the combined negative circumstances of being susceptible to T2D by virtue of American acculturation, experiencing potential exposure to infectious disease from other recent immigrants and lacking the healthcare necessary to treat these diseases. Preventing the compounded negative health effects of these comorbidities both in the US and globally will require a combination of political and social reforms and more intensive research to fill in the many knowledge gaps that remain.

References

1. Chen, L., Magliano, D., & Zimmet, P. (2011). The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol Nature Reviews Endocrinology, 228-236. doi: 10.1038/nrendo.2011.183
2. Marullo, L., Moustafa, J., & Prokopenko, I. (2014). Insights into the Genetic Susceptibility to Type 2 Diabetes from Genome-Wide Association Studies of Glycaemic Traits. Curr Diab Rep Current Diabetes Reports.
3. Hu, F. (2011). Globalization of Diabetes: The role of diet, lifestyle, and genes. Diabetes Care, 1249-1257.
4. Mushtaq, G., Khan, J., Kumosani, T., & Kamal, M. (n.d.). Alzheimer's disease and type 2 diabetes via chronic inflammatory mechanisms. Saudi Journal of Biological Sciences, 22(1), 4-13. doi:10.1016/j.sjbs.2014.05.003
5. Restrepo, B., & Schlesinger, L. (2013). Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. Tuberculosis, 93, S10-S14. doi:10.1016/S1472-9792(13)70004-0
6. Nagajyothi, F., Zhao, D., Machado, F., Weiss, L., Schwartz, G., Desruisseaux, et al. (2010). Crucial Role of the Central Leptin Receptor in Murine Trypanosoma cruzi (Brazil Strain) Infection. The Journal of Infectious Diseases, 202(7), 1104-1113. doi:10.1086/656189
7. Lee, I., Hsieh, C., Chen, R., Yang, Z., Wang, L., Chen, C., et al. (2013). Increased Production of Interleukin-4, Interleukin-10, and Granulocyte-Macrophage Colony-Stimulating Factor by Type 2 Diabetes' Mononuclear Cells Infected with Dengue Virus, but Not Increased Intracellular Viral Multiplication. BioMed Research International. doi:10.1155/2013/965853
8. Flu and People with Diabetes. (2015, March 26). Retrieved from http://www.cdc.gov/flu/diabetes/index.htm
9. Joshi, N., Caputo, G., Weitekamp, M., & Karchmer, A. (1999). Infections in Patients with Diabetes Mellitus. N Engl J Med, 341, 1906-1912. doi:10.1056/NEJM199912163412507
10. Viruell-Fuentes, E. (2007). Beyond acculturation: Immigration, discrimination, and health research among Mexicans in the United States. Social Science & Medicine, 65(7), 1524-1535. doi:10.1016/j.socscimed.2007.05.010
11. Oza-Frank, R., Stephenson, R., & Narayan, K. (2011). Diabetes Prevalence by Length of Residence Among US Immigrants. Journal of Immigrant and Minority Health, 13(1), 1-8. doi:10.1007/s10903-009-9283-2.
12. Gordon-Larsen, P., Harris, K., Ward, D., & Popkin, B. (2003). Acculturation and overweight-related behaviors among Hispanic immigrants to the US: The National Longitudinal Study of Adolescent Health. Social Science & Medicine, 57(11), 2023-2034. doi:10.1016/S0277-9536(03)00072-8.
13. Organization, W. H. (2013). TB (tuberculosis)-Endemic Countries. Retrieved from https://www.redlionca.org/uploaded/School_Life/TB_Endemic_Countries.pdf
14. Prevention, C. f. D. C. a. (2014, 21 October 2014). Basics About Diabetes. from http://www.cdc.gov/diabetes/basics/diabetes.html
15. Donath, M., & Shoelson, S. (2011). Type 2 diabetes as an inflammatory disease. Nat Rev Immunol, 11, 98-107. doi:10.1038/nri2925
16. Salzano, S., Checconi, P., Hanschmann, E., Lillig, C., Bowler, L., Chan, P., . . . Ghezzi, P. (2014). Linkage of inflammation and oxidative stress via release of glutathionylated peroxiredoxin-2, which acts as a danger signal. Proceedings of the National Academy of Science of the United States of America, 111(33), 12157-12162. doi:10.1073/pnas.1401712111
17. WHO. (2014). Tuberculosis. Fact sheets. from http://www.who.int/mediacentre/factsheets/fs104/en/
18. Bourzac, K. (2014). Infectious disease: Beating the big three. Nature, 507, S4-S7. doi: 10.1038/507S4a
19. CDC. (2014). Tuberculosis Fact Sheet. Retrieved from http://www.cdc.gov/tb/publications/factsheets/statistics/tbtrends.htm.
20. CDC. (2015). Tuberculosis Trends--United States, 2014. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6410a2.htm#Fig1
21. Institute, M. P. (2015). State Immigration Data Profiles. Retrieved from http://www.migrationpolicy.org/programs/data-hub/state-immigration-data-profiles.
22. Niazi, A., & Kalra, S. (2012). Diabetes and tuberculosis: A review of the role of optimal glycemic control. J Diabetes Metab Disord, 11(28). doi:10.1186/2251-6581-11-28
23. International Diabetes Foundation (2011). Percentage of TB cases attributable to diabetes, 2011 (Age 20-79). International Diabetes Federation World Diabetes Atlas.
24. Restrepo, B., Fisher-Hoch, S., Crespo, J., Whitney, E., Perez, A., Smith, B., & Mccormick, J. (2007). Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiology and Infection, 135(3), 483.
25. Saeed, W. (2012). Cavitating pulmonary tuberculosis: a global challenge. Clinical Medicine, 12(1), 40-41. doi:10.7861/clinmedicine.12-1-40
26. Pérez-Navarro, L. M., Fuentes-Domínguez, F. J., & Zenteno-Cuevas, R. (2015). Type 2 diabetes mellitus and its influence in the development of multidrug resistance tuberculosis in patients from southeastern Mexico. Journal of Diabetes and its Complications, 29(1), 77-82. doi:10.1016/j.jdiacomp.2014.09.007
27. Pérez-Navarro, L. M., Fuentes-Domínguez, F. J., & Zenteno-Cuevas, R. (2011). Factors associated to pulmonary tuberculosis in patients with diabetes mellitus from Veracruz, México. Gaceta Médica de México, 147(3), 219-225.
28. Chang, J.T., Dou, H. Y., Yen, C. L., Wu, Y. H., Huang, R. M., Lin, H. J., Su, I. J., & Shieh, C. C. (2011). Effect of Type 2 Diabetes Mellitus on the Clinical Severity and Treatment Outcome in Patients With Pulmonary Tuberculosis: A Potential Role in the Emergence of Multidrug-resistance. Journal of the Formosan Medical Association, 110(6), 372-381. doi:10.1016/S0929-6646(11)60055-7.
29. Schluger, N. W. & Rom, WN. (1998). The Host Immune Response to Tuberculosis. Am J Respir Crit Care Med., 157, 679-691. doi:10.1164/ajrccm.157.3.9708002
30. CDC. (2014). National Diabetes Statistics Report, 2014. Retrieved from http://www.cdc.gov/diabetes/pdfs/data/2014-report-estimates-of-diabetes-and-its-burden-in-the-united-states.pdf
31. Oza-Frank, R. & Narayan, K. M. (2010). Overweight and Diabetes Prevalence Among US Immigrants. American Journal of Public Health, 100(4), 661-668. doi:10.2105/AJPH.2008.149492
32. Singh, G. K., Rodriguez-Laines, A., & Kogan, M. D. (2013). Immigrant Health Inequalities in the United States: Use of Eight Major National Data Systems. The Scientific World Journal, 2013, 21. doi:10.1155/2013/512313
33. S.A. Camarota. (2012). Immigrants in the United States, 2010: A Profile of America's Foreign-Born Population: Center for Immigration Studies.
34. Pang, J. et al. (2014). Epidemiology of Tuberculosis in Young Children in the United States. Pediatrics, 133(3), e494-e504. doi:10.1542/peds.2013-2570
35. CDC. (2015). Current Cigarette Smoking Among Adults in the United States. Retrieved from http://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm#national
36. Goers, M. & Settgast, A. (2015). Think globally, act locally: Diagnosis and management of latent tuberculosis in Minnesota's foreign-born population. Minnesota Medicine, 98(9), 49-52.
37. National Collaborating Centre for Chronic Conditions. (2008). Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). London: Royal College of Physicians (UK).
38. Chung-Delgado, K. et al. (2011). Factors Associated with Anti-Tuberculosis Medication Adverse Effects: A Case-Control Study in Lima, Peru. PLoS One, 6(11), e27610. doi:10.1371/journal.pone.0027610
39. Park, J. Y., Kim, K. A., Park, P. W., Park, C. W., & Shin, J. G. (2003). Effect of rifampin on the pharmacokinetics and pharmacodynamics of gliclazide. Clin Pharmacol Ther, 74(4), 334-340.
40. Tousif, S., Singh, D. K., Ahmad, S., Moodley, P., Bhattacharyya, M., Van Kaer, L., & Das, G. (2014). Isoniazid Induces Apoptosis of Activated CD4+ T Cells: Implications for Post-Therapy Tuberculosis Reactivation and Reinfection. Journal of Biological Chemistry, 289(44), 30190-30195. doi:10.1074/jbc.C114.598946
41. CDC. (2012). Overview of Tuberculosis Epidemiology in the United States: Centers for Disease Control and Prevention. Retrieved from http://www.cdc.gov/tb/education/corecurr/pdf/chapter1.pdf.
42. Dye, C., Trunz, B. B., Lonnroth, K., Roglic, G., & Williams, B. G. (2011). Nutrition, Diabetes and Tuberculosis in the Epidemiological Transition. PLoS One, 6(6), e21161. doi:10.1371/journal.pone.0021161
43. CDC. (2014). The Difference Between Latent TB Infection and TB Disease. Fact Sheets. Retrieved from http://www.cdc.gov/tb/publications/factsheets/general/ltbiandactivetb.htm
44. CDC. (2013). Reported Tuberculosis in the United States, 2013. from http://www.cdc.gov/tb/statistics/reports/2013/executivecommentary.htm
45. Marks, S.M., Flood, J., Seaworth, B., Hirsch-Moverman, Y., Armstrong, L., Mase, S. et al. (2014). Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis, United States, 2005-2007. Emerging Infectious Diseases, 20(5). doi:10.3201/eid2005.131037
46. CDC. (2010). National TB Surveillance System. Retrieved from https://www.healthypeople.gov/2020/data-source/national-tb-surveillance-system.
47. Huang, F., Cheng, S., Du, X., Chen, W., Scano, F., Falzon, D., & Wang L. (2014). Electronic recording and reporting system for tuberculosis in China: experience and opportunities. J Am Med Inform Association, 21(5), 938-941. doi:10.1136/amiajnl-2013-00200
48. Stimpson, J. P., Wilson, F. A., & Su, D. (2013). Unauthorized Immigrants Spend Less Than Other Immigrants And US Natives On Healthcare. Health Affairs, 32(7), 1313-1318. doi: 10.1377/hlthaff.2013.0113