A conversation with Dr. Bavesh Kana, December 16, 2015

Participants

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Note: These notes were compiled by GiveWell and give an overview of the major points made by Dr. Bavesh Kana.

Summary

The Open Philanthropy Project spoke with Dr. Bavesh Kana of the University of the Witwatersrand as part of its investigation into tuberculosis. Conversation topics included tuberculosis epidemics, barriers to effective treatment, strategies for addressing the epidemics, and funding priorities.

Tuberculosis epidemic

Globally, tuberculosis causes more deaths than any other bacterial pathogen. Many developing countries are experiencing tuberculosis epidemics despite the combinatorial treatment regimen mandated by the World Health Organization (WHO) and the widespread use of the Bacillus Calmette-Guerin (BCG) vaccine, which may be the most widely-administered vaccine in human history.

Southern Africa

According to an analysis of death certificates, more deaths in South Africa are attributable to tuberculosis than to any other disease. This is in part due to the high incidence of human immunodeficiency virus (HIV), which worsens the effects of tuberculosis in patients who are infected with both diseases. HIV causes depletion of T-cells, which are needed to form granulomas to contain tuberculosis infections to the lungs. Without these granulomas, the tuberculosis infection is able to proliferate rapidly and spread to other organs of the body. Treatment is complicated by challenges associated with administering HIV and tuberculosis medications together.

Barriers to effective treatment

Lack of fundamental research

Fundamental tuberculosis research is globally under-resourced, and the lack of understanding of the biology of the disease is a significant barrier to effective treatment. In order to make meaningful progress on the tuberculosis epidemic, there will need to be a focused, sustained effort on fundamental research.

Comparison to HIV research

Tuberculosis research is about two decades behind HIV research in terms of scientists' understanding of the biology of the disease, response to treatment and the identification of biomarkers that predict vaccine and treatment efficacy. Significant progress was made on the HIV epidemic when scientists gained a greater understanding of what makes people susceptible to HIV and how the virus enters the body. The increased understanding of the biology of the disease facilitated the development of the first antiretroviral drugs. Similarly, it will be necessary to gain a greater understanding of the biology of tuberculosis in order to develop treatment strategies that will have a significant impact on the epidemic.

Long-term cohort study

A long-term cohort study, across endemic and low incidence counties, on tuberculosis, comparable to the Framingham Heart Study, would be a valuable resource, but no such studies have been conducted. However, some strides have been made recently in this regard. CRDF Global has funded the Regional Prospective Observational Research for Tuberculosis in the Republic of South Africa (RePORT SA) program, which aims to enable researchers to start an observational cohort. It will do this by giving researchers a common protocol to use when recruiting patients and collecting, storing, and curating samples, so that a large amount of samples from genetically distinct populations can be reliably compared to one another. It remains to be seen what effect this resource will have on research because it is in the beginning stages of implementation.

Lack of representative models

Many fundamental questions about tuberculosis have not been addressed. This is in part due to the model systems that are used in experiments to mimic the environment in a human lung are, which not very representative of the full spectrum of human disease. Small animal models such as mice are not representative. Non-human primates are representative models, but only a few groups in the world are able to work with these animals because this type of work is prohibitively expensive and difficult to fund. Many researchers continue to experiment on mice because they are easily accessible and provide a tractable means to test new drugs or new drug combinations.

While the lack of representative animal models restricts the amount of research that can be done, it is possible to learn about the biology of the disease in humans, including which biological pathways are vulnerable to disease, by studying the bacterial physiology of the tubercle bacillus in human samples. This research is currently being done using sputum samples and lung resections. Lung resections are taken from patients who have drug-resistant tuberculosis and are not responding to treatment. These lesions are used to study bacterial gene expression, immunology, and distribution of antibiotics.

Research has also been done on model bacteria such as *Escherichia coli.* However, while work on model viruses was a productive strategy in HIV research because it paralleled the HIV infection cycle, the bacterial physiology of *E. coli* is not representative of tuberculosis because *E. coli* is less complex. For example, *E. coli* may have one pathway for a particular function where tuberculosis has five, which raises questions about the reasons for this redundancy.

Focus on immediate impact

The current approach to addressing tuberculosis epidemics focuses heavily on immediately delivering drugs. This is a difficult process as TB drug development is slow and hampered by the lack of novel small molecules that readily enter into the tubercle bacillus. Furthermore, governments in endemic countries have shifted more funding toward implementation research. Whilst this is a sound approach, it does create gaps in the early drug development pipeline which will be felt as the need for novel therapeutic options becomes dire.

It also takes a long time to measure impact in this area because treatment is protracted. Patients who have drug-sensitive tuberculosis are treated for 6 months, and those who have drug-resistant tuberculosis are treated for 2 years. To develop a drug typically takes many years, requiring multiple studies conducted one after the other. As a result, there is an urgent need to develop biomarkers that are strongly predictive of early treatment response with novel agents/drug combinations.

Diagnostic difficulties

Until 10 years ago, the main diagnostic method was to do a smear, which had a 50% false positive rate, and culture. The smear method used has been in use for 100 years.

Culture (or growth) of the tubercle bacillus is problematic because the organism grow slowly and it can take up to 6-8 weeks to deliver a diagnostic result. This diagnostic delay causes several negative downstream effects and devising a faster method of diagnosis could potentially have a significant impact on the epidemic by enabling people to start treatment sooner.

A new molecular diagnostic called GeneXpert, which is capable of delivering diagnostic results in 2.5 hours, became available in 2010. However, a study published in 2014 found that the introduction of this technology had no impact on mortality. Perhaps, this was in part because GeneXpert's expected impact was overestimated, and in part because the improved speed of diagnosis was not accompanied by improvements in the healthcare system. Patients who were quickly diagnosed using GeneXpert did not necessarily begin treatment immediately and/or the treatment may not have been sustained for a sufficient length of time. It may be

necessary to facilitate diagnosis within the community, using a model of decentralized care.

Dr. Kana thinks that existing diagnostic platforms are technically sound and could impact on the epidemic, if deployed effectively and integrated into the healthcare system. Intervention-based research may be necessary to determine the best way to accomplish this. Also, the development of a new point-of-care diagnostic, perhaps one that diagnoses people in a household setting, would be useful.

Pediatric tuberculosis

Pediatric tuberculosis is poorly managed, and the diagnostic methods used are less reliable than those used to diagnose adults. Children infected with tuberculosis do not present with the same pulmonary physiology as adults. They do not produce sufficient sputum, with bacteria, which is typically used to diagnose the disease in adults. Pediatric tuberculosis is instead diagnosed using gastric aspirates, which is a poor diagnostic method because the acidic conditions of the stomach lead to poor bacterial recovery. In many cases children who are suspected of having tuberculosis are given tuberculosis medication and are diagnosed retroactively if the drugs seem to have a positive effect.

Treating pediatric tuberculosis is seen as having a lower impact than treating adults because children do not transmit the disease, and it can be difficult to fund research in this area.

Drug resistance

Drug resistance poses a growing challenge to fighting disease globally, but primarily in Africa and Asia. This has led to an increase in the use of alternative medications that are less effective, more expensive, require longer treatment, and can have debilitating side effects. For example, the treatment regimen for multi-drug-resistant (MDR) tuberculosis causes hearing impairment in many patients. Civil society and advocacy groups have protested against this treatment regimen, but there are currently no viable alternatives that can be deployed at a country-wide level. It is really sad that patients with drug-resistant TB have to bear such suffering.

MDR tuberculosis accounts for 9-20% of tuberculosis cases in southern Africa. While this is a minority of the total cases, the ministries of health in endemic countries spend a disproportionately high amount of money on treatment for MDR tuberculosis as compared to drug-sensitive tuberculosis.

Strategies for addressing the epidemics

It can be difficult to prioritize work on the tuberculosis epidemics, but a recent meeting held by WHO and the Medical Research Council of South Africa that was convened to identify key priorities in tuberculosis research yielded five immediate priorities:

1. Identifying determinants of susceptibility to infection. Studying the immunogenetics of tuberculosis progressors and non-progressors may be key to preventing transmission in the future.
2. Blocking transmission systemically using vaccines for infection control.
3. Investing in the development of new drugs and the creation of new treatment regimens using innovative combinations of existing drugs and those that are in early clinical development.
4. Identifying high-risk individuals and immediately putting them in a program that supports treatment and functional cure.
5. Strengthening and integrating HIV and tuberculosis treatment in the healthcare system. In South Africa, tuberculosis clinics are separate from antiretroviral treatment clinics, but these services would ideally be integrated in a single clinic.

These five priorities are the most time-sensitive, but fundamental research is also needed to underpin thee areas and create new knowledge.

Requests for proposal

If Dr. Kana were to put out three requests for proposal (RFPs) for basic research, he would pursue:

1. The molecular determinants of susceptibility to infection.
2. New drug and vaccine targets.
3. Either pediatric tuberculosis or implementation research.

Health systems research would be the lowest priority of the three, because there is a lot of activity in this area.

Molecular determinants of susceptibility to infection

Dr. Kana is not aware of any large-scale cohort-based studies that are being done on identifying the molecular determinants of susceptibility to tuberculosis infection, and an answer to this fundamental question would likely have a significant impact on the field.

In terms of susceptibility to both tuberculosis and HIV infection, people tend to fall into three groups:

1. People who are regularly exposed to the disease (e.g. healthcare workers, house-hold contact) but do not get infected.
2. People who are exposed and get infected, but the disease remains latent. These people do not develop pulmonary tuberculosis.
3. People who are exposed, get infected, and progress to active pulmonary tuberculosis.

Research on people who are regularly exposed to HIV (e.g. sex workers) and fall into one of the first two categories above suggests that these "non-progressors" have genetic differences and specialized neutralizing antibodies that prevent HIV from

progressing into acquired immune deficiency syndrome (AIDS). The identification of these antibodies should now form a strong basis for the development of an AIDS vaccine. Similarly, tuberculosis "non-progressors" could be studied to develop a preventative tuberculosis vaccine that would protect both children and adults.

Dr. Kana is interested in studying genetic and immunological differences between people in these three groups to isolate any factors that may be causing the first group's members' immunity. Their immunity may be a result of their phage receptors preventing bacteria from being internalized, or macrophages rapidly clearing an infection.

Research on these groups could involve studying macrophage function by examining the transcriptome in the alveolar macrophages, because these macrophages and the alveolar dendritic cells are the first organisms in the body that encounter tuberculosis and may be playing a key role in immunity. Alveolar macrophages could be isolated and exposed to tuberculosis infections in vitro in order to study how the macrophages respond and what role they play in susceptibility to infection.

Genome sequencing could also be used to identify key differences between people in the groups, although it would be necessary to have a large cohort of patients in order to do a genome-wide association study.

A multi-generational longitudinal study could be conducted on epigenetics, but this would be a long-term investment.

Identifying new drug and vaccine targets

There will need to be a significant investment in finding new drug targets and progressing this knowledge towards developing new tuberculosis drugs in the near future as drug resistance grows. If drug resistance doubles, it will become very difficult to manage and will deplete resources, which will hinder the management of drug-sensitive tuberculosis as well.

Key areas to study include:

- The bacterial physiology of the disease in humans.
- Key contributors to virulence and pathogenesis.
- The local and systemic immune responses to tuberculosis infection in HIV-infected and -uninfected individuals, and how the responses can be manipulated to be more protective.
- Host-adjunctive therapy aimed at accelerated bacterial killing. There has been research in this area recently, and the Bill and Melinda Gates Foundation (Gates Foundation) and other funders have expressed interest in funding work in this area.

Drug development is difficult in part because tuberculosis bacteria belong to the *Actinomyces* genus which behaves very differently from the bacteria genera of other diseases, and it is difficult to predict how biological pathways will react to a particular drug treatment or to the infection environment in humans.

The Gates Foundation's TB Drug Accelerator program is working to accelerate drug development. Many people are investing in drug development, but progress has been slow as this is a difficult undertaking. That said, there are numerous new agents in the early pipeline that await clinical characterization, an exciting prospect for the development of a new regimen. It will be interesting to see how these studies turn out.

Vaccine development for tuberculosis is also under-resourced and would also be a good area for investment.

Pediatric tuberculosis or implementation research

The third RFP would focus on either pediatric tuberculosis, because this is an under-resourced area, or implementation research, because this would spread the portfolio across the value chain. An RFP on implementation research could involve identifying high-risk individuals or integrating tuberculosis and HIV treatment.

Reducing transmission

The causes of the sustained rate of transmission of both drug-sensitive and drug-resistant tuberculosis in many communities in South Africa are not fully understood, but transmission can be reduced using physical barriers and vaccines to protect people against infection. WHO modeling indicates that interrupting transmission will be a major factor in reducing the epidemic in the long term. This area must feature prominently in future studies if we are to have impact on the TB epidemic.

Vaccination

The BCG vaccine effectively prevents children from contracting tuberculosis and disseminated disease, such as meningitis. However, their immunity is lost during adolescence and they are not protected against developing pulmonary tuberculosis as adults. There is not currently a vaccine that prevents adolescents and adults from developing pulmonary tuberculosis.

There is some debate over the potential efficacy of a tuberculosis vaccine. Given that contracting tuberculosis once does not prevent subsequent infections, some scientists think it is unlikely that a vaccine could effectively protect people against the disease. However, Dr. Kana and others are optimistic that there may be a way to modulate the immune system, through vaccination, to get sustained protection. Dr. Kana believes that a lot of support will be required to develop new vaccines and that this area should be pursued actively going forward.

Researching functional cures

Research indicates that drug treatments may produce a functional cure without killing every tuberculosis organism, and the remaining viable organisms may be the cause of relapse in some patients. Additional research is needed in this area.

Biomarkers

Developing biomarkers that would predict in the first few days of treatment whether the patient is likely to be cured and whether they are likely to get a recurrence of the disease would enable healthcare providers to identify patients who are at a higher risk of relapse and follow those patients more closely. Between 7-15% of tuberculosis cases are relapses, and detecting a high risk of relapse could help to significantly reduce the total number of tuberculosis infections.

Biomarkers could also be used to determine whether a new drug or vaccine is likely to be effective.

Improving healthcare systems

The healthcare systems in South Africa, India, and China provide insufficient integrated support to patients through the process of diagnosis and treatment for tuberculosis.

Preventative treatment

The majority of people infected with tuberculosis have a latent infection and do not display symptoms. There is some strong advocacy for preventative treatment for high-risk patients with latent tuberculosis to prevent their infection from progressing to active pulmonary tuberculosis. There are some clinical trials ongoing that are using isoniazid, rifapentine, and other agents as preventative treatment for individuals who are more vulnerable to infection, such as those with both HIV and latent tuberculosis.

Because infection pressure in endemic areas is high, patients are likely to get reinfected with tuberculosis soon after their preventative treatment ends. For this reason, it is of utmost importance that preventative treatments be implemented alongside an equally-resourced program focused on preventing transmission of new infections.

Advocacy

There is an insufficient amount of advocacy for tuberculosis. It will be necessary to change the public perception of the disease in order to effectively address the epidemics.

Dr. Kana was asked to chair the 4th annual South African Tuberculosis Conference last year. In preparation for this, he went with colleagues to several communities in

South Africa with a high rate of infection in order to gain a better understanding of how the epidemic affects these communities and to understand obstacles to treatment. They asked people in these communities for their opinions on tuberculosis, and many said that they were not concerned about contracting the disease and assumed that if they did contract it, they would be cured. People tended to think of tuberculosis as less serious than HIV.

The misconception in these communities that tuberculosis is no longer a problem prevents people from taking adequate precautions to protect themselves from the disease. People are more aware of the risks of HIV, despite the fact that tuberculosis has a greater negative impact on society and is more difficult to prevent. It is easier to protect oneself against HIV because this is a behavioral disease, whereas tuberculosis is transmitted by proximity to an infected individual.

Non-governmental organization for tuberculosis advocacy

Dr. Kana proposes starting a non-governmental organization (NGO) for tuberculosis advocacy because this is a significant gap. An NGO could be a helpful tool for convincing decision makers that this is an important area of focus, learning more about patients' relationships to tuberculosis, and changing patient behavior.

Too little attention is paid to tuberculosis within affected communities, in the business sector, and on the diplomatic level. It is under-resourced and underfunded. The scope of the problem is beginning to become clear, but more resources need to be shifted toward tuberculosis and major decision makers need to be convinced to address the problem.

Civil society organizations such as Section 27, Médecins Sans Frontières, and a local treatment action group all have weighed in to some extent on the tuberculosis problem. However, this effort will need to be scaled up as it does not compare with the sustained, long-term effort that was undertaken for HIV. More work in this area is required as the message that we need to send out for TB is complex and multi-faceted. We also need to approach different sectors of society differently. For example, one would need a different approach with the healthcare system compared to the private sector.

A key factor in fighting the epidemics will be to gain a better understanding of the patients' relationship to tuberculosis, including the socioeconomic, sociopolitical, and sociocultural issues that prevent people from both understanding the gravity of the disease and seeking the treatment and support they need. The research community, healthcare system, and funders involved in combating tuberculosis epidemics need to gain a better understanding of the patients who are being targeted for treatment. If this understanding is not improved, the best treatment regimens will be ineffective against the epidemic because implementation will continue to suffer.

Changing patient behavior

Studying and modifying the behavior of healthcare workers and patients may have a large impact on the epidemic at the community level. One gets the impression that people view the health system as a hostile environment. As a result, research shows that people often wait until their disease has progressed to an advanced stage before going to their local health clinic, at which point treatment is less effective than it would be earlier in the disease progression. Investigating patients' reasons for waiting to go to a clinic and convincing them to go sooner could make treatments more effective.

Immunology of tuberculosis in HIV-infected individuals

Dr. Kana recently spoke with a representative of the National Institutes of Health (NIH) about researching the immunology of tuberculosis in HIV-infected individuals, including immune responses to tuberculosis infections and how immunity changes over time. Although concurrent HIV and tuberculosis infections have been a problem for 20 years, this question is only beginning to be investigated.

This is in part because new tools have been developed in the last 5-10 years that enable scientists to answer more questions. Molecular genetic and immunological tools that have been developed in the last five years enable researchers to learn about the biology of tuberculosis and study the disease at a higher level of granularity. Fluorescence-activated cell sorting technology has made great advances in the last two years, and there have also been associated advances in developing antibodies and stains.

Another reason this is only beginning to be discussed is because there is a growing appreciation that an understanding of immunology is necessary for management of the disease. However, it has recently become clear that there is a high level of variation in immune reactions to tuberculosis and HIV medications between individual patients, which suggests a reason for strongly advocating for a personalized medicine approach.

For example, patients who have both HIV and tuberculosis can present with lesions in various locations on their bodies as a result of immune reconstitution inflammatory syndrome (IRIS) after starting antiretroviral therapy. This is because the depletion of T-cells prevents granulomas from forming in the lungs and allows the tuberculosis infection to spread throughout the body, and when aggressive antiretroviral treatment is started and the immune system is quickly reconstituted, it can attack infections in areas outside of the lungs.

Length of treatment

Another question that needs to be examined is why treatment must continue over a period of 6 months, and whether this timeline can be shortened. Some people say it

may be possible to create a 2-week treatment regimen, but this has yet to be demonstrated in humans and it is unclear whether such a fast treatment would be feasible and sufficient to prevent relapse. It is also unclear whether the drugs that are currently being used can be combined in a novel way to create shorter treatment regimens.

Potential study design

To investigate why treatment timelines are so long, Dr. Kana would recruit a prospective clinical cohort of patients presenting with their first episode of drug-sensitive tuberculosis. This cohort would need to be large enough to get an even distribution of men and women and of HIV-infected and HIV-uninfected patients, and results would be corrected for age bias, if necessary. These patients would be put on treatment with samples of sputum, plasma, and whole blood collected at closely-spaced intervals (e.g. day 1, day 3, day 7, day 14, and then once per week until the end of treatment). Blood would be used for transcriptional analysis, and blood and sputum would be used for pharmacokinetic dynamic analysis of drug levels.

Results would then be analyzed to determine which patients responded to treatment more quickly or slowly than average. Whole genome RNA sequencing could be used to determine whether these patients have biomarkers that correlate to fast or slow response to treatment. If correlations are found, they would prompt questions about the immunological and biological reasons why these biomarkers might cause fast or slow response to treatment.

Funding priorities

There are many areas of research that need funding, and it can be difficult for a funder to determine funding priorities. When considering funding priorities, funders must take into account the total amount of funding they are willing to provide and for how long they are willing to fund a particular project. For example, supporting the development of new drugs and vaccines would require at least 10 years of sustained funding. Vaccines may have a slightly longer timeline because after a vaccine is developed, its implementation must be studied for at the least a few years to determine whether it has had an impact.

Vaccines

Vaccine development requires more basic research than drug development because the key antigens have not been identified, and a large amount of resources are needed to account for the low rate of success. A recent trial on MVA85 showed no effect, despite the large amount of work that was invested in it. This highlights the urgent need for investment in this area.

Distribution of resources in fundamental and implementation research

Funding is needed to improve implementation because the healthcare systems in endemic communities are unable to provide the necessary services to tuberculosis patients, and these systems will need to be improved to adequately deliver any new treatment regimens that are developed. However, more funding will be needed to support fundamental tuberculosis research because this will lay the foundation for future work on tuberculosis. More resources will be needed because many ideas will need to be investigated in order to identify those that are feasible, commercializable, inexpensive to patients, can be produced on a large scale, and seem to work well in test runs in local healthcare systems.

Fundamental research

Fundamental research can be prioritized based on immediate clinical need. For example, there is currently a need to identify vulnerable drug pathways that can be used to kill tuberculosis bacteria quickly.