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World TB Day

QUESTION AND ANSWER

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World TB Day 2016: an interview with leading experts in tuberculosis research

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Abstract

In this interview, we talk to leading tuberculosis (TB) experts from University College London and the London School of Hygiene and Tropical Medicine about the current challenges in TB research. The video of this interview is available here: https://www.youtube.com/watch?v=75Die7MQBec&feature=youtu.be. The video can also be downloaded via Additional file 1.

Keywords: BCG, Biomarker, Diagnosis, Transmission, Treatment, Tuberculosis, Vaccines

Edited transcript

Introduction

Patrick Phillips (PPJP)

Tuberculosis (TB) is the leading infectious disease killer at the moment. The recent surveillance reports have showed that more people die from TB every year than from HIV or any other infectious disease. So it's critically important that we tackle TB.

Helen Fletcher (HF)

Whereas people know about HIV and malaria, less people know about TB. In some ways, it is a silent pathogen. It is there in the community, it causes huge amounts of health problems, huge amounts of morbidity, and yet we have really under-invested in and neglected this disease as a global health problem.

Ibrahim Abubakar (IA)

If we are to contain the global burden of TB, we need new tools and diagnostics as well as new treatments and a vaccine. In order to achieve this, researchers have a key role to play.

The re-emergence of TB

HF

TB has always been there. We've never been close to eradication.

PPJP

In Western Europe, we've seen something of a decline in TB over the years, but TB is still a problem in many parts of the world. There has been a particular increase in the last 10–20 years or so due to a number of factors. The emergence of the HIV epidemic – HIV knocks out a person's immune system and makes them much more susceptible to TB – but also we have seen increasing rates of drug resistance.

Marc Lipman (MCIL)

We also know that social cohesion in a society is incredibly important in reducing the rates of TB. This is associated with poverty and, therefore, often in parts of the world where there is civil conflict, rates of TB, as well as those for other infections, start to rise. This extremely important in terms of where TB went to – or more importantly – why it has not gone away.

TB transmission

IA

TB is an infectious disease acquired from person to person. It is fundamental to the control of TB that we understand transmission, because if we can stop transmission then we have a chance in ultimately eliminating TB, as is the case with the goal of the End TB Strategy. It is therefore of interest to me that we use the best technology available, whether that is whole genome sequencing, geographical mapping of cases, tools to identify clusters of cases, as well as computer programs that predict where transmission is happening, and improved statistical

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approaches to pinning down exactly where transmission is happening. Those are the key steps we require.

Increasingly, we are recognising that transmission does not necessarily happen in peoples' households; that a lot of transmission, especially in high burden settings, actually happens out there in indoor-congregate community settings. Therefore, knowing exactly where these congregate settings are, and putting in interventions to stop transmission in those settings, is the key to containing TB.

Drug resistance

MCIL

Although we are definitely seeing an improvement in outcomes in terms of TB, we are also starting to see issues such as drug resistance. That is a direct consequence of treatment regimens that have been ineffective.

Timothy McHugh (TMcH)

There are two aspects to why drug resistance emerges. The first is wholly about the patient and the relationship between the patient and the clinician. So it is the drugs that are given and whether the patient has been given drugs that are going to work, and whether they are the right drugs, and then whether the patient is able to take those in the way that we require them to. It might be that the drugs make them feel ill, so they don't want to take them. Or it might be that the patient is leading a chaotic lifestyle and so isn't able to take the drugs on a regular basis. That is what my clinician colleagues focus on – they have to manage that process.

What I'm interested in, and what my team look at, is the evolution of drug resistance – or how it emerges at a biological level for the bug itself. For me it is a question of, almost, compartments. TB is tucked away within the host, within the patient. It is a difficult site to get drugs to. Drug resistance develops when you treat an organism with not enough of the compound, so not enough drug is getting to the bug. If you're tucked away in a compartment within the patient, where the drug isn't going to get to, then you're already giving a sub-optimal dose of the drug. The compounds that we use have to get over those barriers.

Diagnostics

TMcH

For many years we've used a smear test; that is, sputum put onto a slide and then used to identify *Mycobacterium tuberculosis*. This is a robust, simple tool, and has served us well for over 100 years. However, it doesn't serve us well in the days when we need to understand drug resistance in a quick and efficient way.

MCIL

The importance of diagnostics in the current era is that we want to be able to make a diagnosis promptly. We've got better and better at that. The introduction of molecular diagnostics such as GeneExpert have undoubtedly improved the sensitivity, and also the speed, of diagnosis. What's interesting about areas such as this, is that you need both a very good test which, in general terms, can be used close to the patient – so a point-of-care test. However, you also need to re-educate your healthcare workforce, and individuals who are being tested, on the implications and value of the test.

Treatment

MCIL

One of the big questions about treating TB is that, because the mycobacterium is both a slow-growing organism, and also because it is relatively hardy to being killed by antimicrobials, it takes a long time to treat and effectively cure TB. For example, the standard therapy to deal with latent TB is 3 months of treatment, continuously. The standard treatment for drug-sensitive active TB is 6 months of treatment. These are drugs that have potential toxicities. That in itself is a problem because, again, if someone is feeling more unwell on the therapy, then there's a good chance that they may stop treatment.

PPJP

Unfortunately, we haven't seen any improvement in the treatment of drug-sensitive TB really for 30 or 40 years. Whilst those were very effective trials and the regimen works very well in trial settings – as we've seen in the history of the TB epidemic, the regimen is inadequate to control the disease. So we do need treatments; we need better treatments, safer treatments, shorter treatments that are easier for patients to take.

There have been a number of trials published in the last 2 years looking at 4-month treatments. The idea being that a shorter, 4-month regimen would be easier to take for patients and, if it could be shown to be as good as the current standard of care, then that would greatly improve outcomes in practice and make it easier for TB programs to roll out treatment for a larger number of patients. Unfortunately, those three large trials show that none of the 4-month regimens being evaluated were as good as the standard of care. So we're still looking for shorter treatments that can result in better outcomes for TB.

A lot of the work in trials at the moment is looking at how we can best identify the most promising regimens to take forward to large expensive trials. So some of the work that we've done, some of the research that's being presented in the *BMC Medicine* series, is looking at better ways of doing clinical trials to identify those regimens to take forward to large Phase III trials.

Immune correlates

HF

At this particular time, immune correlates have emerged as an important issue because we have begun, as a TB community, to invest more in developing TB vaccines. If you look pre-clinically, there's now quite an exciting pipeline of vaccine candidates waiting to be moved into clinical trials. What we don't have at the moment is any real way of assessing which of those pre-clinical candidates are going to be the one that works and to go forward, because we don't have a correlate of immune protection.

Of course, we can't invest in efficacy testing for every one of those candidate TB vaccines. So we need tools – we need biomarkers and immune correlates – to really select the most effective vaccines and to progress the clinical development as quickly as we can. The reason we need to do this is because – if we do want to end TB by 2035 – we're going need an effective vaccine by the year 2025.

Typically, we say it takes 10 years to develop a TB vaccine, so if we don't start doing something about this today, we're not going to have that vaccine candidate by 2025.

WHO End TB Strategy

IA

The WHO has had, together with national TB programs, great success in tackling the problem of TB. Over the last cycle of international programs that contain TB, millions – tens of millions, over 40 million – lives are estimated to have been saved. As a result of this success, and building on it in relation to the United Nations Sustainable Development Goals, the WHO has developed a new strategy which is based on the vision that we want a world that is rid of TB.

The strategy is based on three key pillars. These pillars are important, including the need to have better integrated patient-centred care, the need to have strengthening of programs and systems to support the delivery of interventions, and better research and innovation. Research and innovation is one area that those of us in universities have a key role to play and should contribute to the discovery of new tools, so that we can achieve the goals of the End TB Strategy by 2035.

Further reading

See reference list [1–9].

Additional file

Additional file 1: Interview with (TB) experts from University College London and the London School of Hygiene and Tropical Medicine about the current challenges in TB research. (MP4 67204 kb)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors read and approved the final manuscript.

Authors' information

Patrick Phillips is senior statistician and programme leader track at the UK Medical Research Council Clinical Trials Unit (MRC CTU) at University College London (UCL). He has worked on late-phase clinical trials in TB and Alzheimer's disease for more than a decade, most recently as trial statistician in the REMoxTB and RIFAQUIN phase III TB trials published in 2014. He is part of the European/African PanACEA consortium evaluating novel regimens for the treatment of TB, designing the PanACEA MAMS-TB phase II trial with an adaptive design with results to be published in 2015. He is trial statistician for the STREAM trial evaluating novel MDR-TB regimens, is trial statistician and PI for the MRC/DFID/Wellcome grant for the TRUNCATE trial collaborating with the National University of Singapore, and is in collaboration with individuals from the CDC TB Trials Consortium and Boston University on other clinical trials to improve the treatment of TB. His PhD from the London School of Hygiene and Tropical Medicine (LSHTM) focused on the evaluation of prognostic and surrogate markers for TB treatment trials. Ongoing methodological areas of interest include the evaluation and use of surrogate endpoints, the conduct and analysis of non-inferiority trials, and trial design with a focus on adaptive designs.

Helen Fletcher is a Senior Lecturer in Immunology and Director of the TB Centre at the LSHTM. Helen gained a PhD in Medical Microbiology and became interested in TB during her first postdoctoral position at University College London in 1999. In 2002, she moved to the Jenner Institute at the University of Oxford as an immunologist for the first-in-human trial of a new TB vaccine, MVA85A. After 10 years at the Jenner Institute, Helen moved to the LSHTM to establish her own group, based in the Immunology and Infection Department and focusing on immune correlates and the host response to TB vaccination. In 2015, Helen became Director of the TB Centre at the LSHTM and, in 2016, she became co-chair of the T-cell Immunology working group for the Collaboration for TB Vaccine Discovery at the Bill & Melinda Gates Foundation.

Ibrahim Abubakar is the Director of the UCL Centre for Infectious Disease Epidemiology and Professor in Infectious Disease Epidemiology at UCL. He is a senior investigator at the MRC Clinical Trials Unit, director of the UCL TB Centre and head of TB at Public Health England, London, UK. Prior to his appointment at UCL, he was Professor in Health Protection at the Norwich Medical School, Norwich, UK. He qualified in medicine in 1992 and initially trained in general medicine before specialising in public health medicine. His academic public health training was undertaken at the London School of Hygiene and Tropical Medicine, University of Cambridge and the University of East Anglia. He has served on/chaired several working groups for the European Centre for Disease Control and the WHO, where is currently chair of the global Latent TB Task Force and a member of STAG-TB. Ibrahim led the team that developed the collaborative TB strategy for England, chaired the UK NICE guideline development group for TB and led the WHO Europe TB Elimination Plan Advisory Group. Ibrahim runs a programme of translational and health services research on tuberculosis, HIV and other infectious diseases.

Marc Lipman is Senior Lecturer & Honorary Consultant Physician in Respiratory & HIV Medicine. He is Deputy Director of UCL-TB Centre. He trained in Clinical Academic Medicine in the UK, and as a Harkness Fellow in the USA, based at Johns Hopkins School of Public Health. Aside from heading up a large clinical TB & HIV service, his present commitments include: UK NICE TB Clinical Guidelines Development & Service Delivery Groups; Public Health England National Respiratory Programme Board and the TB National Knowledge Project; UK MDR TB Expert Advisory Group and the WHO/European Respiratory Society MDR TB Consilium. He is the former Co-lead for TB in London and Chair of the British Thoracic Society TB Specialist Advisory Group. His research interests focus on tuberculosis, HIV and respiratory disease – and seek to enable high quality, evidence-based care to be provided to people at risk of TB and other related diseases.

Timothy McHugh is Deputy Director of UCL TB and Director of the UCL Centre for Clinical Microbiology, located at the Royal Free Hospital. His group contributes to all stages of the TB drug development pathway with projects on evaluation of new compounds as well as supporting the laboratory aspects of clinical trials for new treatments. An underlying theme is the development of biomarkers of treatment outcome, whether transcriptomic analysis of in vitro treatments or the more complex

picture of monitoring outcome in patients. An important element of his work is capacity development, providing training for laboratory scientists both on site and in London.

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