

PLOS Science Wednesday: Hi Reddit, we're Dr. Claudia Denkinger and Dr. David Dowdy. We published a study in PLOS ONE modeling tuberculosis transmission in a high-population setting using different stra

PLOSScienceWednesday¹ and r/Science AMAs¹

¹Affiliation not available

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Hi Drs. Denkinger and Dowdy, thanks for spending some time to hop on [/r/science](#) today.

I was thinking a little bit about MDR-TB this morning in the context of Multi-drug Resistant Organisms in general. One of the common talking points we hear a lot is how the 'misuse of antibiotics' is leading to a massive public health concern, rendering our most potent antibacterials all but useless. While I don't want to totally dismiss this claim, because I do think that we could be using antibacterials more effectively and responsibly, I wonder if things like MDR-TB and MDR-HIV are a good example of how these fears may be overblown/out of context. Rather, the occurrence of MDR across many pathogenic organisms is an inherent and natural consequence of therapeutic intervention, regardless of the scenario. Do you think this is fair to say? Multi-drug resistance in viral infections and other opportunistic bacterial/fungal infections is growing to be a huge issue, and seems to me to be under-appreciated in the public eye.

I know that this does not relate directly to the population dynamics of MDR-TB, but in the broader sense I wonder if highlighting the occurrence of MDR pathogens that are likely to have limited/no connection to antibiotic use in livestock and/or overuse of common first-line drugs (penicillins, cephalosporins, tetracyclines, etc.) can rephrase our discussion in regards to public health. I think that accurate public perception of our coming struggles with antimicrobials is going to be critical in motivating research efforts and funding to find alternate strategies to combat MDR diseases. I do not want to ignore the issues of antibacterial use in agriculture and over-prescription/under-adherence, but I wonder if a paradigm shift is necessary in public perception and education on how resistance mechanisms actually arise. Due to the nature of resistance evolution, even in an ideal world with 100% patient compliance we are likely to see these issues as well, and I think we need to shift the blame away from 'antibiotic misuse' to 'coping with natural consequence of antimicrobial therapies' and start discussing the problem in a broader context.

Curious to hear your thoughts, thanks!

[glr123](#)

David: I think this is a great point, namely that we should be thinking about antimicrobial resistance from a mechanistic perspective, and as a natural outgrowth of treatment. TB is actually relatively

unique in this regard, as it highlights the different dynamics inherent with different drugs. Resistance to isoniazid, for example, emerges rapidly, whereas resistant to rifampin seems much more difficult for *M. tb* to establish (rates still only 5% despite using this drug for ~50 years). But agreed - we can definitely move this discussion on a national/global level away from one of "terror" and toward one of understanding the biological mechanisms at play. Thanks for the great question!!

Given your focus on treatment-resistant TB strains, how do you feel about public policies that demand compliance with TB medication regimens? (as you can tell by my username, I live in a high-burden population and treatment-resistant TB can be a serious problem.)

[rbaltimore](#)

David: To my mind, ultimately, the goal is to get as many people treated as possible - and ideally without infringing on people's rights. On one hand, forcing people to take drugs creates a negative incentive for people to even step forward. On the other hand, if people aren't compelled to stick to a 6-month regimen (even after they start to feel better), they won't finish treatment, with the result that they transmit the disease to more people in the community. It's a tough balance to achieve - not sure I have the right answer, but I do think it's a discussion worth having.

Perhaps this is anecdotal, but I've found that in the US, most of the TB I have treated involves immunocompromised patients (mainly HIV). Do you believe the results of your study would change if you were to use such a population? Would you even consider looking at rifabutin or a different set of drugs knowing that HIV patients don't always go on the same therapies due to drug interaction issues?

[l2-OH](#)

David: Great question. The difference when using immunocompromised patients is that they often die of the disease sooner than those who have healthy immune systems, so transmission of TB is often still propagated by those who are immunocompetent. I'm not sure I have a great feel for exactly how things would change in a population that is, say, largely HIV-driven - but even in those settings, a majority of TB transmission is thought to originate from those who are HIV-negative. We could consider looking at other drugs, but with these models, the complexity can multiply exponentially as one tries to fit resistance patterns to multiple drugs - so even just adding one more drug into the mix would make the model 4 times as complex (in some respects).

What are the most common misrepresentations, mistakes, myths or otherwise unfounded "facts" about the TB disease that the public erroneously believes?

Thank you for your work on advancing the medical field and hopefully the quality of life.

[don_Mugurel](#)

David: Thank YOU for your interest and focus on improving medicine and quality of life. In the developed world, I think the most common myth is that TB is a disease of the past - that nobody really dies of TB anymore. In reality, TB is the leading infectious cause of death worldwide, killing 1.5 million people. With respect to drug-resistant TB, I think that many people feel that this is an uncontrollable problem that is spiraling out of control. In reality, where countries and other organizations have done a good job of responding to the epidemic of drug-resistant TB, ongoing transmission of drug-resistant TB can grind to a halt...and at a faster pace than for normal TB. The *percentage* of TB that is drug-resistant is much lower, for example, in North America and Western Europe than in other parts of the world - something that is not necessarily seen with other pathogens like *S. aureus*.

Hey guys, thanks for fielding our questions!

Wondering if you could cast some light on the role of medical prophylaxis in developing countries.

What kind of research (if any) is currently being done on developing novel agents for TB prophylaxis in endemic areas?

[porschedriver37](#)

David: Another great question. There is a LOT of work being done in South Africa regarding TB preventive therapy - South Africa is responsible for a large proportion of all people who take preventive therapy worldwide (most of them have HIV - it's a standard recommendation for people living with HIV to take TB preventive therapy). Last year, a new regimen was approved for TB preventive therapy - so it's now possible to take an entire course in 12 weekly doses, rather than 6 months of daily pills. It will be interesting to see how this regimen changes the face of preventive therapy in most high-burden settings, where it is recommended but almost never actually implemented.

Is there anything you would want the average Redditor to know about TB that they are likely currently ignorant of?

[Lordica](#)

David: Good question! I think I mentioned above that TB is the leading infectious cause of death worldwide - so, responsible for more deaths than influenza, malaria, or (depending on how you count people with TB and HIV) even HIV. It's also important for people to know that TB is one of the few truly airborne diseases - so everyone who breathes the air is potentially exposed. You can walk into a room hours after someone with TB has been coughing there, and you can still contract the infection. So TB really is a true public health issue, and one we all need to be taking seriously!

Good morning Doctors and thank you for your time. My question pertains to your statement of a drug resistant TB epidemic. In regions of the world where TB is virtually non-existent, could we expect a resurgence of cases over the coming decades, and as this issue grows what new methods of treatment are the next step in combating diseases such as this?

Thank you for your time and all you do.

[Rcove28](#)

David: Thanks for your kind message. My feeling is that, in areas where TB is better controlled (there aren't too many places where TB is non-existent...even in the USA we have 9,000 cases per year), I don't see reasons to suspect a huge resurgence in TB cases - but I do believe that the declines we have been seeing for the past 50+ years are about to flatten out. Unless we are more aggressive in preventing TB in these settings, we're not going to be able to sustain declines in incidence much longer.

Good morning Doctors and thank you for your time. My question pertains to your statement of a drug resistant TB epidemic. In regions of the world where TB is virtually non-existent, could we expect a resurgence of cases over the coming decades, and as this issue grows what new methods of treatment are the next step in combating diseases such as this?

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[Rcove28](#)

Claudia: Hello Rcove28. Great question. There was a study published in the NEJM by Kevin Schwartzman and colleagues a couple of years ago that suggested that the best thing that low prevalence settings like the US or Europe can do is to invest into TB control in adjacent high-burden countries. That being said, with increasing migration as for example in Germany currently there will be increasing TB but under good living conditions and with good medical care, those outbreaks are likely going to be limited and restricted to high risk groups. It is important that we detect cases early though. For that people and doctors need to be aware of the problem. This gets back to the advocacy I was referring to above.

A number of years ago I read Mountains Beyond Mountains which was my first introduction to the problems of TB in the modern world. I never knew that it was still such a devastating disease and had always thought of it as "consumption", a tragic artifact of 19th century Europe. It's a little horrifying that something that affects so many is so little discussed in the general western health conversation.

What, if anything, can I do to help the fight against TB? And when I travel in these areas what, if anything, can I do to ensure I don't contract TB myself?

[seanmharcailin](#)

David: Great question. As far as how to help the fight against TB, there are lots of things that we need. One is just for more people in low-burden settings to be aware of what a huge problem it is. Another is for more people on the ground to actually be there for the patients who have TB. And of course more research always helps too! As for what to do when you travel, other than avoiding areas where TB is likely to be spread (hospital waiting rooms come to mind), there's not too much that I would recommend. If you're in direct contact with someone who has TB, you can wear a special kind of mask (the most common of which is called an N95 respirator) - but you can't really go around wearing those all day.

In the end, the risk of contracting TB is relatively low, so you should travel and enjoy. But get more people to realize that TB is still a big problem, and not only a big problem, but also one that affects the poorest people in the world - those who can least afford to deal with getting a potentially deadly disease. If you can raise that kind of awareness, that's a big step!

Hello Dr. Denkinger and Dr. Dowdy thank you for your time.

1. Does smoking or alcohol consumption play a major role in the prevalence of MDR-TB globally?
2. Does the current global TB control strategy have any flaws?

Thanks!

[askmeaboutmyweiner22](#)

David: While smoking and (heavy) alcohol use are both risk factors for developing TB, I'm not aware of convincing evidence that they are particular risk factors for MDR-TB. I think that everyone has a different opinion about the current global TB control strategy - mine is that it's a good start, but real progress is made on the local level, not necessarily the global one. So it's important for the WHO and other such organizations to come up with global guidance for fighting TB, but in the end, the fight against TB is won or lost at the city or sub-district level...and there's no such thing as a "one size fits all" solution for TB control.

Hello Dr. Denkinger and Dr. Dowdy thank you for your time.

1. Does smoking or alcohol consumption play a major role in the prevalence of MDR-TB globally?
2. Does the current global TB control strategy have any flaws?

Thanks!

[askmeaboutmyweiner22](#)

Claudia: Smoking has definitely been associated with increased risk of TB but it applies to all kinds of TB not only MDR TB. Alcohol is not an issue. Your second question is a hard one! I think the major flaw is that it is underfunded. Another flaw in general terms might be that not enough attention is given to stakeholder input from high burden countries. But generally the WHO End TB strategy is ambitious and well thought through

Why does South Africa have such high rates of TB which predates HIV? Poverty is clearly a factor, but South Africa is one of the wealthiest countries in Africa.

Could it be because the Western Cape where TB is rife is one of the coldest places in Africa?

[jamjamdave](#)

David: This is a fantastic question, and one that nobody really knows the answer to. It's not about temperature, because there are plenty of colder places in the world that are not teeming with TB. And as you say, it's not really poverty either - South Africa is much wealthier than most African countries, yet it has the highest incidence of TB. Nor is it entirely attributable to HIV (though South Africa also has extremely high rates of HIV, even relative to most other African countries). But there's something about the Western Cape that has somehow always fostered TB there - I would love to hear if anyone else has any better answers than this. But even within South Africa, the Western Cape is the wealthiest district, and still has TB rates on par with, or higher than, all the other districts in the country (though not the same prevalence of drug-resistant TB).

Hi I'm doing a bit of research on antibiotic resistance and it seems this is becoming a big problem. Why aren't more pharmaceutical companies attempting to develop antibiotics? Is there no profit in it?

[dabasegawd](#)

David: It really depends on the disease. For example, some of the biggest-selling drugs (by total dollar amount sold) last year were for treatment of hepatitis C. But this is because hepatitis C is very prevalent in wealthier countries. Similar dynamics are seen for HIV, where many people have to take antiretrovirals for life, and the number of people living with HIV in countries like the USA numbers in the millions. But for diseases like TB, there's much less (if any) profit to be had - so yes, this is a chronic problem in the TB world, and we need people who are dedicated to developing these drugs so that we can make the situation better for people who have TB!

How accurate are the cheap prolific skin tb tests? I recently failed one but after having about five in my life I think my immune system has started reacting to them and am getting false positives. Thanks.

Edit: I was subsequently cleared by x-ray.

[Codizzle0024](#)

David: TB skin tests are actually pretty effective. There are definitely false-positives, but the more important thing to know is that there's a difference between TB *infection* (which is what the skin test is for) and TB *disease* (which means having symptoms, being contagious - that's what the x-ray was for). It's estimated that about 1 in 3 people in the world has TB infection (meaning, they would test positive by skin test), but clearly only a small fraction have TB disease. So it's likely that you have TB infection - meaning you will always test positive on the skin test, and you have a risk of developing disease at any point in your life. You would probably be recommended to take preventive therapy to reduce this risk going forward. But to answer your question, while the skin test is far from perfect, a positive test is usually right.

If testing for isoniazid resistance did not prove to have a significant benefit (although in my heart, 4% is significant especially for the sufferers and their families), do you have plans to investigate other resistance targets? Are there any other antibiotics you commonly see TB strains resistant to?

Thanks for your time.

[boringoldcookie](#)

David: Thanks for your question. I wouldn't want to say that testing for isoniazid isn't significant *for patients*, it's just not likely to influence dynamics of TB at the global level. This is a really important point - we wouldn't want our work to suggest that we shouldn't be testing for isoniazid resistance (we should absolutely!! as you say, it's important for those patients). Rather, we want to be clear that we're doing it for the patients' benefit, not in the hope of curbing future epidemics of MDR-TB. There's ongoing work looking at testing for resistance to pyrazinamide and many of the commonly used second-line drugs (especially fluoroquinolones), as well as rifampin (which, when combined with isoniazid resistance, defines MDR-TB).

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Thanks for your time.

[boringoldcookie](#)

Claudia: Dear boringoldcookie, I appreciate your comment. It is very important. There is a difference between population level impact and patient level impact. As a doctor I would want to know whether my patient has isoniazid resistance because in the circumstances that I practice in, I can make changes in regards to individualized therapy. However, as a person working for FIND right now, where we attempt to develop improved tests for patients afflicted by TB in resource-limited settings, I have to consider trade-offs. So, if I only had limitation on what I can target with a test or the addition of isoniazid detection would result in substantial increase cost of the test and I would have to decide whether to detect isoniazid or not. Or a government needs to decide what tests to implement. If most isoniazid resistance is associated with rifampicin resistance, is it worth the cost to the system to detect the additional % or could this money be spent better elsewhere. To your second question: multi-drug resistance is resistance to isoniazid and rifampin; extensively drug resistance TB is resistance to those two and other second line drugs. It is much less common but an even bigger problem in regards to treatment

Considering cigarette smokers have impaired/defective pulmonary immunity, and patients who smoke which are on anti-TB medicine have a higher chance of being persistently smear positive, making them possibly having a higher chance of developing resistant strains?. Is there/should there be a more strict/advance treatment regimen for these patients no matter the cost increase?

[vulcanworlds](#)

David: This is a good question. I think it's important to remember that, while as you say, smoking impairs immunity and also lengthens time to culture/smear conversion, the absolute differences between smokers and non-smokers are relatively small. So yes, I do think that smokers are an important focus population - but I also think there are many others as well (for example, the same things could be said about HIV), and I'm not sure if we want to recommend being stricter on one segment of the population than another.

As someone who has done a little bit on MDR-TB, what are your thoughts on bedaquiline? IIRC treatment of MDR-TB usually requires at minimum 4 drugs however there's weak evidence suggesting which 4. Is it population- or availability-related as to which combination they get?

[herrop4nda](#)

David: There aren't great comparative data between the various drugs, but we have a long history of knowing that the current first-line treatment (isoniazid, rifampin, pyrazinamide, and ethambutol) works, and there's a lot of scientific evidence to back that regimen up. So I wouldn't recommend bedaquiline as a first-line agent, especially given concerns about toxicity. But for those who are resistant to both isoniazid and rifampin, additional drugs are needed. Right now, those second-line regimens don't include bedaquiline either (it's generally only reserved for last-ditch compassionate use) - but as more evidence emerges, that may change.

Hi Dr. Denkinger, thanks for doing this AMA! I am curious to know more about translational research on ways to improve screening and treatment in resource poor settings. I am thinking in particular of Eastern Russia where XDR-TB is rampant in incarcerated individuals - which seems to be due to a simple institutional inability to provide basic care and follow up (or political disinterest). It would be wonderful to see up-to-date international clinical guidelines that are easy to follow and implement, *actually* being implemented. Do you have any thoughts on how to get compliance with best practices from countries with endemic MDR/XDR-TB?

Edit: Not to answer my own question, but a quick Google search lead me to [this book](#) - "[The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICs](#)", which could be of interest to those involved in public health policy.

[Serenderpiter](#)

David: Thanks for this post, I couldn't agree more. (I will let Claudia reply as well if she is able to.) It's true that drug-resistant TB is very prevalent in the former Soviet Union - but much of this reflects transmission of older strains, due to policies in the 1980s. Once these epidemics of drug-resistant TB are initiated, they are very difficult to contain (though it can be done!). I'm not sure that I have great recommendations for easy-to-implement international clinical guidelines, but Partners In Health has a big program in Tomsk Oblast, Russia - and they've shown some pretty impressive results. One of their most recent papers (showing very low rates of recurrence after effective treatment) is here: <http://www.ncbi.nlm.nih.gov/pubmed/25859994>

Hello! I was curious - does your research primarily focus on which drugs do and do not confer resistance quickly, and whether or not combinations will delay resistance or do you also seek to find novel drugs to combat the mechanistic reasons behind the resistance?

[sukriti1995](#)

David: Good question. Our work is primarily related to modeling the dynamics of TB transmission in populations - so the questions of the drugs to which *M. tuberculosis* develops resistance most easily are clearly relevant, but we're not looking, for example, in mice to see which regimens appear to be most effective. Other groups are working on these topics, though - it's a very active area of research!

Thanks for doing this AMA, can you explain a bit the *rpoB* I491F mutation and how its spread might disrupt current detection efforts considering how widely Xpert MTB/RIF is used?

[PHealthy](#)

David: This is a good question. I'm not aware that TB with this particular mutation is on a substantial rise right now - so it will always likely be responsible for some false-negative RIF resistance results with Xpert, but I would keep in mind that we haven't been using any drug susceptibility testing for the majority of the past 40 years - and there hasn't been any substantive change in the standard first-line TB treatment regimen during that time. So I'm skeptical that scaling up Xpert will suddenly create a huge pool of these mutants, when poor treatment without any drug susceptibility testing hasn't.

In Los Angeles, we have a large homeless population. Do you know anything about TB being spread among the homeless? What is the most common way to get TB?

[lastdaysofdairy](#)

David: In lower-incidence settings like the USA, the majority of ongoing TB transmission takes place in high-risk populations like the homeless and the incarcerated population - and often in large outbreaks like the one seen in LA. But still, the most common source of TB in these countries are people who immigrate from higher-burden countries, having been infected in their home countries. So from the perspective of getting TB, it's dangerous to be homeless in the USA, but much more dangerous to be a member of the general population in Africa or South/Southeast Asia.

Hello, casual science enthusiast here. What trends have you found in the evolution of drug resistant tuberculosis. Is it as big of a threat as the more publicized MRSA? How screwed (scientific term) would we be if tuberculosis developed complete resistance to drugs?

Are there any other diseases that you would be interested in modeling their spread?

Grape jelly or Strawberry Jam?

[cspruce89](#)

David: Great question. The interesting thing about the evolution of drug-resistant TB is that, for some drugs, it has been quite explosive, as we have seen with MRSA. For example, within a couple of years of streptomycin (the first TB drug) being introduced, a huge proportion of TB was resistant to it. But with rifampin, we've been using it for almost 50 years, and rates of resistance are still relatively slow. That being said, in the rare cases where TB does develop extensive resistance, we are in trouble, because the number of drugs that are truly effective against TB is really limited. Even if you have a strain that is resistant to just rifampin and isoniazid, that's signing you up for a 2-year course, including

daily injections for 8 months. So you don't want to lose any drugs to resistance when it comes to TB. I'm personally also interested in HIV, but I think that TB is largely neglected in this realm also - the number of TB modelers is much lower than the number of people modeling other infectious diseases. Grape jelly for me.

Thank you for this AMA! I'm currently work as a public health nurse. I'm noticing a greater number of TB contacts that are immunocompromised as a result of being diabetics. How do you think chronic diseases like diabetes will shape the nature of TB treatment and research?

[al626](#)

David: Thank you for participating! This is a great question. My personal feeling is that comorbidities like diabetes will cause a noticeable uptick in TB rates, and especially in places like India where it is rapidly becoming more prevalent. But even then, TB will still be a disease of the poor, and a disease that everyone is at risk of developing. The "standard" TB case will still be an otherwise healthy 30-ish year-old man living in poverty and trying to support his family. Even if we do see more diabetics and more 80-year-olds moving into the future.

Thank you for doing this AMA! I'm not sure if this is quite within your field, but I'll give it a shot anyway. Some contributing factors in spread the spread of disease, like diet and access to health care, are, I guess, fairly well know among us laypeople. I was wondering if you, in your group's research for creating the model, encountered any interesting lesser known societal factor that contribute to, or prevent, the spread of tuberculosis or other communicative diseases? Are there other known factors like family structure, social habits and customs, access to public transport or geographical population distribution that seem to influence the spread of disease or resistance?

[intergalactic_spork](#)

David: Thanks for this question...but unfortunately, with this model, we were trying to keep things relatively simple. Some of the issues you raise (migration, public transit, population mixing patterns) are really fascinating in terms of their likely connection to TB transmission - we're hoping to collect some data to inform these questions in places like Nepal, but the published model didn't include any of these factors. There's been a lot more work in this area related to diseases like influenza or vector-borne disease, where the time between infection and disease isn't as long as it is for TB.

Claudia, great to see you doing such good work. See you at CROI? -Brett Williams

[Brettwilliams0](#)

Claudia: Good to hear from you. I am in Boston yes. Hope to see you!

Was anything of value actually learned from the Canadian government's experimentation on Aboriginal people to study the interaction between nutrition and TB? Or any of the other experiments on humans involving TB and a lack of consent?

I hope some good came from it :(

What is the main thing you would like to teach people about TB/your work in a few sentences?

[stuckwithculchies](#)

David: I'm unfortunately not familiar with the Canadian government's experimentation on Aboriginals to study nutrition and TB - will have to go read up on that, sounds like a dark chapter in the history of TB research. As far as things regarding our work, I think the main thing to understand is that drug-resistant TB is not a monolithic entity - resistance to one drug may act very differently from resistance to another drug. It's important to remember these things and to consider each drug resistance pattern separately, rather than just assuming that drug-resistant TB is predestined to explode in certain populations. Treating rifampin-resistant TB can actually be very effective in reducing epidemics of MDR-TB!

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[stuckwithculchies](#)

Claudia: I would like to refer to David's comment above in regards to the second question. In regards to the first, there has been a lot of wrong done in the name of medicine and research across many disciplines. The main learning is that we should not repeat it and serve our patients to the best of our abilities. In regards to the Canadian Aboriginal population, there is still a lot of ongoing TB transmission and still a lot of need for improved care.