1
00:00:14,510 --> 00:00:15,709
So I'm Helen McShane,

2
00:00:15,710 --> 00:00:25,370
and I'm the director of the NIHR Oxford Biomedical Research Centre that is hosting this Oxford Reads Kafka TB event for us this evening.

3
00:00:26,690 --> 00:00:33,800
The BRC represents a partnership between the University of Oxford and Oxford University Hospitals NHS Foundation Trust.

4
00:00:35,180 --> 00:00:41,060
Sorry. Excuse me. We're funded by the government to conduct translational research for patient benefit.

5
00:00:41,420 --> 00:00:49,100
That means developing new vaccines, new drugs, new diagnostic tests, new tools, all of which are designed to improve the health.

6
00:00:51,620 --> 00:00:55,550
And wealth of the patient, of of patients and the NHS.

7
00:00:56,840 --> 00:00:59,360
The BRC is organised into 15 themes,

8
00:00:59,630 --> 00:01:06,950
one of which is called life saving vaccines and one of which is called Modernising Medical Microbiology and Big Infection Data.

9
00:01:07,580 --> 00:01:13,520
The work of my research group sits within the vaccines theme, and the work of Phil's uh,

10
00:01:13,520 --> 00:01:18,140
group sits within the modest Modernising Medical Microbiology group.

11
00:01:18,680 --> 00:01:24,649
We both work on TB, so that's why we're here to talk to you today, because of course, the the whole,

12
00:01:24,650 --> 00:01:33,530
um, of this week's events are really focussed around the fact that Kafka died 100 years ago of TB.

13
00:01:34,190 --> 00:01:41,330

Um, uh, so that's that's why we're here today. I'm going to give a talk updating you on some of the progress in vaccine development.

14
00:01:41,690 --> 00:01:46,190
Uh, we're then going to hear from Amy about the lived experience of having tuberculosis.

15
00:01:46,490 --> 00:01:51,440
Uh, and then Phil is going to talk to us about, uh, some updates on diagnostic tests.

16
00:01:53,240 --> 00:02:02,420
So when I was thinking about this talk, uh, I found this quote, um, or this comment where that Kafka saw his TB as a liberation.

17
00:02:02,960 --> 00:02:11,560
I'm not quite sure I agree with that. Uh, and I'm quite sure that the 10.6 million, uh, people who developed TB in 2022,

18
00:02:11,570 --> 00:02:18,290
not to mention the 1.3 million people who died in 2022 of TB, would describe it as a liberation.

19
00:02:19,010 --> 00:02:23,390
TB remains a very significant global health problem around the world today.

20
00:02:24,080 --> 00:02:28,280
It is probably, again the leading cause, infectious cause of death.

21
00:02:28,280 --> 00:02:33,260
So I think it's overtaken Covid. Uh, and and got back into that number one position.

22
00:02:33,620 --> 00:02:39,019
Drug resistance is an increasing problem. About half a million people have drug resistant TB every year.

23
00:02:39,020 --> 00:02:40,790
And Phil will talk a little bit about that.

24
00:02:41,300 --> 00:02:49,970
The geographical overlap with the HIV epidemic, which makes people more susceptible to TB and the burden of latent infection,

25
00:02:49,970 --> 00:02:57,200

it's estimated that about a quarter of the world's population are latently infected with TB, and are at risk of reactivation.

26
00:02:57,470 --> 00:03:01,310
Should that latent, uh, should they become immunocompromised for any reason.

27
00:03:03,470 --> 00:03:11,420
TB is different to HIV and malaria. The other big what used to be called the big three pathogens in that we already have a vaccine,

28
00:03:11,420 --> 00:03:14,840
BCG, which is one of the world's most widely used vaccines.

29
00:03:15,110 --> 00:03:18,110
It's been given to over 3 billion people around the world.

30
00:03:19,040 --> 00:03:21,920
And BCG has been around for over 100 years.

31
00:03:22,340 --> 00:03:32,330
It was first given orally in 1921, and there have been many, many studies over the years looking at how well BCG works to protect people against TB.

32
00:03:32,810 --> 00:03:36,800
We know that when it's given at birth, as it is throughout most of the developing world,

33
00:03:37,100 --> 00:03:42,070
that it confers very good and reliable protection against disseminated TB.

34
00:03:42,080 --> 00:03:48,800
So that's TB that's spread outside of the lungs, particularly that spread to the to the brain, something we call TB meningitis.

35
00:03:49,880 --> 00:03:56,180
But what it really doesn't do very consistently is protect against lung disease, particularly in young adults.

36
00:03:56,210 --> 00:04:01,560
Uh, and adolescents. It's very variable, the protection it confers against lung disease.

37
00:04:01,580 --> 00:04:12,200

So the British MRC study conducted in this country in the 1950s shows the BCG was 80% protective, and that protected protection lasted for 20 years.

38
00:04:12,710 --> 00:04:18,320
In comparison, protection seen in, for example, India or Africa is close to zero.

39
00:04:19,880 --> 00:04:23,390
So one of the real challenges is what's underlying that variability.

40
00:04:23,990 --> 00:04:28,070
And how can we develop better vaccines that protect more universally.

41
00:04:28,640 --> 00:04:31,790
We know that giving BCG more than once doesn't make any difference.

42
00:04:31,790 --> 00:04:39,440
It doesn't make it any better. And there is the sort of slightly curious literature which suggests that BCG, when given to neonates,

43
00:04:39,680 --> 00:04:46,280
can protect against what we call all cause mortality, which means it reduces the deaths from things other than TB.

44
00:04:46,580 --> 00:04:54,170
Now that's a variable effect. And it's seen in some studies some of the times, but is quite interesting when you think about how BCG might be working.

45
00:04:55,820 --> 00:05:04,100
So this slide uh, which was taken from a meta analysis, looks at the reasons for the variability in protective efficacy of BCG.

46
00:05:04,670 --> 00:05:08,930
And what we see is that latitude is very important.

47
00:05:09,230 --> 00:05:14,030
So the closer you live to the equator, the less likely BCG is to work.

48
00:05:14,440 --> 00:05:18,700
And we think that's because of exposure to things called non tuberculose mycobacteria.

49
00:05:18,910 --> 00:05:24,400

So pathogens from the same family as TB that don't cause disease unless you're immunocompromised.

50
00:05:25,420 --> 00:05:32,590
We also see that if you give vaccines for the vaccine as a neonates rather than to older age groups, it's much better at protecting.

51
00:05:33,040 --> 00:05:37,690
And that's why W.H.O. policy is to give it ideally within the first seven days of life.

52
00:05:38,710 --> 00:05:44,110
Importantly, what we also see is the BCG strain doesn't seem to make any difference. So BCG,

53
00:05:44,110 --> 00:05:48,459
unlike most of the vaccines we use today, is not the same thing around the world.

54
00:05:48,460 --> 00:05:56,230
It's not clonal. There are lots of different strains of BCG, but there's very little evidence that although those strains are genetically different,

55
00:05:56,470 --> 00:06:01,510
they're probably not very different in how good they are at protecting against TB or not.

56
00:06:04,300 --> 00:06:08,440
So how do we put all this together and how do we design a better vaccine against TB?

57
00:06:08,650 --> 00:06:14,740
Well, because of that protection that BCG confers in the first few years of life against severe disease,

58
00:06:15,040 --> 00:06:19,630
really BCG in some shape or form has to stay part of any new regime.

59
00:06:20,140 --> 00:06:25,960
Um, and we know that you need to induce a very strong what we call cell mediated immune response.

60
00:06:26,080 --> 00:06:28,780
So this means relying on the T cells in your blood.

61

00:06:30,520 --> 00:06:39,160
So we know that, uh, all of the vaccines we give today, apart from BCG, work primarily via the induction of things called antibodies.

62
00:06:39,610 --> 00:06:45,130
Whereas TB is a different ballgame, hides inside cells, which means that antibodies can't get to it.

63
00:06:45,340 --> 00:06:51,880
So we actually need to induce the cell mediated arm of the immune response in order in order to develop a protective vaccine.

64
00:06:52,180 --> 00:06:59,950
And of course, we see that most obviously in patients with HIV, as their CD4 count comes down, the risk of getting TB goes up.

65
00:07:01,060 --> 00:07:04,690
Um, broadly speaking, there are two strategies being pursued in the field.

66
00:07:04,960 --> 00:07:12,790
The first is to say, well, let's leave BCG as it is a well-established part of the expanded program on immunisation led by W.H.O.

67
00:07:13,060 --> 00:07:20,530
And let's develop a second vaccine, a booster vaccine to be given at a later point in time to improve the efficacy of BCG.

68
00:07:21,550 --> 00:07:29,110
The alternative is to say, let's make a better BCG. And there are groups around the world genetically engineering either BCG or in fact,

69
00:07:29,110 --> 00:07:33,910
Mycobacterium tuberculosis, uh, in order to make a better strain of BCG.

70
00:07:34,150 --> 00:07:44,050
And of course, you could put the two together. So this slide illustrates the clinical development pipeline in the year 2000.

71
00:07:44,200 --> 00:07:48,160
So here were all the vaccines that were in clinical trials in the year 2000.

72
00:07:48,580 --> 00:07:54,790
No I haven't forgotten to paste the picture in. There were no new TB vaccines in clinical trials in the year 2000.

73
00:07:55,420 --> 00:08:00,790
Which really for me represents decades of neglect in in funding for this field.

74
00:08:01,060 --> 00:08:09,910
Uh, and I'm really just the idea that actually maybe we'd eradicated TB, whereas of course, we are very, very far from that, uh, that scenario.

75
00:08:10,600 --> 00:08:15,549
So fast forward to 2024, and at least we actually have a pipeline.

76
00:08:15,550 --> 00:08:18,820
Now, there are actually some vaccines in clinical trials.

77
00:08:19,270 --> 00:08:25,270
But, there's always a but with TB, if you look at this more carefully, uh, there are some problems with it.

78
00:08:25,270 --> 00:08:33,370
And there are two problems in particular. The first is, if I put up the pipeline from five years ago, you'd be hard pushed to see anything different.

79
00:08:33,790 --> 00:08:37,270
So it's a very stagnant pipeline. Things are not moving very quickly.

80
00:08:38,380 --> 00:08:43,990
The second problem with it is that it's a very thin pipeline, particularly on the left hand side.

81
00:08:46,300 --> 00:08:52,750
So for clinical development pipelines, we want a very rich early pipeline because of the attrition.

82
00:08:53,020 --> 00:09:00,490
Most things in early development fail. At best, probably 1 in 10 make it through to licensure and deployment.

83
00:09:00,970 --> 00:09:04,840
What that means is we need a huge number of things on the left hand side to make

84
00:09:04,840 --> 00:09:08,500
sure we actually have something we can pull through and make and use in real life.

85
00:09:09,280 --> 00:09:11,790
This is a pretty thin left hand side of the pipeline.

86
00:09:11,830 --> 00:09:20,440
So again, representing really lack of funding, uh, and sort of lack of, of global awareness of, of how pressing a problem this is.

87
00:09:21,760 --> 00:09:29,010
So I'm going to now just illustrate, uh, briefly, uh, a couple of vaccines that have made it through to clinical trials.

88
00:09:29,040 --> 00:09:33,429
So firstly, MVA, 85A, this was a vaccine my laboratory developed.

89
00:09:33,430 --> 00:09:38,560
It was the first new TB vaccine to go into clinical trials anywhere in the world in 2002.

90
00:09:39,040 --> 00:09:46,360
We conducted a very careful clinical development pipeline because it was the first vaccine, and we obviously wanted to be safe above everything else.

91
00:09:46,870 --> 00:09:53,439
And despite eight years of lots of clinical trials and lots of trials showing like this slide does here, um,

92
00:09:53,440 --> 00:09:57,879
that this vaccine was safe and was very potent at stimulating an immune response,

93
00:09:57,880 --> 00:10:04,030
at least when we tested it in this country, when we got to test it in 3000 babies in South Africa,

94
00:10:04,450 --> 00:10:09,580
We sadly saw that there was no difference between the vaccine arm and the placebo arm.

95
00:10:09,790 --> 00:10:13,960
So although the vaccine was safe in this trial and the babies were perfectly.

96
00:10:13,980 --> 00:10:20,790
Safe. There was no improvement in the rates of TB in the babies that got the vaccine compared with the placebo arm.

97
00:10:22,950 --> 00:10:26,280
Enormously disappointing results for us and for the field.

98
00:10:26,790 --> 00:10:31,680
But that's the price you pay for being the first. And we have to work out what we can learn from this study.

99
00:10:32,160 --> 00:10:35,820
We took an immune sample from every single baby in that study.

100
00:10:36,240 --> 00:10:39,600
So we went back to their samples taken at the beginning of the trial and said,

101
00:10:39,600 --> 00:10:43,980
what can we learn from those samples that will help us develop better vaccines?

102
00:10:44,490 --> 00:10:50,010
And what we learnt was two really important things. We learned that activated T cells.

103
00:10:50,160 --> 00:10:53,550
So T cells, if you like, that, are really primed and ready for action.

104
00:10:53,670 --> 00:11:00,749
All of them when were higher in the babies that went on to get TB compared with the controls.

105
00:11:00,750 --> 00:11:04,950
That didn't go on to get TB. What's really interesting, what's causing that activation.

106
00:11:05,490 --> 00:11:11,490
And we also found that the antigen specific response we were trying to induce with the vaccine was,

107
00:11:11,490 --> 00:11:15,780
in fact lower in the babies that went on to get TB compared with the controls.

108
00:11:16,050 --> 00:11:24,660
So perhaps if the vaccine had been a bit more potent and stimulated a stronger response, we might have seen a result that we had hoped to see.

109
00:11:26,340 --> 00:11:30,690
This is slide really is to remind me that serendipity plays an important part in science.

110
00:11:30,690 --> 00:11:36,360
So as part of the controls we do in our lab assays, we look at various, um,

111
00:11:36,510 --> 00:11:41,310
peptides or proteins from other pathogens, really just to check that the cells are alive.

112
00:11:42,090 --> 00:11:48,690
And as part of that, we had a, um, some peptides or some proteins from a virus called CMV, cytomegalovirus.

113
00:11:49,350 --> 00:11:55,889
When we looked at the responses to this, we found that the babies who were CMV infected in about a quarter of them were

114
00:11:55,890 --> 00:12:00,959
in the study were more likely to get TB than the CMV uninfected babies.

115
00:12:00,960 --> 00:12:04,590
And then we knew that. Why is that? Well, we don't know, but we're working on it.

116
00:12:04,950 --> 00:12:12,750
But actually, it reminds me that the infectious milia that people live in has an interaction with their risk of infectious diseases.

117
00:12:14,270 --> 00:12:16,850
So why is TB vaccine development so difficult?

118
00:12:16,880 --> 00:12:21,860
Well, the trials are very big and very expensive and take a long time, and I'll show you that in a minute.

119
00:12:22,280 --> 00:12:26,540
We don't know what the animal models mean in terms of predicting human efficacy.

120
00:12:27,650 --> 00:12:32,420
We don't have an immune correlate of protection, so we can't predict which vaccines will work.

121
00:12:33,080 --> 00:12:37,250
We don't know whether the whole organism vaccines or just a few proteins.

122
00:12:37,250 --> 00:12:41,660
There are 4000 to choose from. So how do we go about deciding, uh, is best?

123
00:12:42,500 --> 00:12:47,090
And we have a very, very clever pathogen that's really good at hiding from the immune system.

124
00:12:49,890 --> 00:12:57,030
So to end on a slightly more positive note, this is the most exciting result in the field in several decades.

125
00:12:57,300 --> 00:13:01,830
So this is a vaccine developed originally by GSK, now being developed by the Gates Foundation.

126
00:13:02,190 --> 00:13:11,040
3500 African adults who were already latently infected, vaccinated either with this vaccine called M72 or placebo.

127
00:13:11,490 --> 00:13:17,850
And unlike the curves in the MVA study, you can see that these are a bit further apart, which is what you want.

128
00:13:17,940 --> 00:13:21,030
And even more importantly, the vaccine arm is on the top.

129
00:13:21,240 --> 00:13:24,510
So about 50% protection seen in this study.

130
00:13:24,690 --> 00:13:28,229
So fantastic result for the field, but only 50%.

131
00:13:28,230 --> 00:13:34,500
We have a Covid vaccine that's nearly 100% effective. We have an HPV vaccine human papillomavirus vaccine.

132
00:13:34,620 --> 00:13:41,410
That's over 100%. We have to do better than this. That result needs repeating in a larger trial.

133
00:13:41,500 --> 00:13:45,150

And just to give you a sense of the challenge, we've got a trial that's just out.

134
00:13:45,170 --> 00:13:50,790
It's got 60 sites in Africa, Indonesia and Vietnam, 20,000 subjects.

135
00:13:50,970 --> 00:13:54,390
This trial is going to cost over half a billion dollars.

136
00:13:54,570 --> 00:13:59,860
We can't do many of these studies. Recruitment is underway and it's due to report in 2028.

137
00:13:59,880 --> 00:14:01,350
So you can see the problem.

138
00:14:03,330 --> 00:14:10,739
One of the things we're doing in my lab is to try and develop a human challenge, models to see if we can actually test vaccines,

139
00:14:10,740 --> 00:14:19,620
to see whether they work in a human challenge model where we deliberately give people an infection before we move to these large efficacy trials.

140
00:14:20,010 --> 00:14:23,850
We can do this in malaria. We can do it influenza. Why can't we do it in TB?

141
00:14:24,330 --> 00:14:28,650
So we started by giving people BCG by the skin route.

142
00:14:29,010 --> 00:14:34,500
And now we're doing this by aerosol directly into the lungs to mimic the natural route of infection.

143
00:14:35,100 --> 00:14:38,670
We think this kind of model will help us test new vaccines.

144
00:14:40,470 --> 00:14:46,270
This I'm going to skip over in the interest of time, but this just shows you the power of doing these kind of studies.

145
00:14:46,320 --> 00:14:51,930
We can look in the lungs at the kind of cells that go into the lungs after we've infected people.

146
00:14:52,080 --> 00:14:59,490
And that gives us new insights into immunity in people, in the target species, rather than in animal models that we don't know the relevance of.

147
00:15:01,230 --> 00:15:04,020
But really, just to finish with a slightly salutary note,

148
00:15:04,410 --> 00:15:11,850
and I'm very grateful to Barry Mannone from the Department of the Faculty of Modern Languages for drawing this to my attention.

149
00:15:12,360 --> 00:15:15,480
There is some evidence that Kafka may have been an anti-vaxxer.

150
00:15:16,200 --> 00:15:20,040
So, uh, he made friends with someone called Maurice Schnitzer.

151
00:15:20,460 --> 00:15:26,250
Um, and you can see here no vaccinations. Uh, record I recorded on his military conscription card.

152
00:15:26,680 --> 00:15:34,930
And there's his name from Doctor Franz Kafka. He's subscribing to this sort of, um, naturopath, uh, journal.

153
00:15:34,950 --> 00:15:40,770
So, um, the irony of all of this is, even if 100 years ago, 110 years ago,

154
00:15:40,860 --> 00:15:44,880
we had an effective vaccine against TB, I'm not sure Kafka would have had it.

155
00:15:45,780 --> 00:15:47,310
So that may not have altered history.

156
00:15:48,300 --> 00:15:54,390
So that, I hope, was just a little snapshot of of perhaps some optimism at the end of where we are with TB vaccine development.

157
00:15:54,870 --> 00:16:01,200
I'm now going to hand over to Amy, who's going to talk you through, really the lived experience of living with TB.

158

00:16:02,340 --> 00:16:24,020
Amy.

159
00:16:24,640 --> 00:16:28,110

160
00:16:29,330 --> 00:16:33,620
So Franz Kafka was just 40 years old when he sadly died from TB.

161
00:16:34,190 --> 00:16:36,560
Which Which is actually the age that I am now.

162
00:16:37,070 --> 00:16:42,950
So during my initial research into his life, I discovered that in addition to being a ferocious writer,

163
00:16:42,950 --> 00:16:46,370
he was also a lawyer and legally educated as I am too.

164
00:16:47,270 --> 00:16:53,630
However, unlike Kafka, I am extremely fortunate to be alive and able to share my story with you today.

165
00:16:54,110 --> 00:16:56,720
I just want to start by saying thank you for being here this evening.

166
00:16:57,350 --> 00:17:01,010
Um, there are a few things I hope you will take away from my personal experience.

167
00:17:01,880 --> 00:17:11,720
Firstly, please never forget that at the heart of this terrible disease are ordinary people from all walks of life with hopes,

168
00:17:11,990 --> 00:17:20,450
fears, worries, expectations, ambitions and dreams, all of whom deserve a chance at a future free from TB.

169
00:17:21,740 --> 00:17:28,880
Secondly, TB has never been eradicated in the UK and if I hear this one more time, I will scream literally.

170
00:17:29,390 --> 00:17:38,180
Um. In fact, confirmed cases of TB in the UK have risen sharply over the last few years since the Covid 19 pandemic.

171
00:17:38,720 --> 00:17:47,480
So, like many other infectious diseases, TB acts as a kind of magnifying glass, exposing existing fault lines and inequalities,

172
00:17:48,080 --> 00:17:55,040
especially in light of current challenges such as the cost of living crisis, housing shortages and poor living conditions,

173
00:17:55,430 --> 00:18:00,980
the hostile environment, major pressures in the NHS and global conflicts.

174
00:18:01,730 --> 00:18:08,630
It is more important than ever to be aware of TB and to understand the devastating consequences it can have.

175
00:18:10,100 --> 00:18:15,230
So I was a student in my late teens when I first developed symptoms of TB.

176
00:18:15,980 --> 00:18:23,660
And the most obvious symptom was a persistent cough or despite numerous courses of antibiotics, wouldn't go away.

177
00:18:24,170 --> 00:18:34,610
And next came a slow, insidious fatigue, unexplained weight loss, lack of appetite, and finally, night after night of waking up, covered in sweat.

178
00:18:35,180 --> 00:18:40,820
It was my friends, family, colleagues and even customers at the bar where I worked

179
00:18:40,850 --> 00:18:49,700
to know just how ill I was before I did. I mean, I was otherwise young and healthy, so I thought, how could I be seriously unwell?

180
00:18:50,180 --> 00:18:56,420
I thought these things happen to other people, not me. After nine months of visits to my GP,

181
00:18:57,050 --> 00:19:05,900
I came home for Christmas from university where I was studying law and my GP finally referred me to hospital for an initial chest x ray,

182
00:19:06,710 --> 00:19:17,130
suspecting I had asthma. I was given another course of antibiotics and a follow up chest x ray, and then I had nothing until two months later,

183
00:19:17,670 --> 00:19:24,960
when I received a phone call from the chest clinic at my local hospital in London, asking why I hadn't turned up for an appointment

184
00:19:25,230 --> 00:19:36,900
I didn't even know I had. So by now my condition had seriously deteriorated and I was in excruciating pain as my left lung had begun to collapse.

185
00:19:37,950 --> 00:19:43,980
My appointment was rescheduled for six weeks later. By this time it was Easter holidays.

186
00:19:44,550 --> 00:19:52,710
I had a bronchoscopy where a camera was inserted into my lungs, and the sample was taken to be tested, as well as three sputum samples.

187
00:19:54,350 --> 00:19:57,860
So by this time I had an inkling that I might have TB.

188
00:19:58,370 --> 00:20:05,510
After speaking to my GP, and when I asked the doctor who carried out the procedure if they thought I had TB, they said yes.

189
00:20:06,170 --> 00:20:15,580
And they told me that if they couldn't diagnose me, I could die. A few weeks later, I got a call from the TB nurse who finally diagnosed me with TB.

190
00:20:15,880 --> 00:20:21,850
She said to me, and this is an exact quote I remember: you have World War three going on inside you.

191
00:20:22,690 --> 00:20:30,310
It didn't actually come as a huge shock, and actually it was more of a relief, which might sound a bit strange, but I initially thought I had cancer.

192
00:20:31,090 --> 00:20:36,460
Um, so now I had the correct diagnosis and I could start the start the start treatment at last.

193
00:20:37,000 --> 00:20:44,320
So by now I weighed five and a half stone. Um, my hair was falling out and my left lung had completely collapsed.

194
00:20:46,000 --> 00:20:56,020
So when TB was first mentioned to me by my GP, I was so shocked because like many people in this country, I thought TB was no longer a threat.

195
00:20:56,560 --> 00:21:01,690
Besides, I'd had the BCG vaccine when I was 13, so I didn't think it was possible to catch it.

196
00:21:02,740 --> 00:21:04,870
I was completely ignorant about it.

197
00:21:05,230 --> 00:21:13,180
I didn't have any awareness of the havoc the disease was wreaking in other parts of the world and in certain affected communities here in the UK.

198
00:21:14,020 --> 00:21:19,360
Um, but, you know, I'm embarrassed to admit that now, but sadly, I'm far from being the only one.

199
00:21:20,500 --> 00:21:26,320
I suspect my GP didn't think of TB either, because I had no social or clinical risk factors.

200
00:21:26,680 --> 00:21:29,230
So I didn't fit the so-called typical profile.

201
00:21:30,130 --> 00:21:36,430
It's so important to remember that while some people are more at risk of TB, anyone who breathes can get TB.

202
00:21:37,360 --> 00:21:40,210
Secondly, with the public so focussed on Covid.

203
00:21:42,790 --> 00:21:50,110
Um, I am concerned that many will misstate their symptoms of TB for Covid and not seek medical help until a much later stage,

204
00:21:50,590 --> 00:21:56,860
leading to delays in diagnosis that could have serious consequences and increase the risk of further transmission.

205
00:21:57,790 --> 00:22:02,950
So by now I've been confined to my bed for about two months.

206

00:22:03,580 --> 00:22:09,280
I felt like a zombie. I had didn't even have the physical energy to move around my house.

207
00:22:09,820 --> 00:22:14,590
Eating was a huge challenge due to waves of nausea, and I couldn't stomach any food.

208
00:22:15,580 --> 00:22:23,590
To avoid being admitted to hospital and fed by tube, I was prescribed a short course of high dose steroids to stimulate my appetite.

209
00:22:25,630 --> 00:22:29,680
I then continue taking these long term to reduce the fluid in my left lung.

210
00:22:33,520 --> 00:22:43,660
So my close contacts were also screened, and I was so afraid of what would happen if I'd infected any of my family, friends and flatmates.

211
00:22:43,990 --> 00:22:48,340
I remember feeling at the time so much fear and guilt and worry.

212
00:22:48,970 --> 00:22:51,850
I thought, how would they react? Or would they blame me?

213
00:22:52,360 --> 00:22:59,560
Thankfully, nobody tested positive and my friends and family were very supportive and fairly level headed by this time.

214
00:22:59,950 --> 00:23:06,670
Most of them knew that TB was curable, so I spent a month in home isolation.

215
00:23:07,270 --> 00:23:11,680
Many of you may now have some idea of what this feels like thanks to thanks to Covid.

216
00:23:12,880 --> 00:23:17,680
Eventually, after a month or so, I noticed an improvement in my energy levels.

217
00:23:18,010 --> 00:23:24,639
Walking around the house felt easier, although I was still very short of breath and I found it difficult to wash my hair and cook meals.

218

00:23:24,640 --> 00:23:34,720
So my mum had to do all of these things for me. I hadn't left the house at all, and my family suggested taking a trip out in the car with a friend.

219
00:23:35,350 --> 00:23:40,780
I was not prepared for how I would feel being outside for the first time in about three months.

220
00:23:41,650 --> 00:23:49,540
As I stepped out of the car, the sound of the other cars, the voices of people around me and even birdsong were magnified in my ears.

221
00:23:49,930 --> 00:23:54,670
Everything felt too loud and too bright. I just wanted to get back to the safety of my bedroom.

222
00:23:55,570 --> 00:24:01,780
I was suddenly overwhelmed with panic and I felt dizzy. I got back in the car immediately and my friend drove me back home.

223
00:24:02,860 --> 00:24:04,930
I had no idea what was happening to me.

224
00:24:05,830 --> 00:24:12,490
Nobody had prepared me for this, but I now know that it's not unusual to experiences after a long period of isolation indoors.

225
00:24:13,450 --> 00:24:16,480
So the course of treatment for drug sensitive TB,

226
00:24:17,410 --> 00:24:25,510
and I should say this also actually includes non TB drugs as well that I took involve taking approximately 13 tablets a day for six months,

227
00:24:25,510 --> 00:24:30,070
although in my case it was extended to nine months. I hated those drugs.

228
00:24:31,060 --> 00:24:40,240
I once heard John Moore-Gillon, who was a top TB specialist at the time, described them as the size of horse tablets and he wasn't wrong either.

229
00:24:41,830 --> 00:24:46,360
The side effects were things like nausea and the most horrendous joint pains.

230

00:24:47,950 --> 00:24:55,330
So back then, TB patients had to pay for their prescriptions out of their own pockets as it wasn't classed as long term treatment.

231
00:24:56,620 --> 00:25:02,710
I wasn't well enough to work, and I came from a low income, working class family who were also struggling financially.

232
00:25:03,280 --> 00:25:10,780
Over Christmas, my dad died very suddenly within 24 hours after a short illness, and things have been really tough ever since.

233
00:25:11,770 --> 00:25:15,250
There was no additional financial support available for my university,

234
00:25:15,760 --> 00:25:20,260
and by this time most of the government funded hardship funds had been allocated.

235
00:25:20,860 --> 00:25:24,490
I wasn't eligible for any benefits because of my student status.

236
00:25:25,270 --> 00:25:30,880
I had to pay for treatment out of my remaining student loan and extend my overdraft to cover this period.

237
00:25:33,040 --> 00:25:41,050
Now, if someone in my situation, I had a roof over my head and family around me, was struggling to afford the cost of treatment.

238
00:25:41,470 --> 00:25:44,890
Can you imagine what it was like for homeless people?

239
00:25:45,310 --> 00:25:47,350
People would normally recourse to public funds.

240
00:25:47,650 --> 00:25:57,070
Refugees and asylum seekers living on ¬£5 a week. To complete treatment in those circumstances would have been a miracle today.

241
00:25:57,100 --> 00:26:02,380
TB treatment is now free and everyone diagnosed with TB is exempt from charges.

242
00:26:03,430 --> 00:26:08,620

The problem is patients don't present with TB, they present with a collection of symptoms.

243
00:26:09,160 --> 00:26:15,940
So it is possible that people may be wrongly charged for treatment and with a hostile environment creeping into the NHS,

244
00:26:16,210 --> 00:26:20,680
this put some communities at risk of racism, discrimination and prejudice.

245
00:26:22,590 --> 00:26:30,960
Once I was no longer infectious, I was admitted to hospital for two weeks of intensive physiotherapy to try to inflate my left lung.

246
00:26:31,560 --> 00:26:33,090
Unfortunately, this didn't work,

247
00:26:33,240 --> 00:26:41,040
although my right lung did actually expand to help compensate as much as possible for the loss of function in the left lung.

248
00:26:41,280 --> 00:26:43,560
It's actually quite amazing what the body can do sometimes.

249
00:26:44,780 --> 00:26:54,590
So during this time I couldn't return to university to sit my interview exams, and later I made the decision to repeat my first year at university.

250
00:26:55,310 --> 00:27:03,290
Once I was back at uni in the autumn, I continue treatment and travel back to London regularly for follow up appointments with my TB specialist team.

251
00:27:04,340 --> 00:27:09,530
I started getting intermittent infections around this time, but otherwise all seemed to be going well.

252
00:27:09,950 --> 00:27:18,250
And after nine months I finished my treatment. About 2 or 3 months later, I noticed changes in my energy levels.

253
00:27:19,030 --> 00:27:24,010
I was sleeping a lot and genuinely not feeling very well. After coughing up quite a bit of blood,

254
00:27:24,460 --> 00:27:32,290
I ended up in A&E. They discovered my heart rate was 167 and as soon as I saw the doctors eyes widened,

255
00:27:32,620 --> 00:27:37,300
I knew what was coming next. They wanted to admit me to hospital for further tests.

256
00:27:38,470 --> 00:27:45,070
To cut a long story short. I ended up heading back to London to see my TB specialist team, and I was treated for a chest infection.

257
00:27:46,150 --> 00:27:51,520
I returned to university after the Easter holidays, but just a few weeks later,

258
00:27:52,060 --> 00:28:01,330
I was admitted to hospital in London with a Pseudomonas infection and an empyema after being rushed into it into the resuscitation area.

259
00:28:02,470 --> 00:28:11,590
This was when I was diagnosed with severe bronchiectasis, a lung condition that can cause infections in the lung due to excessive build-up of mucus.

260
00:28:11,920 --> 00:28:20,290
So TB is one of the underlying causes. If that wasn't bad enough, I was having a relapse of TB and treatment was restarted.

261
00:28:21,940 --> 00:28:29,919
It was also thought that the TB might be drug resistant. So it was an incredibly scary time. All the NHS

262
00:28:29,920 --> 00:28:33,249
workers who entered my room will face masks and PPE,

263
00:28:33,250 --> 00:28:41,410
which at that time was very bewildering and I was told by my TB nurse to prepare to be in hospital for a very long time.

264
00:28:43,170 --> 00:28:50,280
I had to make a very difficult and last minute decision to suspend my degree studies and take a period of intermission for 12 months.

265
00:28:51,750 --> 00:28:55,170
I had no idea how I was going to support myself financially.

266
00:28:56,160 --> 00:28:59,100
I still had student status, so I couldn't apply for benefits,

267
00:28:59,610 --> 00:29:06,900
but I couldn't access the government funded Access to Learning fund because it wasn't supposed to be relied upon as a sole means of income.

268
00:29:07,440 --> 00:29:11,400
So I ended up living off credit cards and my over my student overdraft.

269
00:29:12,120 --> 00:29:17,069
It wasn't long before I fell into debt. There is some good news

270
00:29:17,070 --> 00:29:25,430
believe it or not. I didn't have drug resistant TB, but I would need intensive daily physiotherapy and lung surgery.

271
00:29:25,440 --> 00:29:28,560
A pneumonectomy to me to remove my entire left lung.

272
00:29:29,880 --> 00:29:35,940
This was originally scheduled for January, but unfortunately yes, you guessed it, there was another twist to this story.

273
00:29:36,330 --> 00:29:39,450
I now had TB in my previously healthy right lung.

274
00:29:40,410 --> 00:29:47,010
The damage in my left lung was acting as a reservoir of infection, and it would need to be removed as soon as possible.

275
00:29:47,790 --> 00:29:55,590
So my plan to return to university from intermission was now in jeopardy, and I would need to consider my options and go through an appeal process,

276
00:29:56,340 --> 00:30:02,220
as I didn't have an automatic right to extend my intermission to cover the summer term or repeat the year.

277
00:30:03,900 --> 00:30:10,320
In May of that year, my lung surgery went ahead very successfully and my TB nurse said to me

278
00:30:11,040 --> 00:30:19,250

You can have your life back now. But life had already been on hold for far too long.

279
00:30:20,030 --> 00:30:23,930
I won my appeal and was able to return to university in September.

280
00:30:24,680 --> 00:30:30,860
In November, the treatment for the TB in my right lung ended for good and to focus my recovery from surgery.

281
00:30:32,030 --> 00:30:43,969
I signed up to run A5K race. Four months later, I didn't get medical clearance for that either, but I managed to raise ¬£2,000 for TB alert,

282
00:30:43,970 --> 00:30:49,310
who supported me partway through my treatment journey and gave me a reason not to give up.

283
00:30:51,410 --> 00:30:56,540
So over the course of the academic year, my mental health began to seriously decline.

284
00:30:57,560 --> 00:31:03,140
I was having panic attacks, stress induced meltdowns, and experiencing low moods.

285
00:31:04,010 --> 00:31:10,880
I just stopped functioning altogether. Everything that happened to me over the last few years was starting to catch up with me.

286
00:31:11,780 --> 00:31:15,320
My credit cards and overdraft debts had spiralled out of control,

287
00:31:15,770 --> 00:31:20,810
and by the end of the summer term, I owed money to my university for accommodation rent.

288
00:31:21,350 --> 00:31:24,620
My registration for the following academic year was now at serious risk.

289
00:31:25,820 --> 00:31:32,420
There were so many people at my university, from the money advisor to the student at the students union,

290
00:31:32,420 --> 00:31:40,100

to my student advisor and the head of finance and many others who really came through for me and went above and beyond their jobs.

291
00:31:40,790 --> 00:31:44,750
They became my allies and I will never forget the support they gave to me.

292
00:31:45,990 --> 00:31:49,770
I always got the impression that my university wanted me to succeed.

293
00:31:50,280 --> 00:31:54,810
To cut another long story short, I did finish my degree, even though it took about six years.

294
00:31:56,400 --> 00:32:03,060
Eventually, I was diagnosed with depression and anxiety and started having therapy through my university.

295
00:32:04,020 --> 00:32:08,759
My GP said it was quite common for patients to experience both after having, and this is

296
00:32:08,760 --> 00:32:15,300
his words, come close to death. But I had no idea what the impact that TB would have on my mental health.

297
00:32:16,740 --> 00:32:20,040
Three years later, I was finally discharged from the clinic.

298
00:32:21,030 --> 00:32:29,130
There are a few things I want to highlight here that the TB treatment journey does not end when the patient takes their last pill.

299
00:32:29,700 --> 00:32:32,130
In my case, I still have ongoing breathlessness.

300
00:32:32,640 --> 00:32:39,870
I walk much more slowly than most people, and I have to pace myself and take regular breaks when doing simple household activities.

301
00:32:40,530 --> 00:32:45,780
It takes me weeks to recover from a chest infection and I have a rescue pack of antibiotics on standby.

302
00:32:46,410 --> 00:32:56,070

My right lung is now scarred. I have a permanent chronic cough and a croaky voice and to clear the excess mucus in my right lung.

303
00:32:56,460 --> 00:33:00,780
I do airway clearance exercises twice a day. This is my new normal.

304
00:33:03,280 --> 00:33:10,270
I often wonder how different my story would have been if there had been an effective TB vaccine available.

305
00:33:11,200 --> 00:33:21,010
A vaccine that could have prevented so much suffering and hardship for myself and for millions of people around the world.

306
00:33:21,790 --> 00:33:26,200
We all saw during the Covid pandemic that when there is a will, there is a way.

307
00:33:26,530 --> 00:33:32,379
I've had nine Covid 19 vaccines, but only one TB vaccine, the BCG,

308
00:33:32,380 --> 00:33:36,910
which isn't effective in teenagers and adults against the most common forms of the disease.

309
00:33:37,360 --> 00:33:43,420
I'm delighted by the speed of vaccine development and rollout for Covid 19,

310
00:33:43,720 --> 00:33:52,240
but I can't deny the anger and resentment I feel about TB and affected communities being left behind for so long.

311
00:33:52,600 --> 00:34:03,460
We deserve the same priority and investment. There is no doubt in my mind that if the burden of TB disease was spread more equally around the world,

312
00:34:04,000 --> 00:34:08,650
rather than being concentrated in low income countries, it would be a very different story.

313
00:34:09,040 --> 00:34:12,400
As far as funding is concerned. That speaks volumes.

314
00:34:14,090 --> 00:34:17,180

Ten years ago I was diagnosed in.

315
00:34:21,860 --> 00:34:27,440
Ten years ago, I was diagnosed with an inflammatory condition that affects both my joints and skin.

316
00:34:29,210 --> 00:34:35,870
My history of TB and long surgery meant that they first had to rule out TB in my bones as a differential diagnosis,

317
00:34:36,380 --> 00:34:41,900
and my reduced lung capacity meant that it was too risky to have the first line treatment choice.

318
00:34:42,380 --> 00:34:50,630
I am now severely immunosuppressed, which carries a serious risk of infection, including TB, and I'm back into the care of the chest clinic.

319
00:34:50,990 --> 00:34:55,550
Although with a different hospital trust. I'm monitored very carefully,

320
00:34:55,880 --> 00:35:00,530
by the head of the TB speciality and I am extremely grateful to be so well looked after.

321
00:35:01,370 --> 00:35:05,750
This means that the risk of catching TB again is never off the table.

322
00:35:07,670 --> 00:35:12,350
I experienced so much uncertainty and fear throughout this entire journey.

323
00:35:13,070 --> 00:35:19,820
To say that TB turned my life upside down is a huge understatement, but in some ways it was also a turning point for me.

324
00:35:20,420 --> 00:35:29,810
I've always said that TB politicised me and helped to spark an interest in TB advocacy and social justice, which has led my entire career so far.

325
00:35:30,530 --> 00:35:36,830
I am a member and chair of the TB action Group, the UK's only advocacy network for people affected by TB.

326
00:35:37,370 --> 00:35:44,870

I went from being adamant that I wanted to put this whole awful experience behind me forever and never think about TB again.

327
00:35:45,230 --> 00:35:48,800
But obviously that didn't happen because I wouldn't be here talking to you now.

328
00:35:49,970 --> 00:35:56,000
I just want to end by paying tribute to every TB survivor I've had the privilege to meet,

329
00:35:56,390 --> 00:36:03,980
either in person or online, from all over the UK, and even as far away as the US, India and South Africa.

330
00:36:04,670 --> 00:36:05,690
They know who they are.

331
00:36:06,590 --> 00:36:16,640
Their courage, friendship, solidarity and extraordinary activism inspire and motivate me to do better and to keep believing that progress is possible.

332
00:36:17,180 --> 00:36:21,230
Every single one of us has truly earned the label of TB survivor.

333
00:36:21,830 --> 00:36:38,650
Thank you for listening. Amy, that was absolutely extraordinary.

334
00:36:38,680 --> 00:36:45,330
Thank you for sharing such a very personal and incredibly moving experience with us all.

335
00:36:45,340 --> 00:36:48,880
That's really difficult to follow. Thank you very much.

336
00:36:49,660 --> 00:36:51,250
We now have our third speaker.

337
00:36:51,280 --> 00:36:58,299
There will be an opportunity to ask questions at the end, and all three of us will be outside milling around with the exhibition and drinks.

338
00:36:58,300 --> 00:37:04,000
But I'm going to hand over now to Philip, who's going to give us our third talk on TB diagnostics.

339
00:37:05,440 --> 00:37:09,580
Thank you, Helen.

340
00:37:09,760 --> 00:37:15,550
And thank you, Amy. Um. That's.

341
00:37:22,140 --> 00:37:29,760
So I'm afraid I'm a pacer. So I've got a microphone. So slight change of gear now.

342
00:37:30,330 --> 00:37:42,240
I'm going to talk about fairly recent advancements in diagnostics that hopefully could have helped Amy at least just a bit of that journey.

343
00:37:43,170 --> 00:37:48,959
Um, so as Helen said at the start, I work in the MMM unit,

344
00:37:48,960 --> 00:37:54,750
which is actually set in the top floor of the John Radcliffe Hospital, there's a few people here in the audience.

345
00:37:55,530 --> 00:38:04,020
And one of the things we do, there's quite a few things we do, is translating genetics into, um, clinical microbiology.

346
00:38:04,350 --> 00:38:07,320
And I'm going to talk about, uh, TB.

347
00:38:08,520 --> 00:38:15,270
So because we haven't had enough about TB, just I've come up with some minis I'm buying, I've found these in the literature.

348
00:38:15,270 --> 00:38:24,210
This and nice little snapshot. So just in case you didn't know, TB has killed more people than any other infectious disease ever.

349
00:38:25,080 --> 00:38:31,500
In fact, um, from genetics, we now know that TB is being with humans for tens of thousands of years.

350
00:38:32,340 --> 00:38:39,270
Um, and left Africa when the first humans migrated out of Africa about 70,000 years ago and moved with them around the world.

351

00:38:39,930 --> 00:38:46,920
And actually post industrialisation in Europe, it's estimated that about 20% of all deaths were caused by tuberculosis,

352
00:38:48,150 --> 00:38:52,590
and it's also been estimated in the last 200 years, about a billion people have died of TB.

353
00:38:52,800 --> 00:38:56,700
But we've sort of forgotten about it. Reminds me a bit of Covid.

354
00:38:57,330 --> 00:39:00,659
Um, you know, it's it's it's strange.

355
00:39:00,660 --> 00:39:04,230
It's it's been such a influence on human history.

356
00:39:05,700 --> 00:39:10,440
So we're here because Franz Kafka died in 1924 of laryngeal TB.

357
00:39:10,770 --> 00:39:16,349
Um, if you go to the exhibition, there's a bit more information. But he basically coughed up blood in 1917.

358
00:39:16,350 --> 00:39:21,420
So 77 years before he died, he was in and out of various sanatoriums.

359
00:39:21,930 --> 00:39:30,600
Um, the last one was near Vienna. Now, interestingly, the first, um, suggestion of, uh, sanatarium was by this guy,

360
00:39:30,600 --> 00:39:35,970
George Boddington in Sutton Coldfield in Birmingham, which is again curious because that's where I grew up.

361
00:39:36,120 --> 00:39:40,319
Anyway, that's another story, but TB is full of all these little peculiarities.

362
00:39:40,320 --> 00:39:46,580
And another one I like is the first randomised clinical trial was for TB.

363
00:39:46,590 --> 00:39:52,380
It was streptomycin in 1948. And what they found was that it was very successful.

364
00:39:52,560 --> 00:39:57,120
But quite quickly the, the the bacterium evolved the resistance.

365
00:39:57,510 --> 00:40:01,499
And to this day, as you've heard from Amy, we treat people, well

366
00:40:01,500 --> 00:40:05,250
I don't, but clinicians treat people with multiple antibiotics.

367
00:40:07,250 --> 00:40:13,550
So the current treatment, if you have regular susceptible TB is for drugs that you've probably never heard of,

368
00:40:14,210 --> 00:40:20,270
because they're not the sorts of things you get given when you normally go to the GP because they're pretty specific to TB

369
00:40:20,270 --> 00:40:26,930
usually, um, for six months, which is quite a long time, but it's necessary because of the disease.

370
00:40:28,520 --> 00:40:37,040
Now, resistance is obviously complicated because you're being treated with multiple drugs and there are various definitions, and it's fairly low

371
00:40:37,040 --> 00:40:42,920
globally, it's about 3% of new infections according to the W.H.O., are multi-drug resistant.

372
00:40:43,220 --> 00:40:48,200
But if you've been previously diagnosed or treated for TB, that rises to almost 20%.

373
00:40:48,980 --> 00:40:53,120
And obviously, you know, these proportions are going to rise as we keep using antibiotics.

374
00:40:53,780 --> 00:40:57,770
Um, and then this wasn't a problem that obviously Kafka had to face.

375
00:41:00,770 --> 00:41:04,220
The treating resistant TB is inevitably a lot more complicated.

376
00:41:04,760 --> 00:41:10,790

Um, there have been some new drugs come on in the last couple of years, which has been very helpful.

377
00:41:11,180 --> 00:41:17,960
And also then there have been some new regimens developed and approved and endorsed by the W.H.O.,

378
00:41:18,380 --> 00:41:22,040
um, which is talked about on the right. That's from two years ago.

379
00:41:22,280 --> 00:41:28,580
So there's a new regimen for people who have multidrug resistant TB that's only six months long,

380
00:41:28,970 --> 00:41:33,140
which is a big improvement over the previous, possibly 18 months of treatment.

381
00:41:35,600 --> 00:41:46,850
So, as Amy said, often, uh, if you are suspected of having TB, you will give a sputum sample and that will be sent off for testing.

382
00:41:47,990 --> 00:41:53,540
And the two things are really looking for, uh, are there any mycobacterium tuberculosis in that sample?

383
00:41:54,260 --> 00:41:58,010
And if there are, what antibiotics could you be treated with?

384
00:42:00,040 --> 00:42:09,160
So the traditional way of doing this would be to culture the sample, say to grow it in some nutrients that it likes and the other bacteria don't.

385
00:42:10,600 --> 00:42:15,830
Um, and then I've got ahead of myself by one slide.

386
00:42:15,850 --> 00:42:22,440
Okay. So yeah. So throughout this I want to use a simile of, of imaging.

387
00:42:22,450 --> 00:42:27,969
So when we're looking at a sample in a clinical microbiology lab,

388
00:42:27,970 --> 00:42:32,650
what we're trying to see is which basically trying to capture the picture of what's in there,

389
00:42:32,740 --> 00:42:35,200
you know, uh, is there some TB,

390
00:42:35,200 --> 00:42:41,140
are there some other bacteria or other things that might have been in your upper respiratory tract when you gave the sample?

391
00:42:41,440 --> 00:42:45,550
You know, there's going to be a lot of human cells in there from you, you know, what's in there.

392
00:42:46,030 --> 00:42:52,870
And just like there are different ways of, you know, drawing a picture or capturing an image, there's different ways of looking inside these samples.

393
00:42:55,440 --> 00:42:57,630
So the the traditional way is to grow it.

394
00:42:57,720 --> 00:43:03,299
As I started to say, the problem with that, or the several problems with it, is it just takes a very long time.

395
00:43:03,300 --> 00:43:14,040
So it can take up to some 6 to 8 weeks to get a result back from the lab, because TB just grows so slowly and there's been some nice advances.

396
00:43:14,400 --> 00:43:21,570
Um, these magic tubes, um, because they glow when there's, when there's mycobacterium in there,

397
00:43:21,570 --> 00:43:23,549
So it's made it much easier.

398
00:43:23,550 --> 00:43:30,000
But fundamentally, you know, being told I'll give you a call in two months when the results come back, it's it's not good for anyone.

399
00:43:32,610 --> 00:43:39,670
So in an imaging simile this is a bit like, well, I have to paint the picture because I need you.

400
00:43:39,690 --> 00:43:46,889
It's very skilled. Um, I need some equipment, I need some reagents, I need some experience.

401
00:43:46,890 --> 00:43:55,230
It's a difficult job to to carry out these types of, uh, tests, and it fundamentally, it's going to take you quite a long time.

402
00:44:00,520 --> 00:44:07,420
So then genetics can play a role, and I'm skipping over lots of other ways of diagnosing here that I just don't have time to go into.

403
00:44:07,750 --> 00:44:15,310
Um, and focusing on, um, whole genome sequencing here, you still have to grow it for a bit, but then you can heat kill it.

404
00:44:15,760 --> 00:44:23,500
Take it outside the Cat 3 lab. I should say. You've got to do all this in a BSL 3 lab because TB, it's a very dangerous pathogen.

405
00:44:23,980 --> 00:44:31,209
Then you can put it on a genetic sequencer. That will just give you a whole bunch of fragments of genetic material and say, well,

406
00:44:31,210 --> 00:44:36,010
you work it out I've sort of done the hard bits, which hasn't really, but it gives you this problem.

407
00:44:36,670 --> 00:44:41,590
And then then you need to solve that problem. So that's when you now need a second speciality.

408
00:44:41,590 --> 00:44:44,280
Who hasn't been on the scene until now, which is a bioinformatician

409
00:44:44,290 --> 00:44:51,459
so someone who can handle genetic information and process it and they need to write, uh, what we usually call a pipeline.

410
00:44:51,460 --> 00:44:57,610
So a series of pieces of software that process those reads and hopefully give you the answers you're looking for.

411
00:44:58,510 --> 00:45:04,840
And that's often done on some local compute that you've squirrelled away somewhere in your hospital or public health body.

412
00:45:07,170 --> 00:45:13,050
So this is it's difficult, but it's a big improvement because you can do it in about a week.

413
00:45:13,710 --> 00:45:18,000
So that's a big acceleration from say, 6 to 8 weeks to a week.

414
00:45:18,420 --> 00:45:22,260
So that's that in itself is a is a huge advantage.

415
00:45:22,920 --> 00:45:26,220
Um, but as I'll come back to it's it's quite tough to do.

416
00:45:26,850 --> 00:45:30,620
So in my simile this is a little bit like, I think the invention of photography.

417
00:45:30,630 --> 00:45:34,920
So wow. You know we've now got large plate cameras. They're expensive.

418
00:45:35,700 --> 00:45:40,229
But you can take an image pretty quickly. But then you also need a thing called a dark room.

419
00:45:40,230 --> 00:45:43,770
And you need to get you need to go and buy a developer. You need to keep buying all these reagents.

420
00:45:43,770 --> 00:45:47,730
And you need to learn the skill of how to develop, um, photographs.

421
00:45:48,930 --> 00:45:52,170
So it's possible, but it's the kind of the preserve of the few.

422
00:45:52,830 --> 00:46:00,930
So it's done in high income countries, in, um, public health institutes, large tertiary research hospitals, that sort of thing.

423
00:46:02,430 --> 00:46:09,810
The good news is, England was the first country to implement this at the national public health level back in about 2018,

424
00:46:10,230 --> 00:46:15,500
and that was research that was done in the unit where I am now that got translated out into PHE,

425
00:46:15,570 --> 00:46:19,080
as it was then and the other home nations have followed suit.

426
00:46:19,830 --> 00:46:24,900
So that's really good news. Anyone who had a has a suspected mycobacterial infection.

427
00:46:25,290 --> 00:46:28,740
That sample have been sequenced since about that date.

428
00:46:29,580 --> 00:46:36,240
That won't have sped up the GP necessarily, but it will have sped up the process after the sample was sent off.

429
00:46:38,530 --> 00:46:44,679
I just want to spend a very quickly talk about why the genetics is challenging, because these sequences do seem like magic.

430
00:46:44,680 --> 00:46:50,620
But all they, as I said, all they do is they just give you bits of genetic material and say, right, you sort that out.

431
00:46:51,880 --> 00:46:56,530
Um, and it's a bit like doing a jigsaw puzzle with a few rather important differences.

432
00:46:56,540 --> 00:47:00,790
One is you might have up to 10 million pieces, which is going to make it a bit harder.

433
00:47:01,570 --> 00:47:06,430
The pieces will also overlap with each other. And you don't know how because the fragments are quite random.

434
00:47:07,160 --> 00:47:11,200
The some of them are going to have errors because the machines aren't perfect and you don't know which ones.

435
00:47:11,740 --> 00:47:21,470
Which is so hard. And because you've got, you know, you've almost certainly got multiple bacterial, um, pieces of DNA in there.

436
00:47:21,490 --> 00:47:24,219
It's a bit like having, you know, doing a jigsaw,

437
00:47:24,220 --> 00:47:30,730

or rather taking several jigsaws and mixing them up and then trying to just do one of them and not put in the wrong piece and that sort of thing.

438
00:47:31,390 --> 00:47:39,610
So it's it's very difficult. And bioinformatics is a, is a difficult, um, subject, so why bother.

439
00:47:39,640 --> 00:47:46,240
We've already said one of the key things is speed is we can do this much more quickly, which for TB is really important.

440
00:47:46,810 --> 00:47:50,230
Two other things. Um, accuracy.

441
00:47:50,260 --> 00:47:57,819
This is it's arguably more accurate, but that's difficult to prove because you're comparing it to something that is hard,

442
00:47:57,820 --> 00:48:04,030
which is culture and difficult because it's TB. And then the second one is epidemiology.

443
00:48:04,030 --> 00:48:08,710
And that's something you basically get for free with genetics because you've got the entire genome.

444
00:48:09,070 --> 00:48:14,560
So what do I mean by that. Well in Covid we got quite used to this idea of we can infer, uh,

445
00:48:15,550 --> 00:48:23,920
if two samples taken from two people are part of the same outbreak or cluster because the genomes of their pathogen are very similar.

446
00:48:24,460 --> 00:48:35,500
And you can do exactly the same thing with TB. And this was an example back from 2018, um, where they were able to show how, uh,

447
00:48:35,500 --> 00:48:42,670
patients with multi-drug resistant TB moved through Europe and caused these, um, separate outbreaks in different countries.

448
00:48:42,670 --> 00:48:48,370
And then, of course, you can do something about it and you can find these people and treat them and stop those outbreaks.

449
00:48:49,630 --> 00:48:57,459
Just to point out, the threshold they were using was only five, uh, snips are basically five letter changes in the whole genome.

450
00:48:57,460 --> 00:49:00,760
In the genome of TB is about 4.4 million letters long.

451
00:49:00,760 --> 00:49:05,379
So you've actually in doing that jigsaw puzzle, you've got to get it pretty accurate.

452
00:49:05,380 --> 00:49:10,990
Otherwise you can't do this sort of thing as well. So why is it so difficult?

453
00:49:11,000 --> 00:49:17,170
There's lots of reasons and I'm not going to talk about all of them. Um, I'm going to just talk about two of them.

454
00:49:17,170 --> 00:49:20,440
This is one, which is that actually, even if,

455
00:49:20,920 --> 00:49:27,430
even if you can do all that perfectly and you can work out what the genome of the pathogen that's infecting someone is,

456
00:49:27,430 --> 00:49:30,790
it's still quite hard to work out what antibiotics you should give them.

457
00:49:31,570 --> 00:49:35,860
So some work, um, led from our unit by Derek Crook.

458
00:49:35,860 --> 00:49:40,090
This ran for about six years. This was a major Wellcome project.

459
00:49:40,960 --> 00:49:50,470
Uh, they collected about 20,000 clinical samples of TB worldwide from, uh, memory, 11 different countries with 14 different laboratories.

460
00:49:51,250 --> 00:49:55,030
They were all sequenced. They all had a panel of antibiotics tested.

461
00:49:55,030 --> 00:49:58,210
And as a result, we did some really nice science.

462
00:49:59,560 --> 00:50:02,260
Um, it was picked up in the press a little as well.

463
00:50:02,590 --> 00:50:11,499
But actually the thing that I'm most proud of is that data set, along with some other historical samples and some extra samples we collected actually,

464
00:50:11,500 --> 00:50:18,700
immediately before the pandemic, that whole data set, we kind of did all the data cleaning, and it was handed over to the W.H.O.

465
00:50:19,240 --> 00:50:28,630
And that that indirectly led to them publishing their first catalogue of genetic mutations associated with resistance in TB.

466
00:50:29,290 --> 00:50:38,439
So that was back in June 2021. Uh, and in November last year, um, they've updated it with a slightly improved version.

467
00:50:38,440 --> 00:50:42,280
So that's really good. And that helps move us along this pathway.

468
00:50:43,570 --> 00:50:51,820
So the second thing I'm going to talk about, um, about why it's difficult is there's no standard way of determining the TB genome.

469
00:50:52,060 --> 00:50:57,910
It's basically informatics is hard and it's very difficult for labs to set up.

470
00:50:58,720 --> 00:51:07,660
So the story here starts in May 2021, when we started working with Oracle on a cloud based platform for Covid processing.

471
00:51:09,070 --> 00:51:12,850
And that has led to this thing we call GPAS, which I'm going to call second generation,

472
00:51:13,240 --> 00:51:21,400
where now the biomedical scientists can do the sequencing, but now they just basically drag and drop the file up into the cloud.

473
00:51:21,760 --> 00:51:26,980
It will process the genetics for them. And the, uh, report can come back in less than an hour.

474
00:51:28,240 --> 00:51:37,900
It's not speeding things up a much, just a day or two perhaps, but it makes it much, much simpler and straightforward to do this kind of work.

475
00:51:40,630 --> 00:51:44,950
So I'm just going to quickly go through some screenshots because I wasn't feeling brave enough to do this live.

476
00:51:45,760 --> 00:51:49,120
Um, this was actually some batches I was uploading last night.

477
00:51:49,330 --> 00:51:51,820
Um, I wasn't up at this time. The computer is doing me.

478
00:51:52,240 --> 00:51:59,200
Um, so if we just zoom in, they're all batches of 50 TBs and we go and look at this one because it kind of looks interesting.

479
00:52:00,340 --> 00:52:03,670
Um, this is all in the browser. So a lot of work is gone into this.

480
00:52:04,510 --> 00:52:11,200
Um, what we see is a lineage three TB. It looks pretty good from a kind of quality point of view I don't want to bore you,

481
00:52:11,440 --> 00:52:15,999
but it's definitely MDR, so it's resistant to three of the four first line drugs.

482
00:52:16,000 --> 00:52:18,700
So you do not want to be giving those drugs to that patient.

483
00:52:19,480 --> 00:52:26,500
Um, but healthily, it's resistant to uh, basically the second line drugs, the flow clean lines and so on.

484
00:52:27,430 --> 00:52:34,360
So the hope is that this information would help the clinician choose the appropriate treatment for that patient.

485
00:52:34,750 --> 00:52:41,500
And then you can see down the bottom, um, we get uh, some of the it's part of a cluster as well.

486

00:52:42,880 --> 00:52:51,880
So this kind of I think in my simile brings us up to about 1900, um, which is when Kodak released the Brownie.

487
00:52:51,880 --> 00:52:55,990
And the thing about the Brownie was the film was put inside a cartridge.

488
00:52:56,170 --> 00:53:02,200
And what that meant was you could take photos until your cartridge was all used up,

489
00:53:02,200 --> 00:53:07,630
but then you could send the film off to a lab to be processed, and then you got the photos back.

490
00:53:08,650 --> 00:53:13,900
And so you didn't need a darkroom anymore, and the cameras could be quite made, quite small and cheap.

491
00:53:13,900 --> 00:53:17,470
And I read, I didn't realise that the Brownie started off as a children's toy.

492
00:53:17,490 --> 00:53:26,290
I don't think genetics has. But anyway, um, and so it led to this kind of democratisation of photography.

493
00:53:27,700 --> 00:53:39,870
Um. So if we think back 100 years, um, and go and look in exhibition, there's some quite gruesome artefacts, um, showing, sort of illustrating, uh,

494
00:53:39,870 --> 00:53:43,620
Kafka's journey with TB, you know, 100 years later,

495
00:53:43,620 --> 00:53:50,250
I think we're hopefully on the verge of really beginning to use genetics to help us treat this disease better.

496
00:53:51,660 --> 00:53:56,300
Um, it's interesting thinking forward a 100 years. Um, um, sorry.

497
00:53:56,310 --> 00:54:01,950
Coming up, TB's probably still going to be here I'd expect, even with vaccines and everything.

498

00:54:01,950 --> 00:54:06,059
You know, latently it's in a quarter, a third of the world's lungs.

499
00:54:06,060 --> 00:54:10,290
So it's gonna you know, I don't think eradication is really on the cards.

500
00:54:10,830 --> 00:54:14,100
Will how we we've made it through the whole pandemic.

501
00:54:14,100 --> 00:54:18,140
Will we still be giving antibiotics? But we have to individually diagnose everyone.

502
00:54:18,150 --> 00:54:28,860
I really don't know. So it's just we're thinking on that. Um, a lot of people involved, um, in the past and a lot of this work.

503
00:54:28,860 --> 00:54:33,390
So that's just to show you just how many, I suppose it's all quite small writing.

504
00:54:33,990 --> 00:54:38,490
Um, and lots of, uh, funders and other peoples as well.

505
00:54:38,490 --> 00:54:41,700
So thank you very much.

506
00:54:44,020 --> 00:54:44,290