

***Brucella* Found in Unpasteurized Camel Milk, Israel**

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Jacob Moran-Gilad. He's a professor of clinical microbiology at Ben-Gurion University of Negev in Israel. We'll be discussing an outbreak of human brucellosis associated with unpasteurized, commercially-sold camel milk.

Welcome, Dr. Moran-Gilad.

[Jacob Moran-Gilad] Hello. Thanks for having me.

[Sarah Gregory] What is brucellosis?

[Jacob Moran-Gilad] Brucellosis is a disease caused by a bacterial genus that is called *Brucella*. There are several species that belong to that genus and they are harbored by different animals, and therefore, brucellosis is a zoonotic disease, meaning that humans contract this infection through direct or indirect contact with animals.

[Sarah Gregory] So that's how it's spread, you get it from animals. Do people spread it to other people?

[Jacob Moran-Gilad] Yeah, so brucellosis is mainly contracted from animals. It is quite rarely transmitted between people. So, it's not so much person-to-person transmission, but exposure to different sources. The majority of cases are related to the consumption of milk or dairy products that are consumed raw, so they're unpasteurized. But there are also cases of occupational illness. And also it's worth noting that *Brucella* is a potential bioterrorism agent, so it's also a select agent in the CDC list. So, this is another theoretical way of getting exposed to this bug.

[Sarah Gregory] Oh my, okay.

Is it more common in some populations than others?

[Jacob Moran-Gilad] So as I mentioned, it's a potential occupational hazard. So, people who work with animals—be that animal handlers, farmers, the veterinary doctors, abattoir workers—could be exposed to infected animals or infected animal tissues. And there are, of course, those cases which are foodborne and usually there are specific patient populations who are at greater risk—so those who consume raw dairy products commonly. And this is essentially the case in Israel, it is associated with traditional behavior.

[Sarah Gregory] What animals are most commonly infected with it?

[Jacob Moran-Gilad] There are a variety of animals which could be infected with different species of *Brucella*. So for every species of *Brucella*, there is a natural host reservoir. The most pathogenic species in the genus is *Brucella melitensis*, and *Brucella melitensis* is usually associated with sheep and goats. There is *Brucella abortus* which is also a potential hazard to humans, and that one is associated more with cattle. But actually in the last years we're seeing some shift. So for example, in regions where *Brucella melitensis* is not properly controlled in the veterinary sector, we could also find it among cattle or dairy cows and not only sheep or goats, which are the natural reservoir.

[Sarah Gregory] What are the signs that someone is sick with it?

[Jacob Moran-Gilad] So brucellosis is a very interesting disease, in the sense that it could mimic many other diseases. It is a disease of many faces. Most people have many nonspecific manifestations, like generalized signs and symptoms—fever, myalgia. There is common involvement of the joints and the skeletal system so there could be joint pain, sometimes even joint inflammation. And the disease could manifest after quite a prolonged incubation period and could also have quite an insidious onset. So it's not a hyperacute disease where someone is exposed enough and two days they have this very severe illness, but it usually develops gradually. And occasionally we see patients who have been carrying this syndrome for many weeks (even months) before they seek treatment.

[Sarah Gregory] Seems like so many diseases nowadays are like that, hard to just define and very similar symptoms.

Do animals that are sick with brucellosis show symptoms, and if so, are they the same as people?

[Jacob Moran-Gilad] So animals are commonly asymptomatic, and one of the main manifestations of brucellosis in animals is actually abortion. This is how *Brucella abortus* got its name, because it causes abortions. So if there are sudden cases of abortions in herds, that could be a sign for *Brucella* infection. But not uncommonly we detect the infection just by performing active surveillance. So it's quite difficult to note sometimes.

[Sarah Gregory] So, people have all these nonspecific symptoms like with so many other diseases. Are there specific tests that are used to determine if someone is infected with brucellosis? And if so, are the same tests used on animals?

[Jacob Moran-Gilad] So in order to diagnose brucellosis, first of all one has to suspect it. So definitely if you live in an area where brucellosis is endemic, your index of suspicion will be higher. And if there are any known risk exposures or compatible signs and symptoms, that should also prompt testing. But brucellosis could also be encountered in nonendemic area, for example, by returning travelers. So it should always be in our minds when we manage patients with infectious diseases and potentially zoonotic diseases.

Most of the cases of brucellosis are diagnosed by blood culture, so we obtain a blood sample from the patient like we do for many suspected bacterial diseases. And after several days of incubation, automated blood culture systems could detect the growth of bacteria in blood which could turn out to be *Brucella*. *Brucella* grows a bit slowly as compared to common bacterial infections like *Staph. aureus* or *E. coli*, so it might take a few more days. There is also the possibility of performing serological testing—so to test for antibodies. But as many serological tests, that could be tricky especially in an endemic area. So it might be difficult to differentiate between recent and past exposure to the organism. So these are the main diagnostic strategies and it is sometimes quite difficult to establish the diagnosis, so there could be elusive cases of brucellosis for sure.

[Sarah Gregory] Okay. Is there a treatment for it?

[Jacob Moran-Gilad] Yes, of course. Brucellosis can be treated with antibiotics. Luckily *Brucella* is one organism for which there isn't a big issue with antimicrobial resistance, as opposing to what we face with many other organisms. But on the other hand, the treatment regimens for brucellosis are quite complex in the sense that usually a combination treatment is required (so with several different antimicrobials). And treatment is quite prolonged—so, could be from several weeks to several months—and therefore there is always the risk of patient

adherence that may not be optimal. And occasionally we see cases of brucellosis that relapse after some time, and occasionally this is related to patient adherence. But of course it could also be reinfection. So patients could have a continuous exposure that could result in reinfection.

[Sarah Gregory] And can it be fatal?

[Jacob Moran-Gilad] Quite uncommonly. So the majority of brucellosis patients recover, but if the disease is not properly treated it could become, like, chronic. But it is quite unusual to die of brucellosis. So it has to be either an extremely neglected case or a minority of cases which could have complications as a result of involvement of target organs (for example, the heart). So uncommonly there could be endocarditis infection that involves the heart, the heart valve, and that is of course a life-threatening infection. Uncommonly there could also be involvement of the central nervous system, what we call neurobrucellosis. But again, these are very rare cases, less than 1% of naturally occurring disease.

[Sarah Gregory] What's the best way to prevent transmission of brucellosis from animals to humans?

[Jacob Moran-Gilad] So in order to prevent transmission, we need to act towards both the veterinary sector and also the public health sector. So on the veterinary side, we should have proper regulations, veterinary inspection, and proper animal health. And if we're speaking about farms or herds, then they should be properly treated and tested. And that could, of course, reduce significantly the odds for having animals which are infected by *Brucella* and that will inevitably reduce the chances of having human exposure. And on the other hand, we need to ensure that human exposure is minimized—so if it's occupational, then all the health and safety practices to prevent exposure during work. And of course if we're referring to consumers, it's extremely important that people know that consuming raw dairy products is risky. So there's a lot of...there's a big role for health education in that perspective.

[Sarah Gregory] Even in the United States, people seem to (a certain segment of population) want to drink unpasteurized milk even though scientifically we know that that's not a good idea. Why are people drinking unpasteurized camel milk in Israel?

[Jacob Moran-Gilad] So I guess that it's for the same reason as in other places. Many people believe that unpasteurized milk, either goat milk or camel milk, has unique medicinal properties although this has never been proved in clinical studies. And people consume unpasteurized milk, for example, to treat mouth ulcers. That's a very common indication (if I may call it like that) that I came across. And other people could ascribe different properties for unpasteurized milk, but the truth is that we are not aware of any benefit for consuming such raw products. And of course there is a risk, the risk is not only for acquiring brucellosis but also for many other infectious diseases. So it's generally not a good idea to do that.

[Sarah Gregory] So your study is about a brucellosis outbreak traced to commercially-sold unpasteurized camel milk in Israel, where you are. Why don't you tell us a little bit about how this outbreak began?

[Jacob Moran-Gilad] So in Israel, the majority of brucellosis cases affect the Arab population. And where I work in the southern part of Israel, it is especially the Bedouin Arab population that is affected by the disease. So this population consumes unpasteurized goat milk on a regular basis because of tradition, and therefore about 99% of the cases that we see nationally are cases that affect that population. And this outbreak that was eventually traced to camel milk was

actually quite readily detected because we were seeing an accumulation of brucellosis cases all across the country, especially in the center and the north, where as I said the endemic focus is actually in the south. And the vast majority of those patients were not Bedouin Arab, so they were part of the Jewish community, and this prompted the question of whether there is something unusual going on. And of course, the Ministry of Health performed an outbreak investigation and after a short while it became evident that almost all of those cases reported the consumption of camel milk. Some of them purchased that camel milk from a specific vendor or some of them purchased it online, but eventually all the camel milk appeared to originate from a single manufacturer. So that was quite suspicious as the potential source of the outbreak.

[Sarah Gregory] How many people were infected?

[Jacob Moran-Gilad] So, we know about 20 cases—so there were 20 cases which were diagnosed. But potentially there could have been several additional cases which did not come to our attention. Some of those cases actually were members of the same family, like siblings or spouses.

[Sarah Gregory] You used whole-genome sequencing to link unpasteurized commercially bottled camel milk with this outbreak, as we discussed. How was this whole-genome sequencing used?

[Jacob Moran-Gilad] So, whole-genome sequencing is now the new gold standard for investigating outbreaks of bacterial infection, including foodborne infections. It's also used now widely in the United States by CDC and other agencies charged with food safety. But on a global scale, there is less experience with using whole-genome sequencing for brucellosis. So this is one of the first instances where whole-genome sequencing was successfully used.

We applied whole-genome sequencing on all the bacterial isolates that we had from the patients, and also we managed to grow a few colonies of *Brucella melitensis* from leftover milk that was confiscated during the activity of the Ministry of Agriculture, which is also regulating milk production. So by using whole-genome sequencing we could compare the genetic origin of the different isolates, both the animal- and human-derived isolates. And interestingly, the standard molecular typing technique that is called MLST (multilocus sequence typing) —which until recently was considered the gold standard—that one was not discriminatory. So all the *Brucella melitensis* isolates that we encountered in Israel, they all belong to the same sequence type. So MLST does not help us so much to delineate any transmission change. And by using whole-genome sequencing, we were able to dissect that set of isolates and to understand better which cases were infected by which strain.

[Sarah Gregory] Are there any additional advantages to using whole-genome sequencing compared with other methods?

[Jacob Moran-Gilad] So with whole-genome sequencing, because we're generating the entire sequence of the genome in just one go, we are able not only to perform a phylogenetic analysis in order to rule in or rule out the link between different isolates but we can also use it as an alternate tool to characterize the genome. So if we have a particular interest in looking at genes that confer resistance to treatment or virulence genes (so genes that are associated with disease severity), so all of those could be interrogated by a single test as opposing to performing many different tests as we used to do before whole-genome sequencing became readily available. So definitely it has many advantages.

[Sarah Gregory] What were your findings from your study?

[Jacob Moran-Gilad] So basically we were able to show that the majority of brucellosis cases that we identified as potentially linked to camel milk consumption clustered together, which means that they all had an identical source, and those isolates also clustered tightly with the isolates that we recovered from milk (so from the camel milk that was confiscated). And that is the forensic-level evidence that links the disease cases to that exposure. So it's not only circumstantial evidence, but it's really establishing causality.

Interestingly there were a few cases that did not cluster with that main cluster of isolates, which actually suggests that there could have been more than one clone of *Brucella melitensis* implicated in that outbreak. That actually makes sense because when we performed the investigation, we learned that the camel milk originated from a camel farm which had several dozens of animals. And we were not able to sample all those animals, so potentially there could be more than one *Brucella* strain that contaminated the milk. And on the other hand, there were a few unrelated brucellosis cases.

So cases that we analyzed thinking that they're completely unrelated to the outbreak, we used them as what we define as outliers and some of those actually turned out to be linked to the outbreak. And when we inspected those cases, we were actually seeing an unrecognized chain of transmission from the Negev region (so the southern part of Israel), and so that showed actually the origin of the *Brucella* strain that eventually caused the outbreak. So to summarize that, we were able to prove our suspicion but we also had several surprises which made us understand better this incident.

[Sarah Gregory] Apparently unpasteurized camel milk is becoming popular internationally. Will this make it harder to track outbreaks?

[Jacob Moran-Gilad] I think the answer is very much related to what regulations are in place in different countries. And if we refer to what we increasingly see in many countries (like small agriculture), so this is very difficult to track and very difficult to regulate. But of course, commercial production of camel milk is something that could be properly regulated. So I think it very much depends on the regulatory landscape in different countries.

[Sarah Gregory] In what ways do you hope your research impacts public health going forward?

[Jacob Moran-Gilad] I think first of all, recognizing that camel milk is a potential source for infection (especially brucellosis) and that consuming unregulated, not only milk, but natural products in general could further public health risk. So I think this is common knowledge with respect to many organisms, like *Salmonella* and *E. coli* and *Campylobacter*. And I think what we show here is that camel milk could also be an important vehicle for infection, especially brucellosis. So I think raising awareness to that should have a public health impact. And of course, the success of using whole-genome sequencing for investigating this outbreak of brucellosis should also encourage other people to use this technique for future outbreaks.

[Sarah Gregory] So using your research, what regulations need to be in place to prevent an outbreak like this (or any outbreaks)?

[Jacob Moran-Gilad] Yes. So on one hand, we need on the veterinary side to have proper practices for animal registration and inspection, licensure, having the right permits, periodic testing, and so forth. And on the other hand, we need to have heightened public awareness—so to try and reduce the consumption of raw products. And of course there is also the need for enforcement. In the outbreak that we investigated, the manufacturer of camel milk broke the law.

I mean, of course the milk industry in Israel is tightly regulated as it is in most countries, and this specific manufacturer did not follow the regulations and of course it was also shut down when the outbreak was evident so to prevent further infections. But that also proves the importance of having enforcement and not only just regulations.

[Sarah Gregory] Tell us about your job, where you work, and how you became interested in public health.

[Jacob Moran-Gilad] So I'm a medical doctor, I specialized in clinical microbiology and in public health and I've been working in this field for quite some time. My main interest is in the development and application of advanced technologies for diagnostics, so I'm in particular interested in the genomic-based diagnostics. And I'm especially keen about the public health translation of those techniques, so how we can use genomics in order to inform public health investigations and policymaking. Currently, I hold a joint position that is academic and clinical. So I'm a primary investigator of a research group that is mainly tasked with working on microbial genomics, and I'm also the director of a very busy clinical microbe lab and also an advisor for government on different public health microbiology aspects, such as being a member of our national outbreak control team, which is of course very active these days due to the COVID-19 response.

[Sarah Gregory] You are obviously extremely busy. If you have any free time, what summer activities are you looking forward to? I understand Israel is a very-well-vaccinated-against-COVID country, right?

[Jacob Moran-Gilad] Yes, that's correct. We have a very high vaccine coverage at the moment, but I think we need to still be a little bit careful. We have this Delta variant which is now becoming very common and also questioning whether the effectiveness of vaccination could be slightly reduced, so we are definitely monitoring the situation. So I think this summer is still going to be tricky, but I hope that soon enough we will be able to engage in leisure activity. But my next trip will be for ECCMID (the European Congress for Clinical Microbiology and Infectious Diseases) which is taking place this weekend, mainly online, and we hope that we will be able to engage many attendees from Europe and also overseas.

[Sarah Gregory] The International Conference on Emerging Infectious Diseases is going to be held again in March in Atlanta, as it always is. Are you hoping to be able to come to that?

[Jacob Moran-Gilad] I do hope that by March, we will be able to travel freely and attend in-person conferences. That would be great.

[Sarah Gregory] I will have a booth. I hope you stop by and visit us at the *Emerging Infectious Diseases* booth.

Well, thank you for taking the time to talk with me today. You're clearly a very busy man and I really appreciate you doing this.

[Jacob Moran-Gilad] Thank you very much.

[Sarah Gregory] And thanks for joining me out there. You can listen to the June 2021 article, *Brucellosis Outbreak Traced to Commercially Sold Camel Milk through Whole-Genome Sequencing, Israel*, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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