

One Health Genomic Analysis of Extended-Spectrum β -Lactamase–Producing *Salmonella enterica*, Canada, 2012–2016

[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. Amrita Bharat, the Head of Mycology and Molecular Enteric Antimicrobial Resistance at the National Microbiology Laboratory in Canada. We'll be discussing a genomic analysis of extended-spectrum beta-lactamase–producing *Salmonella enterica*.

Welcome, Dr. Bharat.

[Amrita Bharat] Thank you. Thanks for having me.

[Sarah Gregory] The title of your article is One Health Genomic Analysis of Extended-Spectrum Beta-Lactamase–Producing *Salmonella enterica*, Canada, 2012–2016. Let's dissect that to the start. What is One Health?

[Amrita Bharat] So One Health is a framework that we use for doing research studies or for implementing programs, and it's a framework where we recognize that the health of people is often very closely connected to the health of animals and the environments that both of us live in. So as an example, if we were applying the One Health framework to studying infectious diseases, we would often be looking for an animal source or an environmental source of a germ that's causing illness in people.

[Sarah Gregory] And what is involved in a One Health genomic analysis, generally speaking?

[Amrita Bharat] For the genomic analysis part, we are using a method called whole-genome sequencing that gives us a sort of DNA fingerprint for a biological sample. And it's a very high-resolution fingerprint. So in a One Health genomic analysis, we're comparing these DNA fingerprints across different sources (for example, animal sources and people) and we're looking for similarities across the sources. And if we find these similarities, this implies that there might be potential transmission of that microbe (for example, from animals to people).

[Sarah Gregory] And that leads us to extended-spectrum beta-lactamases. What are they?

[Amrita Bharat] Extended-spectrum beta-lactamases (or we call them ESBLs for short), it's a group of enzymes that can break down cephalosporin and hemoglobins. This is an important class of antimicrobials. And if a bacteria has ESBL enzymes, then we say it's resistant to cephalosporin, which would mean that that drug would no longer be effective for treatment.

[Sarah Gregory] And how does *Salmonella enterica* produce these ESBLs?

[Amrita Bharat] One of the most common ways that bacteria acquire antimicrobial resistance is by picking up circular pieces of DNA from the environment (they often get these from other bacteria), and these circular pieces of DNA are called plasmids. And so, if that plasmid has a gene for an ESBL, then it would make the ESBL enzyme and that's how they produce it. So there are different types of ESBL enzymes, and the most common ones are called CTX or SHV and we have variants of these.

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[Sarah Gregory] Are there different kinds of *Salmonella*? Your article talks about nontyphoidal *Salmonella*.

[Amrita Bharat] Yes, there's lots of kinds. So there's about 2,500 different kinds of serotypes of *Salmonella*. But of these 2,500, only about 100 serotypes commonly cause illness in people. We divide these into typhoidal and nontyphoidal *Salmonella*. The typhoidal serotype tends to cause more serious illnesses like typhoid fever (hence the name) and they are only found in people. The nontyphoidal *Salmonella* are all the other kinds and they are found in both people and animals.

[Sarah Gregory] How common is nontyphoidal *Salmonella* globally?

[Amrita Bharat] It's estimated that there's about 150 million cases of *Salmonella* infections with nontyphoidal *Salmonella*, and this is around the world each year. Most of these are gastrointestinal illness, like what we would call food poisoning, and they resolve on their own. But sometimes they can become invasive and cause more serious infections like bloodstream infections, and about half a million of these cases would become invasive. We also estimate that about 59,000 people die each year around the world from *Salmonella* infection.

[Sarah Gregory] Are there other more common forms of *Enterobacteriales* than *Salmonella*?

[Amrita Bharat] So *E. coli* is probably the *Enterobacteriales* that most people have heard of. If we're just looking at the *Enterobacteriales* that carry ESBLs, then *E. coli* and *Klebsiella pneumoniae* are the most common types. But if we're looking at the *Enterobacteriales* that cause foodborne illness in general, then *Salmonella* is the most common type.

[Sarah Gregory] And earlier you mentioned cephalosporins. How do they fit into this picture?

[Amrita Bharat] Antimicrobials are categorized into a few different categories. One of these categories is cephalosporins, and it's considered to be a very important category for human medicines, including for the treatment of serious *Salmonella* infection. The newer generations of cephalosporins, which we call third generation and fourth generation, they are even more valued. And they are referred to as extended-spectrum cephalosporins because they are able to treat a wider spectrum of bacterial infections.

[Sarah Gregory] What's a common name for a cephalosporin? Is that like cipro? Is that one?

[Amrita Bharat] The most common ones would be like ceftriaxone or ceftiofur.

[Sarah Gregory] And why did you choose 2012–2016 to do this study?

[Amrita Bharat] In 2012, we started to become concerned about the emergence of ESBLs in Canada. And around this time, whole-genome sequencing became more accessible and affordable, so we were able to make this a genomic study. By 2016, we had five years of data and we had tested more than 30,000 *Salmonella* samples, so we felt like we had a large enough data set to analyze the trends and saw some meaningful conclusions.

[Sarah Gregory] What specifically were you looking for?

[Amrita Bharat] We were looking for a couple of things. First of all, we wanted to know how common ESBLs were in people and in the food chain in *Salmonella*. And we wanted to know whether the food chain might be contributing to infections in people with ESBL *Salmonella*.

[Sarah Gregory] And how did you go about finding these things?

One Health Genomic Analysis of Extended-Spectrum β -Lactamase–Producing Salmonella enterica, Canada, 2012–2016

[Amrita Bharat] So in Canada, we have a One Health surveillance program called CIPARS, which stands for the Canadian Integrated Program for Antimicrobial Resistance Surveillance. CIPARS collects samples from people as well as food animals from farms and abattoirs, sick animals through veterinary samples, and different kinds of meats from retail stores. We screened more than 15,000 samples of *Salmonella* from people and about 15,000 samples of *Salmonella* from food and animals, and we found the ones that carried ESBL genes and for these we did DNA sequencing. We then looked at how closely related the ESBL *Salmonella* were from these different sources, looking at the chromosome as well as plasmid.

[Sarah Gregory] Putting all of this together, what were you able to find?

[Amrita Bharat] So out of the 30,000 samples that we screened, we only found 95 that carried ESBL. So this is a low proportion of ESBL *Salmonella* (about 0.3%), and this proportion was similar in people and the food chain. In general, the types of ESBL *Salmonella* were different between the sources except for a couple of examples. So for example, we found two samples of a type of *Salmonella* called Heidelberg in two samples from people and one from chicken thighs, and these were almost identical and they carried similar plasmids with similar ESBL genes. But out of the 95 samples, only a small handful were similar between the sources. So our conclusion was that the food chain seems to be a minor reservoir of ESBL *Salmonella* at least in Canada during this specific study period.

[Sarah Gregory] Are there differences in what you found between Canada and other countries, do you think?

[Amrita Bharat] Yes. So there's one very important difference. There's a strain of ESBL *Salmonella* that's now commonly detected in people and in poultry in the United States and other countries. It's called *Salmonella* Infantis that carries CTX-M-65. And this strain was starting to emerge in food animals in the US and other countries during this study period, but we only detected it in people in Canada at that time. So it seems that the emergence of *Salmonella* Infantis with CTX-M-65 was delayed in the food chain in Canada.

[Sarah Gregory] Was this a surprise? Were there any other surprises?

[Amrita Bharat] So this was a surprise. It was...we checked, and this strain is highly similar that we found in Canada. The use of cephalosporin in the agri-food industry has been eliminated over the last two years, so preventative use of antimicrobials that are the most important to human medicine is being phased out. Another surprise was that in the CIPARS program, pets are not routinely part of the program. But we did have 22 samples from a special project. But out of this tiny pool of 22 samples, we were not necessarily expecting to find an ESBL. We did find one in a sample from a domestic cat, and the plasmid in this sample was similar to a plasmid from a person. Again, that wasn't a total surprise because we knew that from other studies, pets tend to carry ESBLs at a higher rate than other food animals. And this might be because cephalosporins are used more often to treat infections in pets compared to the food industry.

[Sarah Gregory] What kinds of challenges are involved in a study like yours?

[Amrita Bharat] So if we find similar strains in the food chain and in people, we say that there is potential transmission between the food chain and people. We can say with 100% certainty what direction this transmission happened in. So antimicrobial resistance can be transferred to people

from the food we eat, but it can also be transferred from people to the food chain through things like food handling or interactions with animals and farms. So with a bit of circumstantial evidence, we can do more advanced modeling to get more information about the potential direction of transfer. But for this study, we say potential transmission between the food chain and people.

[Sarah Gregory] What does what you found mean for public health?

[Amrita Bharat] So I think our study suggested that some of the infections in people would be ESBL *Salmonella*. It might come from the food chain, but some of it might be caused from our own use of cephalosporin antimicrobials that's causing resistant strains to arise and circulate between people. So studies like ours contributes to a body of evidence that supports ongoing efforts and antimicrobial stewardship. So this means using antimicrobials responsibly so that we can reserve their effectiveness, and this applies to their use in animal health as well as human medicine.

[Sarah Gregory] Are there any follow-up studies you recommend?

[Amrita Bharat] Our study period was 2012–2016 for this study. We are doing a follow-up of 2017–2021, so the last five years of data. And it will be interesting to see how things have changed. A risk assessment study would also be valuable, so more quantifiable data on the potential risk that ESBLs might pose at different stages of the food production cycle.

[Sarah Gregory] How did you become involved in this study?

[Amrita Bharat] When I started in my current role, part of my responsibility was helping with research and surveillance within the CIPARS program. Before that, during my postdoctoral fellowship, I was doing genomic studies of other bacteria like *C. difficile* and *Neisseria gonorrhoeae*. So I was excited to apply those skills to this new challenge of ESBL *Salmonella*, which at the time, that was the most concerning issue we had in terms of resistance in *Salmonella*.

[Sarah Gregory] Who were some of your partners in this study?

[Amrita Bharat] So within that One Health program, CIPARS, we have a team of epidemiologists who run the program and who we work with closely. We have the 10 provincial public health labs in Canada who provide samples and expertise, and there's also farms and veterinarians across Canada who participate voluntarily in the program. At the National Microbiology Lab, we also have excellent genomics and bioinformatics departments who provide us with support.

[Sarah Gregory] On that note, tell us about your job.

[Amrita Bharat] So I'm at the National Microbiology Lab, which is Canada's equivalent of the CDC, and this is within the Public Health Agency of Canada. The NML is located in Winnipeg, Manitoba, which is in the center of Canada. It's a place that's known for being very cold, but Manitoba also has really nice national beauty like lakes and good hiking. And I'm head of the unit called Mycology and Molecular Enteric Antimicrobial Resistance. So the mycology part of that is resourced through the study of fungal pathogens, and I'm doing national surveillance of a fungal pathogen called *Candida auris*, which is causing a lot of public health concern. And for

the enteric antimicrobial resistance, I help to manage the CIPARS program and another One Health program called FoodNet Canada, and the focus there is on antimicrobial resistance.

So I find my job in public service and infectious diseases to be extremely rewarding. There's always something to respond to. There's never a dull moment, and I'm very grateful to be working alongside other public health experts and clinicians on issues that are important...that feel important. So it has been really great the last few years.

[Sarah Gregory] The United States CDC has a FoodNet also. Do they talk to each other?

[Amrita Bharat] Yes. So the FoodNet programs communicate and work together. And the samples that are within the CIPARS program...so we're interested in antimicrobial resistance, but these samples are also part of PulseNet Canada (which is part of PulseNet International) and works closely with the CDC's PulseNet program.

[Sarah Gregory] Well, back to you for a second. What do you think is the most interesting thing you have worked on in your career?

[Amrita Bharat] I think it has been an exciting time to be a microbiologist. Whole-genome sequencing is really transforming the field of infectious diseases. Recently, I've been working on developing methods for being able to detect antimicrobial resistance directly from DNA sequences. So traditionally, we would grow up the bacteria in a broth that has drugs of different concentrations, and we're looking for what kills the bacteria. And that's how we determine what its resistance is. With this new genetic method, hopefully we can get to a place where we can get the resistance information faster and be able to get this information to clinicians sooner to help them make treatment decisions. This genetic method also has other advantages, like telling us not just that the bacteria is resistant but what the gene or mutation that's causing the resistance. This allows us to do our surveillance more precisely. In terms of being able to use it for clinical diagnosis, we're not there yet. But it's a future that we're working towards, and it's very exciting.

[Sarah Gregory] It sounds exciting.

Well, thank you so much for taking the time to talk with me today, Dr. Bharat.

[Amrita Bharat] Thanks for having me.

[Sarah Gregory] And thanks for joining me out there. You can read the July 2022 article, One Health Genomic Analysis of Extended-Spectrum Beta-Lactamase–Producing *Salmonella enterica*, Canada, 2012–2016, online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

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