

# Fetal Loss and Preterm Birth Caused by Intraamniotic *Haemophilus influenzae* Infection, New Zealand

[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. Thomas Hills, a physician and research fellow based in Auckland, New Zealand. We'll be discussing fetal loss and preterm birth caused by *Haemophilus influenzae* infection.

Welcome, Dr. Hills.

[Thomas Hills] Hi, Sarah. Thank you for having me.

[Sarah Gregory] What is *Haemophilus influenzae* serotype B?

[Thomas Hills] *Haemophilus influenzae* serotype B is bacterium. It's an aerobic gram-negative rod. It was initially cultured from sputum of patients who had influenza a long time ago (the late 19th century), and that is how it got its name (how the *influenzae* came into the name of the organism) and it was postulated to be the cause of influenza. Back then, we obviously didn't have the same understanding of what causes influenza and what causes different infections. And we now recognize that obviously this isn't the cause of influenza, but it can cause a secondary bacterial infection in some patients who have the influenza virus. But it causes a whole range of different infections, and we recognize it as an important bacterial pathogen in humans, and most of those cases have nothing to do with influenza. But as a slightly confusing thing for medical students, it still retains influenza in its name.

[Sarah Gregory] What syndromes does it cause?

[Thomas Hills] It can cause a range of different infections, and that may have changed over time. But infections of the respiratory tract are important, including up near the top of the respiratory tract—the epiglottis, which is tissue in the back of the throat that protects our airway when we are swallowing, and so it can be a nasty place to get an infection (epiglottitis). *Haemophilus* causes pneumonia. And a particularly important infection would be meningitis, and *Haemophilus influenzae* meningitis in neonates and young babies is a particularly devastating type of *Haemophilus* infection. And then there are some patients who just have sepsis or a bacteremia, and we don't know exactly where that *Haemophilus influenzae* infection arose, but it can cause a significant bloodstream infection (or bacteremia).

[Sarah Gregory] But there's a vaccine for this one, right?

[Thomas Hills] There is a vaccine for *Haemophilus influenzae* serotype B (we sometimes call that 'Hib' for short), and that Hib vaccine has been a fantastically successful vaccine that has dramatically reduced the burden of infections caused by *Haemophilus influenzae*. And I guess I alluded to maybe things changing over time, and probably the biggest change in terms of the infections and the burden of infections from *Haemophilus influenzae*...it was the introduction of that Hib vaccine. And so, that Hib vaccine was very successful. But Hib is not the only type

of *Haemophilus influenzae*. It's one of the serotypes, and it was the most important that caused a huge number of cases, particularly in young children. But it isn't the only type of *Haemophilus influenzae*.

[Sarah Gregory] So there are different versions other than the serotype B. What are they?

[Thomas Hills] Yeah, there are other versions. And if we go back to how we learned about *Haemophilus* over time, people identified that there was this bacillus that caused a range of different infections. And then in the 1930s, I think, it was noted that the isolates that were from the fluid (the cerebrospinal fluid in cases of meningitis or the isolates from the blood), that the isolates from the most severe cases were usually encapsulated (they had this polysaccharide capsule on the outside of the bacterium to shield it from the immune system) and it was noted that there was six different types of that capsule that you could tell apart in the laboratory. And by far the most common type in those serious infections when you were looking at samples from the CSF or the blood were...by far the most common type was *Haemophilus influenzae* serotype B. And so, that was the one that was prioritized for vaccine development.

[Sarah Gregory] But there's one called nontypeable *Haemophilus influenzae*. Does it cause different diseases than the serotype B?

[Thomas Hills] Yeah. So there are those six different serotypes, which *Haemophilus influenzae* isolates with six different capsules labeled...named A to F. And then there are a group of *Haemophilus influenzae* isolates that don't make a capsule, and we call those nontypable. The typing methods are designed to understand whether you've got *Haemophilus influenzae* serotype A or B or C. And then we have nontypeable, that when you do those typing tests, you can't find what type it is and that's because it doesn't have a capsule. And nontypeable *Haemophilus* is something that we see a lot now clinically, and it can still affect the very young like Hib did, particularly in the pre-vaccine era. But it will also affect elderly people, it can cause syndromes like *pneumoniae* and very common syndromes that we see in the hospital. And so it's possible that nontypeable *Haemophilus* causes different disease than what we saw with Hib, but it's always a little tricky to fully understand potential differences when much of the disease caused by Hib was historic and thankfully, we see a lot less now. And much of the *Haemophilus* that we see with nontypeable *Haemophilus* is disease we're seeing now, and so we're not comparing directly the same time groups (same time period) in many of the studies.

[Sarah Gregory] But there's no vaccine for these nontypeable ones?

[Thomas Hills] No, there isn't a vaccine and I guess that's for a few reasons. But the first reason would be that when *Haemophilus influenzae* was causing such a significant burden of infection—that was the Hib, the serotype B; those were responsible for most of them—and the vaccine was developed against the capsule from the serogroup B. That capsule is a tricky thing for the immune system to respond to. So a clever vaccine design, couple that still with something that the immune system could more easily recognize (and we call that a conjugate vaccine), and it targets the capsule. And the nontypeable *Haemophilus* doesn't have a capsule. So a vaccine against a nontypeable *Haemophilus* would require a different technology (a different type of vaccine). And I guess it also hasn't been a priority when by far the greatest burden of disease from *Haemophilus influenzae* was caused by Hib.

[Sarah Gregory] Your study is about invasive *Haemophilus influenzae* and fetal loss and preterm birth. Why did you do this study?

[Thomas Hills] I guess like many more observational studies like this is it started with a patient I was seeing, and I saw a pregnant woman who had invasive infection with *Haemophilus influenzae* and I hadn't seen that before and wanted to read around the case, not least because I knew she'd have a lot of very reasonable questions she wanted to ask me as I was coming along to consults on her case for the infectious diseases service that I was working for. And when I reviewed the literature and was looking at *Haemophilus influenzae* infection in pregnancy, *Haemophilus influenzae* infection is not described as a common cause of infection within the uterus or within the lining, the chorion and the amnion that are around the fetus. And we call that chorioamnionitis, that infection or intraamniotic infection.

And *Haemophilus influenzae* is not listed in the long list of bacteria you might see in a review article of bacteria that caused intraamniotic infection. But there are studies that say if you're pregnant, your risk of invasive *Haemophilus influenzae* infection is higher. And so, I was interested...you know, this lady I'm seeing, she has this infection, it doesn't seem to be a common cause of intraamniotic infection, what's going on here? And I had a quick look at our local lab numbers, and I could see that *Haemophilus influenzae* in our laboratories was affecting elderly men and women as is well described in the literature, some cases in infants as is well described. And then, there was this cluster of case numbers in women of child-bearing age, and so I became more interested in understanding this and this as a clinical problem.

[Sarah Gregory] So you found pregnancy is associated with an increase in *Haemophilus influenzae*?

[Thomas Hills] Yeah. There's a fantastic paper published in *JAMA* in 2014 by Collins, et al. And they had looked at the Public Health England database that covers all of England and Wales for notifiable diseases like *Haemophilus influenzae* infection, and they found in that big study and a big population 171 cases of *Haemophilus influenzae* infection in women of childbearing age. And they, I guess in the same way I had looked at our lab data and seen a little cluster in women of childbearing age, is they were looking at a huge data set and they found that cluster in women of childbearing age. So they wrote to the GPs (or family doctors) of those cases and asked for clinical information, and almost half of those women of childbearing age with invasive *Haemophilus influenzae* infection were pregnant. Most of them presented with sepsis or bacteremia. And in that study, there was a 17-fold increase in the rate of *Haemophilus influenzae* in pregnant women compared to non-pregnant women. So there's a striking increase in your risk of developing invasive *Haemophilus influenzae* infection if you are pregnant.

[Sarah Gregory] How does intraamniotic infection affect birth outcomes?

[Thomas Hills] That, of course, is the key question for pregnant women. If you're seeing one of these (thankfully) uncommon cases, it's the key question that pregnant women will want your help answering. And unfortunately the pregnancy outcomes are really poor. And so, I was looking at this when I was seeing my first patient with this problem. And particularly early in pregnancy—I think Collins, et al. used the first 24 weeks to define those earlier stages of pregnancy—fetal loss, still birth, or spontaneous abortion occurred in over 90% of cases. And in the later stages of pregnancy, outcomes were still bad. There were fewer cases of stillbirth or fetal loss beyond 24 weeks, but a lot of premature birth. And so, it's an infection with really poor outcomes for the fetus (poor pregnancy outcomes). In contrast, the mothers tend to do okay.

There's not much maternal mortality, but there's a lot of mortality in terms of poor outcomes for the fetus.

[Sarah Gregory] How do these women get infected with it in the first place?

[Thomas Hills] I don't think we know. And that's one of the really important unanswered questions, here. *Haemophilus influenzae* generally is a bug that can just live in people's throats, for example. And so, it can be there in a carrier state. And that used to be the case for Hib. A small proportion of people would carry Hib, and that's a lot lower in the vaccine era. But these other types of *Haemophilus* could be carried by people, but we don't really know how the *Haemophilus influenzae* in these women was either acquired or went from a carrier state to causing disease. There's just a lot of unanswered questions there.

[Sarah Gregory] You said it's rare, so what percentage of women get these infections?

[Thomas Hills] Yes, I mean thankfully these infections are rare. Probably the best data would come from that Collins *Jama* paper that I mentioned. And if you followed 100,000 pregnant women for a year—or maybe because women aren't pregnant for a whole year—if you followed 200,000 pregnant women for six months, you'd diagnose three cases. There are three cases per 100,000 woman-years in that study in pregnant women. And so, it's a rare infection, and it's just that the outcomes are really poor, and that's why I wanted to understand more of it and to do the study that I've done.

[Sarah Gregory] So even if it is rare, it's devastating for the women. Are there signs or symptoms of infections that could be spotted earlier by clinicians? Or a test that all women could get?

[Thomas Hills] Yeah, there are signs and symptoms when women become unwell with this infection. And so, a pregnant woman presenting with invasive *Haemophilus influenzae* infection may just have a fever. And in that situation, blood cultures are really important tests. But often these women also present with localizing features that give the clinicians a clue that there is infection affecting the pregnancy. So they may have abdominal pain, vaginal discharge or bleeding—these sorts of symptoms—that might alert the clinician to the presence of intraamniotic infection. I don't think that there's a test that could be done for all pregnant women to exclude this infection. I think there's an incomplete understanding of how this infection arises and how it goes on to cause these poor outcomes. And so, I don't think that there would be a test that could provide reassurance.

And I think the main thing for clinicians would be vigilance for signs and symptoms of intraamniotic infection in pregnant women who present unwell, particularly women presenting unwell with a fever, and then blood cultures and samples from the genital tract (if that's clinically appropriate) to try and understand which infection is causing the women to be unwell. Because *Haemophilus influenzae* is just one of many infections that could cause chorioamnionitis or intraamniotic infection. And I'm focusing on it here because I think it's an underrecognized cause. It's not commonly described as a cause of chorioamnionitis. But the emerging data from my study, from studies like Collins, et al. suggests that it's a rare but a devastating cause of intraamniotic infection.

[Sarah Gregory] So if a clinician detects it or decides the woman has it, is early intervention going to be more helpful? Or is it just knowing that this bad thing is going to happen?

[Thomas Hills] I think early treatment would be the key and recognizing an infection like this and treating it early would be really important. And most clinicians will recognize that a

pregnant woman has an infection like this before knowing which bacterium is causing the woman to be unwell. And many women presenting with these sorts of symptoms will get empiric antibiotics. and most of the antibiotics recommended in guidelines would be antibiotics that are active against *Haemophilus influenzae*, along with the other organisms that can cause these sorts of infection.

[Sarah Gregory] Dr. Hills, how did you go about doing this study? Tell us about it.

[Thomas Hills] I did the study with a group of colleagues who work in infectious diseases, obstetric medicine, microbiology, and laboratories. And we decided to look at a 10-year period up until 2018 in the Auckland region of New Zealand—so that's the biggest city in New Zealand. Our region is the largest region by population in New Zealand. And we used the CDC definition of invasive *Haemophilus influenzae* infection, which is essentially identification of *Haemophilus influenzae* from a normally sterile site (like the CSF, the blood, placental specimens) and we identified cases from the laboratory records over those 10 years. And in New Zealand, pregnancy care and microbiological testing occurs through the public health system network of laboratories. And so, our microbiological records cover the pregnancies across the region for the 10-year period. We saw this very often in New Zealand (this pregnancy associated *Haemophilus influenzae* infection), and then we wanted to look closely at those cases that did occur in pregnancy. And so to find our cases, we had to look at all the cases of *Haemophilus influenzae*, including cases that were in blood cultures, but the person clearly had pneumonia, and we had to drill down and find which patients were pregnant.

[Sarah Gregory] What did you find?

[Thomas Hills] We found that, as is described in the literature, this is thankfully a rare infection. So in our study, it caused approximately 20 cases for every 100,000 births. But like the literature, we found that there were poor outcomes with fetal loss, preterm birth, or birth of an infant who had to go to an intensive care-type unit in 94% of the pregnancies. So we had 54 cases in that 10-year period in the Auckland region here, and we found 94% of the pregnancies that we studied had a poor outcome in terms of the fetal outcome (the pregnancy outcome). And so, that was very consistent with the international literature. In the literature that, for example, I alluded to before from Collins, et al., 60% of the pregnancies in that study resulted in fetal loss. In our study, it was 35%. And I think that might reflect that we were looking at sterile site samples from the mom or the baby (it might have been in the neonatal intensive care unit). So by including both maternal and neonatal samples, we might have found a higher number of those cases in the neonatal intensive care unit who had survived to be born, but to be born with a requirement of that special care. And so, we found more of those cases where fetal loss hadn't occurred. So I think that's probably why our rates of fetal loss were a little lower than that Collins, et al. publication where it was 60%. But a 35% fetal loss rate is still a really sad example of how these infections can be really serious.

We also found that there was microbiological evidence. So when we looked at the laboratory results, that *Haemophilus influenzae* was causing infection within the womb. That's because in two-thirds of cases, we saw that the placental samples or the samples that were described as the products of conception or samples from the higher part of the genital tract (like high vaginal swabs) were growing the *Haemophilus influenzae* in these cases. And we felt that that was a really important finding because the Collins paper that I've alluded to a couple of times paints the scene that this is a really serious infection in pregnancy and that pregnant women get this

infection more. But it wasn't really clear why pregnancies would suffer so much during this infection. We wondered whether it might be because the infection directly affects the pregnancy if it can get into the womb and cause that intraamniotic infection. And our data suggests that is the case. So in two-thirds of cases, we could find the *Haemophilus* there causing intraamniotic infection. And I think that was probably a key finding for us, and I think we should reconsider that list of organisms that causes...that can cause intraamniotic infection. I think *Haemophilus influenzae* needs to be considered one of those organisms.

[Sarah Gregory] Was any of this unexpected?

[Thomas Hills] We had our suspicions that *Haemophilus influenzae* was causing intraamniotic infection. But most of the evidence in this area was from epidemiological-type studies (like Collins, et al.) saying that this is a problem that you're at higher risk of if you're pregnant, and the pregnancy outcomes are poor. But we didn't have any of that mechanistic information about why pregnancy outcomes were poor. So we were suspicious that *Haemophilus influenzae* might cause direct infection of the pregnancy (that chorioamnionitis), but our data I think provides fairly strong evidence for that. We could identify the organism in those samples in our patients. So that was not entirely unexpected, but I think is a new piece of evidence in our understanding of this rare infection. And interestingly, *Haemophilus influenzae* isn't something that you'd occasionally find in the genital tract of healthy pregnant women. When people look at the flora, the commensals of the genital tract in pregnant women, they don't find *Haemophilus influenzae* there. And so, this must be an infection that women either acquire before pregnancy or during pregnancy (perhaps uncommonly), and uncommonly it goes on to cause this severe infection with very poor outcomes for the fetus.

I guess another finding for our study that's important in a New Zealand context is that the rates of pregnancy associated *Haemophilus influenzae* were much higher in our indigenous Māori population. Rates were 3.3 times higher in that population group when compared to the New Zealand/European population. And then, we see inequities in many infectious diseases in New Zealand, but that's quite a striking finding that was, I guess, unexpected to see such a magnitude of effect. Although, we could never say were unexpected by some of the inequities that we see with infectious diseases in New Zealand without Māori population experiencing a high burden of many infectious diseases.

[Sarah Gregory] But we don't know why this is the case with this particular disease?

[Thomas Hills] We don't know why. There is some information out there on other serious infections in pregnancy, such as group B *Streptococcus*. And rates in Māori are not dramatically higher for those other serious infections in pregnancy. And so, I don't know why it's higher with this particular infection.

[Sarah Gregory] Your article also mentions listeriosis during pregnancy. Tell us about the connection. Is there a connection? Is there something we need to know about the two of them?

[Thomas Hills] There's no direct connection between the bugs, but they're both...well, *Listeria* is a very well-recognized cause of pregnancy infection. And most pregnant women will be very aware of the risks of *Listeria*, and they'll be thinking about foods from a delicatessen or soft cheeses and these things that are recognized as potential risks for acquiring *Listeria* during pregnancy. And *Listeria* during pregnancy is really serious and has poor outcomes for the fetus. So there are some parallels there. But I guess the real difference

between *Listeria* and *Haemophilus influenzae* is that *Listeria* is something that's really in the eye of the public in terms of its risk during pregnancy and it's in the mind of clinicians when they are seeing somebody with a serious infection during pregnancy, whereas *Haemophilus influenzae* isn't.

And I think you always have to be careful when you are comparing data from two different sources. But when we looked at our study, the rate for *Haemophilus influenzae* was 19.9 cases per 100,000 births. And when you look in New Zealand at the rate of pregnancy-associated listeriosis, which we've got pretty good data on because it's a notifiable condition in New Zealand...and so, if you looked at 20 years' worth of that data, the rate of pregnancy-associated listeriosis is 12.3 cases per 100,000 live births. And so, the burden of *Haemophilus influenzae* is significant when you compare it to listeriosis, which is a really important infection. And I... myself and my coauthors, we put that in there in our discussion just to highlight that there's this listeriosis that's really well-recognized and we do a lot of things to try and reduce the risk and it's a notifiable disease that we collect information on, but here we've got an infection with something I think is underrecognized (*Haemophilus influenzae*) during pregnancy. And I guess we made a related comparison in the discussion with early-onset neonatal group B *Streptococcus*, which is something that we work hard to reduce the rates of in New Zealand (it's another pregnancy-associated infection with poor outcomes for the fetus or neonate). And in New Zealand, we see about 23 cases per 100,000 live births in the era where we are screening for that and treating for it. And so, we think those are really, really important infections, and we just wanted to draw attention to the fact that the incidence rate of *Haemophilus influenzae* in our study was not that different from those other two well-recognized infections.

[Sarah Gregory] Maybe listeriosis, because there's a known cause (or what can cause it), it's easier to get a communication handle on it.

[Thomas Hills] Yeah, I think that's right. I think that we have an understanding of how pregnancy-associated listeriosis occurs and there are clear things that can be done in terms of our food safety, things that can be done at a population level in terms of food production and ensuring there is a low level of *Listeria* in foods that are bought and sold in our society. And there are things that an individual can do to reduce their risk of pregnancy-associated listeriosis. So that's something...that's an infection that's a lot further down the road in terms of our understanding of its impact and what we can do to reduce that impact. Whereas I think for *Haemophilus influenzae*, this study just highlights that it is a serious infection that causes poor pregnancy outcomes by causing infection within the womb of the developing pregnancy, but we don't have the answers to how this occurs or what we should do about it. And I think that's where research will need to take us next.

[Sarah Gregory] What do you consider the most important contribution your study has made to the body of public health knowledge?

[Thomas Hills] I think we've added another small piece of the jigsaw puzzle that builds on some of the previous work that identified *Haemophilus influenzae* as an important infection in pregnancy, and one with poor outcomes. And we're adding information on how those poor outcomes arise, with *Haemophilus influenzae* seemingly infecting the developing pregnancy within the womb, causing chorioamnionitis or intraamniotic infection. And I think there are a number of questions that arise now that will need to be the focus of future work, such as how

does *Haemophilus influenzae* cause that infection? How does it get into the womb and how is the infection acquired?

[Sarah Gregory] Well then, what future studies do you think need to be done?

[Thomas Hills] I think it would be useful for similar studies to be done in other settings—looking back at cases, reviewing clinical details, microbiology—in a similar way to what we've done to look and see whether this is a consistent observation (that the *Haemophilus influenzae* causes intraamniotic infection). But then I think key future studies will be trying to understand how this infection arises. So those might be case-control studies or cohort studies trying to understand what are the risk factors for the development of this infection during pregnancy.

[Sarah Gregory] Are there ways that women can protect themselves from getting these infections?

[Thomas Hills] I don't think so. I wish that there was an easy answer to that. This is a really uncommon infection, and we only have a small amount of data on the exact mechanism by which it causes poor pregnancy outcomes. But I don't think we know how the infection is acquired or what could be done to reduce the risk of the infection.

[Sarah Gregory] Well Dr. Hills, tell us about your job and where your work.

[Thomas Hills] I work at Auckland City Hospital, which is a big referral hospital here in Auckland, New Zealand. And I've worked across the other hospitals in Auckland during my infectious diseases training. And I'm a clinician—I work in clinical immunology and infectious diseases, and I am interested in the overlap between those two interest areas (infections in the immunocompromised host and the inflammatory response to infection). And I'm a researcher. I mostly do clinical trial-type research with the Medical Research Institute of New Zealand here. And so, I don't do all that much observational research and I'm always struck by how challenging it is to do this observational research, even a small and relatively simple study like this one that we've done sometimes means you go in with some questions and you leave with just a bunch of different questions. And it's great to be able to do this research, and I love that link between my clinical practice where I can see a patient and then the research environment where I can try and understand what has happened. And I'm really lucky, a lot of my coauthors on this publication are people who have helped me through my training and have been very supportive of me seeking to build little research projects out of cases that I've seen during my training here in Auckland.

[Sarah Gregory] What do you think is the most interesting or important issue you've worked on?

[Thomas Hills] For a few years now, I've been involved in a big study called REMAP-CAP, which is actually a randomized trial of severe pneumonia. And that has been a fantastic experience for me. I'm interested in infections in specific populations like the critically ill, and I'm interested in the immune response to infections. And we've had the opportunity to study a raft of different things, like immune modulators in people with severe pneumonia/severe COVID, and that has been a wonderful experience and I've really enjoyed that study and my involvement, and it's a study that's designed to be prepared for a pandemic and then the arrival of a pandemic. And this wonderful but busy experience of doing research during the pandemic, I mean, that's probably been both the most interesting and most important research that I've been lucky enough to be involved in.



[Sarah Gregory] Thank you so much for taking the time to have this conversation with me today, Dr. Hills. It was a pleasure to have you.

[Thomas Hills] No worries. Thank you for having me.

[Sarah Gregory] And thanks for joining me out there. You can read the September 2022 article, Fetal Loss and Preterm Birth Caused by Intraamniotic *Haemophilus influenzae* Infection, New Zealand, online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

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