

***Streptococcus dysgalactiae* Bloodstream Infections, Norway, 1999–2021**

[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. Oddvar Oppegaard, an infectious disease specialist at Haukeland University Hospital and an associate professor at the University of Bergen. We'll be discussing *Streptococcus dysgalactiae* bloodstream infections in Norway.

Welcome, Dr. Oppegaard.

[Oddvar Oppegaard] Well, thank you, Sarah. Thanks for having me on your podcast.

[Sarah Gregory] What is *Streptococcus dysgalactiae* and how is it different from other streps?

[Oddvar Oppegaard] Well, to answer that, Sarah, we need to delve into the world of microbes for a second. *Streptococcus dysgalactiae* is a bacterial species, and it's just one of many bacterial species belonging to the larger family of *Streptococcus*. And the second part of its name, *dysgalactiae*, is Latin for "bad milk" and alludes to this particular microbe's propensity to cause mastitis in cows.

But nevermind the cows, *dysgalactiae* is also fully capable of causing disease in people. I'm guessing that many of the listeners may not have heard about *dysgalactiae*, but they might be familiar with its closest sibling, the group A strep, or *Streptococcus pyogenes* in Latin. It produces the strep throat, and it's also a notable cause of school sores or impetigo. So you might have come across it in your youth.

Now, *dysgalactiae* is genetically very similar to the group A strep, and the range of diseases they can produce is also highly overlapping. However, *dysgalactiae* has always had the role of the baby brother in this relationship, both in terms of disease frequency and severity. So it hasn't earned a lot of time in the spotlight, or at least not yet.

[Sarah Gregory] So is it becoming more of a public health threat?

[Oddvar Oppegaard] Well, looking back at history, *Streptococcus dysgalactiae* was initially considered to be a commensal microbe, meaning a microbe that co-resides with us in harmony, for instance as part of the microbial community living in our gut.

However, the past decades there has been a growing concern that *dysgalactiae* may not be as innocent as first presumed. In fact, accumulating evidence points to a fairly substantial disease burden. And we recently reviewed all blood stream infections in our region caused by this pathogen for the past decades. And looking at the temporal trends for annual incidence rate, Sarah, there was no doubt severe *dysgalactiae* infections are definitely on the rise.

[Sarah Gregory] And how much has it increased during the period that you studied?

[Oddvar Oppegaard] In our study, we covered a span of 23 years, all the way from 1999 up to 2021. And during this period, we found the incidence rates of *dysgalactiae* blood stream infections increased more than 500% in our community.

In plain numbers, that means that in our hospital we went from having five patients per year in 1999 to 35 patients in 2021. So a fairly substantial increase.

[Sarah Gregory] How does it compare with other bloodborne pathogens? What's the incident rate compared to the others?

[Oddvar Oppegaard] So that's a good question, Sarah. Most previous studies on *dysgalactiae* have just looked at the incidence rates for this specific pathogen. And like I said, they generally find increasing rates, but how does it compare to other pathogens? Perhaps they are all increasing at the same rate?

So to look into this, we examined the species-specific incidence rates for all bloodborne pathogens in our region the past decade, and then we ranked them in terms of frequency. And doing this, we observed that *dysgalactiae* had gradually climbed from being the 16th to the 5th most common cause of blood stream infections in our region. And *dysgalactiae* was also one of only three bacterial species that displayed a significant increase during this period. It was also the pathogen with the largest annual increment in percent. So *dysgalactiae* is definitely a rising star in the microbiological community, at least in terms of bloodborne infections.

[Sarah Gregory] Your article is about causing, as you just said, bloodborne infections particularly, but does it cause any other kinds of infections?

[Oddvar Oppegaard] Bloodborne infections simply means that the bacteria were cultivated from the patient's blood samples. This doesn't mean that the infection was confined just to the bloodstream, nor that this was the primary origin of the infection. Quite the contrary; in almost 80% of the patients with bloodborne infections, we identify a completely different primary source of infection. And the most common sites by far are skin infections, such as cellulitis, and bone and joint infections, for instance arthritis. And occasionally, we also observe more aggressive infections targeting the heart valves (called endocarditis), or infections causing rapid destruction of deeper skin tissues, often named "flesh eating bacteria" in the media. So the fact that we find bacteria in the blood stream is really more of a marker, signifying that the infection has progressed to a very severe disease state.

I would like to stress though that the vast majority of infections due to this microbe are not associated with bloodborne infection. Most people acquire superficial skin infections, such as impetigo or upper respiratory tract infections, including strep throat. But as you see, all in all, this bug has a quite wide repertoire of disease, from harmonic co-existence to rapid flesh eating.

[Sarah Gregory] Well then, how does it get in the blood? Say you have a skin infection—how does it get in the blood?

[Oddvar Oppegaard] There are usually three elements to that equation, and it's fairly similar for all microbes, really. Firstly, the bacteria need to be equipped with tools for breaking through our defense barriers, often called virulence factors. Most *dysgalactiae* isolates possess such virulence factors that enable them to latch on to various body surfaces, to cut through tissue barriers, and to evade our immune system. So most *dysgalactiae* bugs definitely have the potential for breaking and entering, so to speak.

Now secondly, the person needs to be susceptible to this particular microbe. If you, for instance, have encountered a similar microbe previously, you will likely have generated immunity, and the bug will be cleared by your immune system before you even know it. But if you have never met this kind of microbe before, or if your immune system for some reason is impaired, you might not be as fortunate.

And thirdly, the microbe needs a moment of opportunity. It could be a minor breach in your skin integrity, such as a scratch on your knee or a sore in your gut, enabling the bacteria to bypass your first line of defense and engage in combat. Or it could be that your immune system is temporarily impaired from medicines, such as chemotherapy. So basically, it's like a tragic love story, really—the right bug meeting the right person at the right moment. Or perhaps at the moment of vulnerability is more correct. It certainly doesn't happen often, but if all these three stars align, you might be unlucky as to develop a bloodborne infection.

[Sarah Gregory] So having said that, how dangerous is it?

[Oddvar Oppegaard] Well firstly, I think it's important to note that *dysgalactiae* is still predominantly a commensal microbe, a microbe that co-resides with us in harmony. So at any given time, a large proportion of the population harbors these bacteria in their gut or in their throat or on their skin, without even noticing it.

So should you be afraid if you meet this microbe in a dark alley? No, not at all.

For most people, it's perfectly harmless. However, should you be so unlucky as to acquire a bloodborne infection with this pathogen, well, the mortality rates are suddenly 10% within the next 30 days. So, it's best to stay at friendly terms with this bug.

[Sarah Gregory] Your article is specifically about Norway, but do you think these bloodborne infections are increasing elsewhere and if so, where?

[Oddvar Oppegaard] Most definitely, Sarah. We are not alone in this. Increasing incidence rates for *dysgalactiae* have been noted in several regions, including other European countries, Canada, Australia, and Japan.

However, surveillance of this pathogen has long been hampered by imprecision in the identification procedures in the microbiological laboratories. And what does that mean? Well, until recently, the identification of this particular branch of streptococcal species has relied on rather crude lab methods developed in the 1930s that simply divide them into the group A strep, the group B strep, the group C strep, and so forth. The problem is that *dysgalactiae* does not belong to one specific group. It can sometimes be sorted in the group C, sometimes group G, and occasionally even group A or L. And to make matters even worse, there are other bacterial species that would also be sorted as group C or G. So in effect, the disease burden of *dysgalactiae* has been first split into several different groups and then pooled together with other bacterial species. So needless to say that this has caused a lot of confusion and frustration. But fortunately, more modern methods for identifying bacterial species have emerged, and these can accurately identify *dysgalactiae*. So we are beginning to see an improvement in the precision in epidemiological reports for this pathogen.

[Sarah Gregory] You mentioned at the beginning that it had increased quite a bit over this last 20 years, especially recently. So why is it increasing? Do we know?

[Oddvar Oppegaard] Well, at least we definitely know that it's multifactorial, and we can sort these factors into three principal groups: changes that have occurred in the microbes, changes in people, and societal changes. Now, firstly looking at the microbes, have the *dysgalactiae* bugs become more aggressive? Well, that's difficult to establish because we really don't have a lot of old microbes from decades back to compare them with. But we do find that a large proportion of the increase we observe is caused by a particular clone called stG62647. And that's not just in Norway, this clone is dominant all over Europe and also in Canada. So this could, of course,

indicate that this clone is more competent in causing disease, but to be honest, exactly why it has taken over the market, so to speak, has not been elucidated.

And secondly, concerning societal changes, the fact that labs currently identify *dysgalactiae* more precisely will definitely influence the incidence rates. Now the C's and the G's come together in one category. Moreover, there is an increased sampling of patients in many countries. We take more blood cultures, therefore we find more bacteria. But even when we correct for these two societal factors, the incidence rates for *dysgalactiae* are increasing, so it's definitely not the whole truth and nothing but the truth. And finally, are people becoming more prone to contracting *dysgalactiae* infections? Well, it does appear so, Sarah. At least the number of people prone to contracting *dysgalactiae* infections is increasing.

[Sarah Gregory] Does it affect a particular group of people more than any other?

[Oddvar Oppegaard] Yeah, I think that's exactly it. It certainly does. Most notably, it appears to have an affinity for the elderly. So in our study, the average age was 75 years for the *dysgalactiae* cases. In fact, we found that people acquiring *dysgalactiae* infections were significantly older than those infected by any of the other common streptococcal species. So this age fetish was a very distinguishing feature for *dysgalactiae*. Moreover, patient's health status also appears to be relevant. Several studies have found that diabetes and obesity are major risk factors for contracting *dysgalactiae* infections.

Importantly, during our study period, the average life expectancy in Norway increased by five years, and the number of people with diabetes and overweight in our community were more than doubled. So jumping back to your previous question, Sarah, I think this is probably one of the major reasons why *dysgalactiae* infections are increasing. In terms of our tragic love story analogy, it seems that more and more people turn into the right match for *dysgalactiae*. And I think this demographic development is quite similar in many other countries, and it's also likely to continue. So this might indicate that the love life of *dysgalactiae* microbes will continue to thrive.

[Sarah Gregory] Are clinicians aware of it? If someone becomes sick with it, will doctors even know to look for it and if so, is there a specific test for it?

[Oddvar Oppegaard] To answer the first part of your question first, Sarah, I don't think the average clinician has heard about *dysgalactiae*. But in all fairness, this is partially due to the shift in terminology I talked about, moving from the C's and the G's to the *Streptococcus dysgalactiae*. But now that more modern identification methods are becoming widespread, I do hope that *dysgalactiae* will become a household name for clinicians in the future.

But is it of great concern that most doctors are unaware of this microbe? Well, perhaps not.

In the majority of cases, doctors commence antibacterial treatment based on a medical diagnosis, without knowing exactly which bacteria that has caused it. So most countries, they have guidelines for antibacterial agents to choose if you, for instance, have a patient with cellulitis or arthritis. And these antibiotics will in general also cover *dysgalactiae*. So in summary, you don't really need a specific test for it.

[Sarah Gregory] So it's treated with antibiotics no matter what it may or may not be, as long as it's bacterial. Is that what you are saying?

[Oddvar Oppegaard] Yeah. Penicillin, plain and simple. That's the usual treatment.

[Sarah Gregory] What if someone is allergic to penicillin?

[Oddvar Oppegaard] It's not a very hot microbe when it comes to antimicrobial resistance because good old penicillin will always do the trick. But occasionally there is the need for alternatives, Sarah, for instance, like you said if you have a penicillin allergy. For the second line alternatives, antibiotic resistance actually is a growing concern. In the United Kingdom, for instance, more than 40% of the *dysgalactiae* isolates are resistant to the most common second line alternatives, and even higher numbers have been reported from southeast Asia. So I guess we need to keep our eyes open also for this aspect in the future.

[Sarah Gregory] Why did you do this study? What were you looking for?

[Oddvar Oppegaard] Well, we (as others) had a growing concern that *dysgalactiae* infections were on the rise. And at the same time, many clinicians and health authorities are unaware of it, particularly due to the insufficient identification in the labs. The United Kingdom for instance, still report their national surveillance data with one curve for the group C strep and another separate incidence curve for the group G strep. So even at the level of government reports there is room for improvement. So we sought to put the searchlight on the magnitude of the problem, as well as address the need for enhanced precision in describing and monitoring these pathogens.

[Sarah Gregory] Tell us how you went about it (the study).

[Oddvar Oppegaard] We searched through our electronic archives at our Department of Microbiology looking for *dysgalactiae* bloodstream infections during 1999–2021. But as I pointed out, until recently, the identification of these streptococcal species was a bit crude also in our lab, so we had to confirm the species identity using more modern technology. So I had to rummage through deep freezers to retrieve all these isolates, and then we reconfirmed the identity. I think we examined more than 1,100 streptococcal isolates in this manner. And since it was not feasible to be this meticulous for all possible microbial species, the comparison to all other species was only conducted to bloodborne infections during 2012–2021 because in this later period, our lab had started using more reliable identification routines. So the need for reconfirmation of identity was not that strong. And then it was all down to statistical analysis, really.

[Sarah Gregory] Were there challenges?

[Oddvar Oppegaard] Rummaging through deep freezers searching for bacterial isolates deposited more than two decades ago was really not my favorite. I don't know how many hours I spent with my head below zero. It was freezing.

[Sarah Gregory] What about surprises? Were there any surprises in all this?

[Oddvar Oppegaard] We were really surprised to find that *dysgalactiae* was the fifth most common microbe causing bloodborne infections. We knew it was increasing, but the ranking was unexpected. I bet if we conducted a survey among Norwegian infectious disease specialists and asked them to rate the five most common bacterial species causing blood stream infections in Norway, well I don't think *Streptococcus dysgalactiae* would be mentioned at all.

[Sarah Gregory] Did COVID prevention measures have any impact on the spread of this pathogen?

[Oddvar Oppegaard] That is a very interesting question, Sarah. There was absolutely a major impact on the spread of several bacterial pathogens as a result of social distancing and other COVID prevention measures. For instance, we found an abrupt decline in the incidence rates for the group A strep. And like COVID, the group A strep is also usually transmitted by droplets. So it makes sense that the COVID prevention measures had an impact.

However, for *dysgalactiae*, we observed no notable impact of the pandemic. So what does that mean? Well, it could of course infer that the *dysgalactiae* bloodstream infections are predominantly caused by your own bacterial flora and not by person-to-person transmission. In other words, our commensal bacteria you already have in your gut or on your skin, that somehow found an opportunity to convert to being pathogenic. It's at least an interesting theory, but honestly, we really don't know.

[Sarah Gregory] What do you personally think is needed to better monitor this pathogen?

[Oddvar Oppegaard] Well, firstly, enhanced precision in species identification. But that's already in progress. But secondly, increased awareness of the pathogen. Now, many countries already have surveillance programs for several other streptococcal pathogens. And *dysgalactiae* has surpassed these in terms of frequency in many geographic regions, yet to the best of my knowledge, surveillance programs for *dysgalactiae* have not been established in any countries, or at least not if you don't count those who split them into C's and G's.

[Sarah Gregory] What about studies? Are there future studies you suggest?

[Oddvar Oppegaard] More knowledge on the mechanisms causing this increase would be appreciated, including factors both in the bacteria and the host. I mean, why do some people get sick with this microbe whereas others live in complete harmony with their *dysgalactiae*? That would be interesting to further elucidate.

[Sarah Gregory] Are there any ways that people can protect themselves personally from this pathogen?

[Oddvar Oppegaard] Well, as indicated by the lack of impact of COVID measures, I don't think it's realistic to avoid contact with this microbe altogether. It probably comes more down to trying to avoid becoming the right match for *dysgalactiae*. And in this regard, I think perhaps the best advice was put forward by Albert Einstein when he said, "Don't grow old, no matter how long you live". But on a more serious note, there are some efforts to produce vaccines for these kinds of strep, but they likely won't be in the shelves at the pharmacy for the next decade or two. And lastly, I would like to emphasize that compared to the number of people who come into contact with this microbe every day, the proportion that actually get sick is extremely small. So to cite another legend, "Don't worry, be happy".

[Sarah Gregory] Tell us about your jobs (since you seem to have two of them here) and how you became interested in studying *Streptococcus*.

[Oddvar Oppegaard] I work at the Haukeland University Hospital in Bergen in Western Norway as a specialist in infectious diseases, and I also hold a position at the University of Bergen as an associate professor, teaching the next generation of medical doctors how to treat patients, but of course also about the importance of *Streptococcus dysgalactiae*.

And how did I get into strep? Well, I think it was almost a matter of indoctrination. There has been a longstanding research interest for streptococcal infections in Bergen, probably dating all

the way back to the early 90s when an upsurge of severe group A strep infections overwhelmed our country. And we still have a strong and dedicated Streptococcal Interest Group in Bergen. But of course, if *dysgalactiae* continues to increase, we might need to expand our team.

[Sarah Gregory] Well thank you so much for taking the time out of what is obviously a very busy schedule to talk with me today, Dr. Oppegaard.

[Oddvar Oppegaard] Thank you again for having me on your podcast, Sarah.

[Sarah Gregory] And thank you for joining me out there. You can read the February 2023 article, *Streptococcus dysgalactiae* Bloodstream Infections, Norway, 1999–2021, online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

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