

Asymptomatic Household Transmission of *C. difficile* Infection from Recently Hospitalized Family Members

[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. Aaron Miller, a research assistant professor at the University of Iowa Roy J. and Lucille A. Carver College of Medicine. We'll be discussing transmission of *C. difficile* to family members from recently hospitalized patients.

Welcome, Dr. Miller.

[Aaron Miller] Thanks. It's good to be here.

[Sarah Gregory] Remind us what a *C. difficile* is. There's so many different kinds of viruses and pathogens and whatever out there, now. How is *C. difficile* different?

[Aaron Miller] Yeah, so *C. difficile* is a bacterium that can cause a type of intestinal infection that typically results in severe diarrhea and colitis (that's an inflammation of the colon). It tends to be transmitted through the fecal-oral route, and the way that infections typically arise are when somebody if exposed to the bacterium typically also receive antibiotics. So this is one of the most common causes of antibiotic-associated diarrhea and colitis. And the way that the infection typically occurs is that a person who might be exposed to the bacterium might have received antibiotics, and the antibiotics might have disrupted the normal intestinal flora that allows the bacterium to multiply and ultimately produce toxins which gives rise to the intestinal infection.

[Sarah Gregory] And where is it most commonly acquired?

[Aaron Miller] So exposure to *C. difficile* can occur really in any environment. *C. difficile* spores have been found in community settings, healthcare settings, even in outdoors. It has been found in food, compost, on pets and other animals, and the spores can typically persist for long periods of time. However, transmission typically occurs in proximity to other infected individuals. So things like healthcare settings, hospitals, nursing homes and long-term care facilities, settings where there's a density of individuals who might have an infection are generally seen as the primary reservoir for infection. And even with inside those settings, proximity to infected cases tend to increase transmission risk. So things like sharing rooms or sharing bathrooms with other infected patients are typically the types of environments where it's most commonly acquired.

[Sarah Gregory] So your study is about household transmission. So do we know much about household infections versus hospital or community acquired infections?

[Aaron Miller] We do. So *C. difficile* and infections have been studied both within household environments and transmission in the community more broadly. We've done studies inside households where specimens have been collected and tested for contamination. And so, we found contamination and *C. difficile* spores on various types of household surfaces. But one of the unique features of our study is that most of the studies of household settings have tended to be small. It's also a bit of a challenge to study household settings just because of the relatively low frequency of *C. difficile* infection. So when you look at most of the research in community-associated transmission, it tends to focus more broadly on risk factors associated with CDI (or *C.*

Asymptomatic Household Transmission of C. difficile Infection from Recently Hospitalized Family Members

difficile infection). So the types of characteristics that patients might put them at greater risk for an infection rather than trying to identify those specific infection linkages in the community.

So when it comes to community versus healthcare settings, the bulk of the research has tended to focus on healthcare environments. One, because transmission tends to occur relatively more frequently in healthcare environments, so it's easier to identify and study cases. And then also by the nature of patients just being admitted to settings like hospitals, it tends to be easier to study transmission linkages. So in terms of community and household-associated transmission, it's definitely a bit of an understudied area in comparison to hospital-associated *C. difficile* infections.

[Sarah Gregory] Are these infections increasing?

[Aaron Miller] Yes. So from the early 2000s to around 2010, cases of both healthcare and community-associated *C. difficile* had been increasing. The severity of *C. difficile* had also been increasing as well in the early 2000s. However, beginning around 2010, 2011, cases of healthcare-associated *C. difficile* have generally been decreasing while cases of community-associated *C. difficile* infection have tended to be fairly constant or having perhaps a slight increase in the first half of the 2010s. But in general, the overall burden has ticked down a bit.

[Sarah Gregory] Ticked down. Okay, well that's some good news.

Is there any kind of treatment for it? You mentioned antibiotics.

[Aaron Miller] Yeah. So *C. difficile*, it's both caused by antibiotics, but it's also treated by antibiotics. So the infections do generally tend to be treated successfully with antibiotics, and they can be treated both in inpatient settings and outpatient settings. And so treatment would generally involve discontinuing any of the inciting antibiotics that may have gave rise to the initial infection, and then initiating new antibiotics that are specifically meant to treat the *C. difficile* infection. So typically, these are either oral vancomycin or fidaxomicin. And in rare cases or severe cases, there might be an alternative treatment that might be used, such as fecal transplantation.

[Sarah Gregory] And why did you do this study?

[Aaron Miller] Yeah, so I'm part of a research group here on campus that is primarily interested in better understanding the transmission pathways of *C. difficile* infection. So in particular, one of the areas that we're interested in is better understanding the connection between hospital and community and the environment. So in particular, questions like how much do community-associated cases of *C. difficile* impact the transmission within hospital environments—so, how often do we see cases from the community coming into the hospital—and then vice versa, how often do infections that arise in a healthcare setting impact the broader transmission within the community? And so we've previously done work using similar data to explore how exposure to a variety of different healthcare settings (like other outpatient settings or ED settings) might increase risk for CDI. And we've also looked at how transmission within a household—so when one family member gets *C. difficile* infection, how much that increases the risk for another family member, and then how often does that lead into an infection that presents in a hospital setting. So this is the next step in our research to better understand the linkages between community and healthcare-associated infections.

[Sarah Gregory] Did you have any hypotheses going in?

Asymptomatic Household Transmission of C. difficile Infection from Recently Hospitalized Family Members

[Aaron Miller] Yeah. So there's a wide body of literature that has informed us that we know household transmission does occur. We've studied it and it has been identified in a number of studies, and we know that exposure to hospital environments increases risk for colonization with *C. difficile*, and that we do know this transmission can occur from asymptotically cases (so individuals that are colonized, but don't necessarily have symptoms). So it seemed like all the pieces were there, and our hypothesis was that because we know household transmission occurs, because we know that hospitalization can increase risk for colonization, and that colonization asymptotically can lead to transmission. We thought, "Well, if a family member goes to the hospital, they might become colonized as a result of staying in the hospital. And even if they don't develop infections, if they're asymptomatic, they might come home colonized and then subsequently transmit the pathogen to other family members in the household environment". Our hypothesis was essentially that if we looked at households where there was a recently hospitalized family member, we might expect to see a higher incidence of *C. difficile* infection as a result of this asymptomatic transmission.

[Sarah Gregory] What kind of data did you use?

[Aaron Miller] Yeah. So we used a pretty large data set that represents millions of commercially insured individuals in the United States. So it's a type of data set that's deidentified, and so it's deidentified in so far as basically the data has been stripped of information that might allow us to identify individual households or individuals themselves. So we can't see things like individual names or very specific geographic information where the individual might live, or the exact types of healthcare facilities they visit. But what we do have access to is... we were able to link hospital stays and healthcare records between individuals and a family that might be enrolled in the same insurance plan. So specifically, we were able to see if one family member is hospitalized, we can then ask the question, "Are there other family members that after that after that hospitalization developed a *C. difficile* infection?". And the advantage of the data set that we were working with, like I said, it's very large at representing millions of commercially insured individuals, and because it spans a period of around 20 years, we have a representation of around 6 billion individual enrollment months where we can follow enrollees across time.

[Sarah Gregory] And how did you conduct this study?

[Aaron Miller] So what we did is we essentially aggregated the information that we had from all of the enrollees into what we call, "monthly exposure bins". So basically, in a given month we would look at the characteristics of different individuals, things like age and sex and size of the household, and then we would also look at exposures that occurred in that household in the previous 60 days. So exposures that we looked at were things like, was an individual exposed to an antibiotic in the previous 60 days? Did they receive a gastric acid suppressor medication that might have increased risk? But then, also the primary variable that we were interested in was, did they have a family member that was in the hospital? And then we also quantified the length of time that the family member spent in the hospital.

And then, what we did is we evaluated CDI incidence in these exposure bins and we asked the question...looking at the incidence in households where one family member was recently hospitalized and compared those to households where there was no other family member that was recently in the hospital, and then asked the question, "Was the incidence different between the households where one family member was hospitalized and those where another family member was not?". And the key design to our study that allowed us to ask the question, "Is what

Asymptomatic Household Transmission of C. difficile Infection from Recently Hospitalized Family Members

we are seeing asymptomatic transmission?", is that we excluded households where another family member was recently diagnosed with CDI (or *C. difficile* infection). So if one family member got the infection within the previous 60 days, we would exclude that household because we think that that would probably have been a symptomatic transmission. And then we also excluded households where an individual was in the hospital themselves. So we wanted to exclude the possibility that the individual themselves went to the hospital, and then they picked up the infection there. And so, this left us with a population to study where we think the source of any potential infections that we observed were due to this asymptomatic transmission associated with prior hospitalization in family members.

[Sarah Gregory] So briefly tell us, is there anything else about your study you want us to know?

[Aaron Miller] Yeah. So in addition to looking at this risk associated with exposure to a family member who had previously been in the hospital, we also did include a number of previously established risk factors for *C. difficile* infection. So we tried to control for any of the other explanatory factors that might explain why the incidence of these infections might be higher in certain households. So we looked at things like high or low risk antibiotics, and we found that certain antibiotics convey greater risk for *C. difficile* infection compared to other antibiotics. We looked at gastric acid suppressors—so, what's known as proton-pump inhibitors—and we found that those were associated with increased risk. And then we also looked at things like the age of individuals in the household and showed that there is increased risk with age. And then finally, we looked at the presence of an infant in the household—so, was there a child less than two years of age—and there's been some suggestion that that might increase risk. And so, in general, we found that all the other risk factors for *C. difficile* infections that have been shown were also associated with increased risk.

[Sarah Gregory] What are the antibiotics that increase risk, given in the hospital or wherever?

[Aaron Miller] So the antibiotics, I would have to look specifically at the antibiotic classifications. But in general, what we did is we were looking primarily at the antibiotics that were received in the outpatient setting. The way that the data is constructed that we have access to, we were only able to see antibiotics that a patient received in outpatient settings, not necessarily the antibiotics that were received in inpatient settings. And so, when we grouped the antibiotics together, what we did is we grouped them into high-risk antibiotics—so, antibiotics that are known to be associated with high risk for CDI—and then also antibiotics that were associated with a low-risk for *C. difficile*. And so, antibiotics that would have fallen into the high-risk class would have included antibiotics like clindamycin, fluoroquinolones, cephalosporins, and then some combinations of penicillin. And then the low-risk antibiotics were things like tetracyclines, macrolides, penicillin. I'd have to look back at the complete list, but in general, what we did is we split it up into antibiotics that were high versus low risk.

[Sarah Gregory] I see. So what else did you find from your study?

[Aaron Miller] Yeah. So the primary finding was, essentially, that when we looked at those households where there was a family member who was recently discharged from a healthcare facility, we did in fact find that there was a greater incidence of *C. difficile* within those households where there was a previously exposed family member. And because our study focused on those households where the individual themselves that we were looking at had not been in the hospital previously and there was no prior *C. difficile* infection in that household in

the previous 60 days, we think that the transmission pathway for most of these infections that we were observing was due to one family member who's going to the hospital, becoming colonized, and then coming home and potentially transmitting to other family members.

[Sarah Gregory] Did length of time of hospital stay impact how contagious these asymptomatic people were?

[Aaron Miller] Yeah. So we not only just looked at households who had a previous family member in the hospital, but how long did those family members that were previously admitted to a hospital stay in the hospital. And what we found is that in households where family members had spent more time in the hospital, after they were discharged the incidence of *C. difficile* in other family members was higher compared to those family members that spent less time in the hospital. So for example, if we look at something like the incidence of *C. difficile* infection in those households where another family member was previously hospitalized, if that previous family member was hospitalized for around one to three days—so, spent a pretty short period of time in the hospital—we found that the incidence rate of *C. difficile* in those households was only about 1.3 times higher than it was in households with no hospitalization. But then when we looked at those families where another family member spent 30 or more days in the hospital, we found that the incidence of *C. difficile* in those households was about 2.5 times greater when compared to households that didn't have any family member in the hospital. So it does look like the longer that family members spent in the hospital, the more likely *C. difficile* was to occur in subsequent family members.

[Sarah Gregory] So if these people are asymptomatic, why would the length of household stay matter?

[Aaron Miller] Yeah, so we think this as the primary explanation for this trend is due to colonization risk. So we do know that the more time you spend in a healthcare facility, the greater the likelihood that you'll come in contact with and become colonized with *C. difficile*. So if you spend one day in the hospital versus 10 days in the hospital, you're probably at greater risk to just become colonized, come in contact with *C. difficile* in the first place the more time that you spend in the hospital. So what we think is going on is that the more time one family member spends in the hospital, the greater the likelihood that they become colonized and the greater the likelihood that they bring that pathogen (*C. difficile*) back home with them when they return home.

[Sarah Gregory] So if family members are getting the infection from people who have been in the hospital but are asymptomatic (have no symptoms at all), how is this infection being transmitted?

[Aaron Miller] Yeah, so we think there's three possible explanations for how the transmission is actually taking place (the exact route of transmission), one that's probably most likely and then a couple that are probably less likely. The most likely explanation is what we hypothesized going in, is that one family member is going to the hospital, they're...becoming in contact with *C. difficile*, they're becoming colonized, and then when they return home, even though they don't have the infection themselves or not showing symptoms of the infection, once they return home, they're shedding the bacterium within the household and then that's allowing infection to occur in other family members.

A second, and this is sort of related, a second way this might be occurring is that it could be that those family members are actually developing a minor or a very mildly symptomatic infection themselves. So maybe the family member who went to the hospital and came home, even though they maybe weren't diagnosed with *C. difficile* infection, maybe they're having very mild symptoms—they might be having very mild diarrhea or something. And so, it could be the case that they do have an infection themselves, but it is just being missed or it's just not being recorded. So that's a second possible route.

And then a third possible route is that it could be that the family members who are becoming infected, what's going on is that they're actually visiting their family members when they're in the hospital, and so they might be picking up the infection in the hospital themselves. We think this is actually probably the least likely explanation, and the reason that we think this is probably not the explanation and instead its asymptomatic transmission is that we've done a number of sensitivity analyses methodologically where we've tried to explore the possibility by varying the time between cases. So looking at was the family member still in the hospital (the other family member who was previously in the hospital), were they still in the hospital or had they been discharged yet, and then looking at how that risk changed. And we think that methodologically, it looks like the most likely explanation could be asymptomatic transmission.

[Sarah Gregory] Okay. So you're saying people asymptotically come home and they shed it, and other family members get it. But I mean, specifically, how does that work? Shedding how? And how is the other family member getting it? It's gastrointestinal. Is it through food? Is it unwashed hands? Is it toilet seats? I'm just trying to understand.

[Aaron Miller] We would think that it's probably through the same mechanistic action as a symptomatic infection. Individuals who are asymptotically colonized have been shown to transmit. They might not transmit the pathogen as readily as, for example, someone who's asymptomatic and may be having severe diarrhea, but it would probably still be transmitting through a fecal-oral route. And so the household environment might just become contaminated through that same process. And so it could be through unwashed hands, through food, various ways that the pathogen could be ingested by other family members.

[Sarah Gregory] And how can the spread be stopped?

[Aaron Miller] Yeah. So in general, I think our results suggest a number of possible avenues where we might think about preventing the potential spread of infection. The first is that assuming that these infections are being generated through this asymptomatic transmission pathway from prior hospital stays, it would suggest that the infection control practices and efforts to curb the spread of *C. difficile* within healthcare facilities could also have a subsequent benefit within community transmission as well through those patients that are discharged back into the community. So specifically things like proper hand hygiene, wearing gowns and gloves, properly cleaning facilities, and cleaning shared spaces within healthcare environments could have an external benefit on preventing potential transmission back into the community from those patients that might become colonized in the hospital stay and then return to the community. It also suggests that improved antibiotic stewardship, both within the hospital itself but also within the broader community, may play a role in preventing transmission. Like I said, we did find that outpatient antibiotics were a risk factor for *C. difficile* infection. So again, if patients are becoming colonized in the community due to this asymptomatic pathway would suggest that improved antibiotic stewardship could also play a role.

Asymptomatic Household Transmission of C. difficile Infection from Recently Hospitalized Family Members

And then, lastly, I think just a broader awareness of this potential transmission pathway associated with prior hospitalization in family members could suggest ways for preventing spread within households when one family member has been in the hospital for a while. So maybe things like increased household hygiene and cleaning practices within a household (washing your hands more, cleaning surfaces more) after a family member has been discharged might also be one way to avoid potential transmission after a hospital stay.

[Sarah Gregory] Is there a timeframe for this? I mean, how long do you think...were you able to tell how long a person might continue to shed this *C. diff* after they are home?

[Aaron Miller] So it's probably in the time period closest to when the family member is discharged. So one of the things that we did do as part of this study is we did a sensitivity analysis where we looked at how our results might change if we opened up or expanded that window of time that we looked for risk after a patient has been discharged. So the primary result that we present in the study are within 60 days. So we looked at whether or not a family member had been in the hospital in the prior 60 days, and then we also opened that window up and went back and looked 90 days in the past, so that would capture family members who have been in the hospital between 60 and 90 days. And what we found is that when we opened up that window, there was still this increased level of risk, but it diminished slightly. And so, we think that as you move beyond 30, 60, 90 days, this risk probably tapers off quite a bit. And this is consistent with some other research that we've done where we've tried to parse out where, what's this temporal pattern that we see when it comes to risk. You have to look back 180 days or 120 days and 90 days. And what we find is typically the highest level of risk occurs within a 30-to-60-day period. So certainly after a period of time, the risk will diminish significantly.

[Sarah Gregory] But that's actually still quite a long time for the average household to keep this in mind, that they have to keep being aware of practicing good hygiene.

[Aaron Miller] And I would just follow up with I do think that this is probably an area that needs to be explored in the future. It's something where we could try to really parse out what that exact time period is. It might just be that the most important timeframe is maybe the first couple of weeks after a patient is discharged. But I think that the risk could persist for a little while but trying to figure what that exact timeframe might be is a question that we need some further investigation.

[Sarah Gregory] Now, what are the main implications of your study? What does this add to what was already known about infection from *C. diff*?

[Aaron Miller] Yeah, so I think that the main finding helps shed some light on the potential transmission pathways of *C. difficile* infection. Although shared environment (so, things like healthcare facilities, patient rooms) have really been implicated in the spread of *C. difficile*, when we've done certain types of studies where we've tried to genotype cases that look like they might be epidemiologically linked—so, cases that occur in either close in proximity in time, meaning that they occur maybe within a few weeks of one another, or they also occur in close spatial proximity (so in the same facility or maybe in the same city—often times when the genotype cases that appear to be epidemiologically linked, we find out that they are in fact not genetically related. And so there's a body of research that's suggested that one potential explanation for these missing genetic links that we sometimes find between cases could be asymptomatic spread. So there could be intermediary cases that are asymptomatic that we don't identify that allow an

infection to transmit from one individual to another without being that direct link. And so, I think that our study helps to shed a little bit of light on this by highlighting the potential household asymptomatic linkage as being one explanation.

And then, I think a second indirect result of our findings is that it does suggest that healthcare facilities themselves may serve an even broader role in the transmission of *C. difficile*, rather than just focusing on the cases that occur within the boundaries of a healthcare facility. So this suggests things like infection control practices in one healthcare facility might have broader impacts in the community at large. Healthcare facilities might also help to shape the reservoir of community-associated CDI cases that result from patients being discharged from them. And so, I think that that's the second area that our study helps to shed light on.

[Sarah Gregory] Were there any surprises?

[Aaron Miller] In a way, I think the overall result was a surprise. Even though we had hypothesized this going in, and even though we knew that all the pieces were there, we knew that asymptomatic transmission occurs, we knew that transmission occurs in households, and we knew that the more time you spend in the hospital tends to increase your risk for exposure and your increased likelihood of becoming colonized. So it really was consistent with what was already known. But given that it was a new result, it's always surprising to find something new, even when it matches your expectations. And I would say, that's also particularly true with being able to find that dose-response effect between the more time that a family member spends in a hospital and the increased risk associated with longer duration stays, we found a very clear dose-response pattern. So even though it matched our expectations, it was certainly surprising to be able to detect it.

[Sarah Gregory] Must be a very nice feeling to have your hypotheses pan out.

[Aaron Miller] Yeah, for sure.

[Sarah Gregory] What about challenges? What were the challenges?

[Aaron Miller] Yeah, so I think from the context of studying households, the advantage that we had was that we had this really large dataset. Because even though we found this increased risk associated with hospitalization, hospitalizations just in general (when you think about a typical household setting) are relatively rare. And then, infections resulting from those hospitalizations, it's even rarer. So in order to be able to detect the effect that we found, we really needed a lot of data that spans lots of households in a long period of time. And so, the administrative claims data that we had access to allowed us to detect this effect in the first place. But the tradeoff was, is that a lot of the granular information on household environments that might allow us to better understand transmission risk within those environments is not necessarily collected in these data, primarily because these data are deidentified to protect enrollee privacy. And so, factors like household size, things like maybe the number of shared bathrooms, the total time that family members spent in the household versus spent out of the household, different things that might affect how two households that might look the same from an insurance claim standpoint might differ dramatically in terms of transmission risk, that information just was not available. And so, it's a bit challenging to infer the other factors that might impact transmission in the household. So that's, I think, one of the biggest challenges with these data was information that was missing that you might be able to collect through other channels, whether you're doing direct collection or surveys of households themselves.

Asymptomatic Household Transmission of C. difficile Infection from Recently Hospitalized Family Members

[Sarah Gregory] You already mentioned a couple, but based on what you found, what future studies are needed?

[Aaron Miller] Yeah, so I would point to three dimensions where I think future studies could really better inform on the results that we found. The first would be, like I mentioned, the information on the structure of households that might inform the risk within households would be one area that could inform on our results. Another area would be direct collection of laboratory results or genetic specimens, so that we could actually link cases in one family member and transmission to another. So I think more granular information on households, both in terms of the household structure and the pathogen itself, could help inform these results.

Another area would be to ask the question, do we see similar effects from other types of healthcare facilities? So in the past, we've shown that exposure to emergency departments or outpatient clinics can increase risk for *C. difficile*. And so, you could ask the question, "Well, if family members spent a lot of time in other outpatient types of facilities, does that also contribute to risk?". So we could look at those types of healthcare facilities. And then a third area where I think we could extend upon these results and future studies would be to evaluate other types of community settings following patient discharge. So do we see similar effects in things like workplaces or schools or other community settings where individuals might return to after leaving a hospital facility? Do we also see an increased risk in those facilities, as well?

[Sarah Gregory] That's a really interesting idea. Given everything you've said and learned, it doesn't seem like there would be a reason that it would not transmit in those places, right?

[Aaron Miller] Right. Yeah, no, it's definitely an interesting area, I think, for future research. I think the biggest challenge there will be trying to identify the types of data that would allow you to measure these types of settings, as well.

[Sarah Gregory] Right. Yeah, probably might have to be a different kind of study, I don't know. Tell us about where you work and what you do and what you like most about it?

[Aaron Miller] Yeah. So I'm a research assistant professor in the University of Iowa College of Medicine. My background is actually...one of the things I like best about my work is that my background is actually a data scientist, not directly in healthcare, although I do have an interest in healthcare-related issues, and in particular, infectious diseases. But my background is more quantitative in nature. And so, I think my position allows me or provides me the ability to explore how I could use various quantitative techniques and large data sources to approach problems in healthcare, particularly infectious diseases, and novel avenues. And so, my position provides me the freedom to address a variety of different research questions using different quantitative techniques, but it also provides me the access, being in a college of medicine, access to the clinical expertise to help guide and inform my research.

[Sarah Gregory] And on a personal note, what do you enjoy doing in your free time?

[Aaron Miller] Mostly when I have free time, I enjoy spending time outdoors, whether that's camping or recreational activities outside (kayaking, biking, hiking). Probably are my biggest hobbies when I have free time.

[Sarah Gregory] Interesting.

Well, thank you for taking the time to talk with me today, Dr. Miller.

Asymptomatic Household Transmission of C. difficile Infection from Recently Hospitalized Family Members

[Aaron Miller] Yeah, thank you very much for having me.

[Sarah Gregory] And thanks for joining me out there. You can read the May 2022 article, Risk for Asymptomatic Household Transmission of *C. difficile* Infection Associated with Recently Hospitalized Family Members, online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

[Announcer] For the most accurate health information, visit [cdc.gov](https://www.cdc.gov) or call 1-800-CDC-INFO.