Oral HPV Infection in Children, Finland

[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. Stina Syrjänen, a professor and chairman emerita at the University of Turku and chief physician in the Department of Pathology at Turku University Hospital in Finland. We'll be discussing the transmission and prevalence of oral HPV infection in children.

Welcome, Dr. Syrjänen.

[Stina Syrjänen] Hi. It's a great pleasure to speak with you. Thank you for inviting me. This is a very nice topic for me.

[Sarah Gregory] Well, we're very glad to have you, indeed. So to start off with, why don't you tell us what HPV is?

[Stina Syrjänen] Yes. HPVs are actually, they are small nonenveloped DNA viruses belonging to big family of *papillomaviridae*. There are more than 200 different HPVs known by now. But these viruses can infect only human beings. The target of the virus is epithelial cells either in the skin or mucosa (like in oral cavity or in the genital tract). However, I think it's important to know that in this context as well that cats and dogs have their own papillomaviruses (as have many other mammalians), and also the birds, snakes, reptiles, and fish have their own papillomaviruses. These cannot be transferred to human beings (or they don't infect human beings). And these viruses are one of the oldest ones. So, the evolution started some 300 million years ago. And that has made them (especially the high-risk type HPV16, a very special virus) hard to control the infected cells, and finally, to cause changes which might progress to cancer cells.

[Sarah Gregory] So, over 300 million years old, it's probably not a worry that they'll start being zoonotic and the animal version will transfer to humans?

[Stina Syrjänen] Yeah, that's actually the development of so-called mucosal viruses, which were not at that time in the human beings, but in the mammalians started some 10 million years ago. So, that is a really long, long evolution. And from 300 million years ago, these viruses were just the normal flora of the ancient reptiles.

[Sarah Gregory] HPV is commonly known as a sexually transmitted infection, but apparently people can get it through ways other than sex, is that right?

[Stina Syrjänen] Yes. There is plenty of data on nonsexual HPV transmission. And the route of HPV transmission is primarily through skin-to-skin or skin-to-mucosa contact. But children, like adults, can acquire HPV infection from siblings or from other householders, relatives, or friends, just likely digital contact. And then we have this other mode of transmission, which is autoinoculation, which means that one person transfers his or her own infection from one site to the multiple other sites (for example, from genital tract to mouth via hands or from mouth to the genital tract). And this is also… the saliva might be a very important liquid for transmission, and it can transfer the viral particles to a new area of the same oral mucosa. There is actually one interesting study from (animal study), which is done with rabbits as they have also this mucosal HPVs. And it's done already, 1942. This is actually one of the most important studies telling

about the natural history of papillomaviruses in rabbits and how they can be transmitted through the mouth and how they can remain there. But this has the ability on the human being side, yes.

[Sarah Gregory] So how contagious is it from person-to-person?

[Stina Syrjänen] So we said HPV from person-to-person, so it can be either sexual transmission (or this is also called horizontal transmission). And then we have vertical transmission, which is actually that we have transmission which is coming from the mother. And there are three different modes of vertical transmission which is related to the time of transmission. There can be so-called periconceptual transmission (which is during the time around fertilization), then prenatal transmission during pregnancy, and perinatal transmission during the birth or immediately thereafter. And then there's horizontal transmission, is the spread of the virus from one individual to another, usually through contact with bodily excretions or fluid such as saliva and moist things in genital tract.

To get an HPV infection, the transmitter has to have a lesion, which is a virus-producing lesion which are shed from the surface of the lesion. And these viral particles have to find an access to wounded skin or mucosa in another person, resulting in HPV infection. So if the skin or mucosa is totally healthy, there will be no infection.

[Sarah Gregory] I see, okay. What are the symptoms of oral HPV?

[Stina Syrjänen] Many of oral HPV infections are asymptomatic. So when just taking the saliva and making the HPV testing, you might find the viral DNA. And even with careful clinical inspection, you might not find anything. This is true also for the genital tract. However, there are clinical lesions as well, and signs, these are overgrowth or warty lesions (lumps), which are mostly caused by benign HPV types like 6 and 11, similarly as found in the genital tract as well. And then there might be tiny thickening of the mucosa, which looks like a more whitish area than the surrounding normal mucosa. Then there's tiny growths (which might be only a size few millimeters) can be found also in the gum or even the gum pockets (so this is the soft tissue which is against the tooth).

[Sarah Gregory] How is it diagnosed? You mentioned nasal swab. Is there other ways?

[Stina Syrjänen] Yeah, I think the basic thing when we are thinking oral HPV lesions or oral HPV infection, is a careful clinical examination of oral mucosa which should be done regularly—always when you are with dentist or if GP is looking in the mouth, he or she should look very carefully at the whole oral mucosa. And very important is to look specifically at the tongue, also the base of the tongue, this is actually part of the oropharynx, which is one of the sites (together with tonsils) mostly prone to HPV-associated cancers during a long-lasting infection.

If there is a lesion, what you might think that this is an HPV lesion. So actually, another possibility is that they can brush sampling of cells on the surface of the lesions and then make the HPV testing. Or the best thing is you should always do—take a biopsy or take the whole lesion away and send to the pathologists to make a final diagnosis of the lesions. But in the oral cavity, some of these warty lesions (even they are HPV6 or 11) possibly might have a bit different histological signs, and they might be not identified as typical HPV lesions.

The other thing is there are plenty of data of gargle samples, but this is actually not a recommended test for the routine use. You might get an HPV-positive result, but then we don't know where the actual lesion is, or it can be very tiny, tiny area where the viral particles are all produced. And this gargle sample widely used to recognize patients at higher risk for HPV-associated malignant lesions, especially with carcinoma. So if you have had one gargle sample positive for HPV16, then after six months or one year if it's still positive then it's very important to try to identify where the lesion is located and to get the biopsy from that area.

[Sarah Gregory] I see, okay. Well, are there treatments for oral HPV?

[Stina Syrjänen] Yes. The treatment for HPV infection itself, we don't have that kind. And this is true also for the genital tract as well. But the normal treatment is that if there is a warty lesion, our plan then is the surgery. This lesion can be excised totally, it can be very often…it can be treated by laser or cryosurgery. But in all cases, the biopsy or the samples would be sent to pathological or histological examination to get the final diagnosis, to find changes which might suggest an early dysplasia, meaning that it could be like a precancer lesion. Usually these warty lesions are benign and they might reoccur, but very seldom there are any association with malignancy even during the long follow-up time.

[Sarah Gregory] So, what are the possible health outcomes if oral HPV goes untreated or unremoved?

[Stina Syrjänen] Yeah, I think that if it…first I think these—benign types still (condyloma and papilloma) mostly caused by HPV6 and 11—so they are viral producing lesions, and there will be (over time) shedding of the virus in saliva, which increases the risk for a new HPV infection either in the other part of the mouth or even in the oropharynx and especially in the base of the tongue and tonsils. Furthermore, this person can transmit the virus to other persons, so this horizontal transmission is quite common. And this occurs via saliva during kissing or sharing the items in the household, like towels, toothbrushes even, and spoons.

But the big question is then the same as in the genital tract, is that chronic HPV infection or persistent HPV infection: which are usually associated with high-risk HPV genotypes or strains HPV16 and the others? And if these high-risk viruses are persistent, this is a mandatory factor for monitoring the transformation and that additional cofactors are needed. And usually when we are thinking the mouth, it’s smoking and heavy drinking that we are discussing with the adults. And we might also (in the oral cavity) we will see these different steps—so-called low intraepithelial neuroplasia and high-grade lesions or high intraepithelial neuroplasia—or they are also called mild, moderate, and severe dysplasia. But that kind of lesions we don't find in children, so this is only for the adults.

[Sarah Gregory] So how are cases of HPV tracked in Finland? Is there a case-reporting system set in place?

[Stina Syrjänen] Yeah, unfortunately, neither HPV infection in any site of the body or benign HPV-related lesions are tracked. And I think this is something which we would urgently need at the moment. We have the Cancer Register, which has started to register also the so-called precancerous lesions in the head and neck region, including oral cavity dysplasia (which I described) or (they are also called) this squamous intraepithelial neoplasia, in addition to

carcinomas as well. But it will take many, many years, in case, before we can get any reliable data on that.

[Sarah Gregory] Your study was particularly about HPV in children. Why were you investigating this?

[Stina Syrjänen] This is actually a very long story dating back to late 1970s when I had my private practice, and one of the families (which I knew quite well), they took their 6-year-old child with them because she had something in the mouth and I could identify a typical condyloma. And when looking at the literature and textbooks, it was always related to incest or sexual transmission, and I couldn't believe all that. So at the same time, in genital tract, these Koilocytes typical HPV in associate with markers in cytology and histological sections were connected with dysplastic changes. So the idea that HPV could cause cervical cancer was very popular, and that was then finally found and described by zur Hausen. So, then we had the possibility to have good antibodies against human papillomavirus, and we thought we could use this antibody to look different oral lesions, and not only oral lesions but also the head and neck lesions in the throat and in upper airways. And we could identify HPV in oral benign lesions in some of the cancers. And when we could get that kind of picture, what we worked with, ten years during the 80s, the next thing was that if you have HPV in the mouth, where do you get it? It's not only sexually transmitted.

So, the first thing really was that we started to look women who had genital HPV infection: do they have the same type also in the mouth? And we didn't find much association with these two sites. Then the next step was to look at the partners, and that was in the early 90s. And then we had hoped that we had this look at the newborns. And that time we had to aspirate when the baby was born, and the nasal/mouth area was well-cleaned by aspirating the nasopharyngeal area. And we could get that sample for HPV testing and we could find the same HPV types in the newborn mouth (or in this case, in nasopharyngeal area) than in mother's genital area.

Then we had also possibility to look at children (older children) who were born to mothers where we knew of the HPV at the time of delivery. And after all that data, I came in a new idea, or it was not an idea, that we had to do a family study to understand HPV transmission in families and not only to look at the genital tract of the mother and the mouth of the newborn, but looking at both the oral cavity and genital tract in the whole family and try to get some kind of better overview on this whole transmission mode.

[Sarah Gregory] You mentioned some differences, like smoking and drinking alcohol in adults, leading to a certain kind of HPV (oral HPVs). Are there different HPVs in children than in adults other than that?

[Stina Syrjänen] Yes, I think this is something which is actually not discussed at all and not even thought is that if you are thinking of HPV infection in children, and especially in these newborns. So these children will get their dentition (first the primary dentition and then the permanent dentition), and this will cause both the trauma and wounding in the mouth. Nobody has ever looked actually whether they could have any association with HPV prevalence in children, comparing the time when there is the whole primary dentition ready or when they have cut, when all permanent tooth have been erupted.

But otherwise if we think of what kind of other differences could be, so there are no specific studies on this. But we could put this question also other way around: that do we find any big differences in HPV in oral cavity than in genital tract? What we know is that the same mucosal genotypes or strains are found in both sites, but there are more skin types with beta-papillomaviruses detectable in the oral mucosa. And this is because of the anatomy of the mouth. Part of the mouth, like the gums and the hard palate, are being covered by heavily keratinized mucosa. Then in mouth, we do get much more small ulcers and erosions, and if there is HPV (especially the viral particles in the mouth) then most probably one might get the infection.

And then another thing which I would like to add is also that actually we have one specific lesion in the mouth which is called focal epithelial hyperplasia (so-called Heck's disease), which is mostly only located in mouth, in oral mucosa, and it's caused by HPV13 and 32. These lesions are coming and going, and sometimes people think that they are typical warty lesions. But they are hereditary, so you will find somebody in the family who has similar lesions. And they are most prevalent among Eskimos and Indians and also in South America as well as the USA. And high prevalence for these kind of lesions are found also in Greenland. And nowadays, we know that there are certain mutations which are associated particularly with this disease, which is called Heck's disease, and it was recognized, early 70s already (1970s).

[Sarah Gregory] I just want to clarify something for our listeners. Just, I want to make sure people understand that HPV in genital and oral is not the same as herpes, right?

[Stina Syrjänen] Yes. So, HPV is human papillomavirus and we have the mucosal types, which actually the mucosal types (which is like 6 and 11, 16, and 18) they usually never infect skin like the skin types, like type 1 and 4 and 2. They can infect oral mucosa because part of the mucosa looks histologically exactly the same as the skin. And herpes simplex virus has nothing to do with totally different viral source, which is human papillomavirus.

[Sarah Gregory] Okay. Is there a specific strain of HPV that occurs the most in children?

[Stina Syrjänen] Actually, they are the same types as found in the genital tract. But surprisingly, what we have found in adults: HPV16 is the most common strain in mouth. And following our study, earlier we have found that HPV6 and 11 (which are the most common benign HPV types) are the next most prevalent, and also HPV18, 31, and 33. And importantly, 33 is actually a so-called 'high-risk' virus also found in the genital tract. But when we think then, maybe I shouldn't have jumped to adults after all, if you like that if I give my answer on the children.

[Sarah Gregory] Yes.

[Stina Syrjänen] HPV16 is the most prevalent strain in head and neck carcinomas. While in the genital carcinomas (cervical carcinoma in women) we can have many different types, so the role of HPV16 is not as clear as we can found in the head and neck region. So, the strains are the same in children and adults, but the difference from the genital tract is that we have also in the mouth so-called 'skin types' which are beta-papillomaviruses.

[Sarah Gregory] How do infants and older children acquire HPV? How is the mother’s HPV status involved in this transmission?

[Stina Syrjänen] The mother might be the main transmitter of her offspring, either vertically at fetal time or at birth or later at early childhood. We have earlier found that there was a high

concordance between newborn oral HPV and maternal genital HPV (meaning the cervical HPV). We also found that oral HPV in newborns was most significantly associated with HPV detection in placenta and cord blood. This means that the newborn has actually caught his or her HPV infection at the fetal time, or the viral particles of the virus can have been in the amniotic fluid as well (we have never studied amniotic fluid). There is also some evidence that HPV transmission can occur via breastmilk. And later, the transmission can occur via mother's hand or saliva (so as a typical horizontal mouth-to-mouth transmission). So to conclude, HPV can transmit from the mother to her offspring both vertically or horizontally. Additionally, in case of horizontal transmission in children (as we discussed already earlier), this can occur via caretakers and other family members and other kids.

[Sarah Gregory] Would you explain about the different prevalence rates at different ages you found in your study?

[Stina Syrjänen] Yes. We actually, when we looked at HPV prevalence, the figures were highest at birth and lowest at the age of three years. And then the prevalence of HPV increased again at the age of six years. At birth, it was nearly 23% of the newborns had HPV and this is most probably because the mothers also have plenty of different strains of HPV in the genital tract. And if the child is delivered or had a vaginal delivery, then I think this is a very likely explanation. However, when we looked at children born by cesarean section or by vaginal delivery, we didn't see any differences. So, it’s meaning that HPV transmission can occur also vertically during the fetal time.

And then, thinking at the age of three years when only 8.7% of the children had HPV detectable in the oral mucosa, this could be explained by the fact that most of the earlier HPVs have already cleared. So, you might get an incident infection which disappears quickly, or maybe there is only virus without causing any HPV infections (so it's on the surface or in the saliva somewhere). But then, based on our study, most of the HPVs cleared or healed during the one or two years. And once again, at the age of six years the children had more HPV detectable in nearly 20% of them (we could get HPV-positive tests). This could be explained by the fact that then the children, they have other kids to play and that could be like a typical horizontal transmission. This is partly speculation because this has not been studied. And yeah, I think this is what we find. But we have to remember that HPV prevalence is more related also to the sampling method, whether it's a gargle sample it also takes HPV from the oropharyngeal area (from the tonsillar area, from the base of the tongue) which is not part of the oral cavity, and then depending on the HPV detection method. And we use a very sensitive nested PCR (meaning double PCR), and we made this because we expected to find only few infected cells which might have very low viral copies among many normal cells. And this is most probably true as other researchers have identified the same thing as well.

[Sarah Gregory] Why is it important to know about these infections in children versus in adults?

[Stina Syrjänen] I think it's very important. So with the whole natural history of HPV, first our data and the data from other studies as well indicate that HPV can be detected in children. And now we have got some estimation of the HPV prevalence in children. We have also identified what types can we find, do we have the same types as the adults, and from where they will get the infection? And the most important thing is the outcome of HPV infection. So if the child has an HPV infection, which would even result in a warty lesion and then they disappear, it would

mean that this child had already an immunity to HPV. Now many times people start to think HPV as a sexual transmitted disease at the time when the girls and boys do get this infection (is around the age of 15–16). However, this would totally ignore the time (the first 15 years of life) which might be critical for HPV immunity.

[Sarah Gregory] Tell us briefly about your study now. Anything you haven't covered?

[Stina Syrjänen] Yes. We established a family study already in 1989 at the Turku University and Turku University Hospital, a very close cooperation with Department of Gynecology, and actually the gynecologist recruited the mothers to come with their spouses when they came to their regular checkup at the department before delivery. And our aim was really to understand the natural history of HPV in families and especially get more information on the HPV infection in children.

This was actually originally planned to be a three-year study but we quickly realized that we should have a longer follow-up. The parents had their first visit before delivery (the mother was at her third trimester), and then the newborns were followed totally in our study now for six years and they had nine visits. Totally, we could get 331 children. And in the present study on oral HPV in children, we included 324 children, and actually we had 2,545 oral samples for HPV analysis, which was plenty of work, especially at the early years. Always when we had the visits for the children, so the children came together with the mother or the whole family participated in the visit because we took samples from the whole family—having the genital sampling, oral sampling, blood sampling, and then the placenta of delivery—and all this, questionnaires about the history of sexual life. And we later sent a questionnaire for the children at the age of three years about the different diseases (what kind of diseases they have had and so on).

And to continue, so we have just currently finished with the month about HPV serology in this cohort (in these children). And what we can find (which is known for other viruses as well) that the maternal HPV antibodies will be transferred to the newborn and they are stable for the first six months. This has been found also for herpes and cytomegalovirus as I expect by many other researchers. But what was also really important to find to support our data here that the children had their own seroconversion, meaning that the virus coming somewhere (or the virus would have become a persistent one) had resulted in a seroconversion reproduction of HPV type–specific antibodies, which is a very important aspect as well, thinking of the outcome of the HPV infection in children.

[Sarah Gregory] Are there any other particularly interesting points that you would like to point out to us?

[Stina Syrjänen] Yes. I think this is one interesting thing that not only could we identify which kind of HPV types that are present in the oral cavity and the association with the mother, but we had also 41% of the children were always HPV-negative. In none of the nine visits we could identify HPV in any of the samples taken. And the other important thing is that nearly 15% of the children had persistent HPV infection, and HPV16 was the most common type to become chronic or persistent infection, followed then by HPV18 and 33, and then HPV6. So, this means that if the child has HPV16 somewhere (which is staying there), there might be a risk later for an HPV-associated lesion which might become a precancerous lesion.

Or then, another important topic is that is the virus only a latent virus which could reactivate every now and then? And when I mentioned this old animal study, they could identify that there were some of these lesions (the papillomas) in the tongue which disappeared. But several years afterwards when just making a tiny irritation on the surface of the mucosa, they could reactivate the virus and the animal got a new papilloma exactly at the same site. So these are important questions for the future, and it also might explain some clinical figuration of what we can find in elderly people when they say they are having genital lesions without having any sexual connections for decades or years.

[Sarah Gregory] You did a longitudinal study rather than a cross-sectional study. Are there advantages to choosing this one over the other?

[Stina Syrjänen] Yeah, I think the only way to understand the natural history of HPV infection is really to make a longitudinal study starting when the infant is born or even earlier when they do not have any previous history of HPV infection. Cross-sectional studies make an observation only once, and it cannot provide any data of the outcome of the infection. We used so-called GEE modeling of the longitudinal data, and this takes into account the individual variation of each study subject so we know what exactly happened with this child that we are following. And the same we have done for studies for oral HPV mothers or fathers. Unfortunately we didn't have any other family members like the siblings of our index child. But 55% of the children were firstborn in our group.

[Sarah Gregory] You touched on this before, but are certain people less susceptible to HPV than others?

[Stina Syrjänen] Yes. If there is an HPV infection which if you think a child who has had seroconversion to HPV, and these antibodies would be neutralizing antibodies, that would mean that next time when she or he will get a new HPV infection these antibodies would protect him or her. And even in our time in the study, we have found that part of the children born to HPV-positive mothers and those who had mothers who had HPV detectable in placenta or the child had a cord blood–positive sample, they had already HPV-specific cell-mediated immunity even they have had no sexual contact, they are not being vaccinated like now in our study as we started before the vaccines were available here in Finland and before we had any governmental decision of HPV vaccination of young girls.

But the question could also be reversed: are some people more susceptible to HPV than others? And I would say yes. We know that immunosuppression as a result of organ transplantation or HIV infection increases the prevalence of HPV significantly. And especially organ transplantation is frequently associated with warty lesions in the mouth, both in young children and in adults.

[Sarah Gregory] What were some of the challenges that you came across? I’m sure keeping track of young participants for the six years wasn’t that easy.

[Stina Syrjänen] Yes, that was really a big question for us. But we got these families from the Department of Gynecology and they had their first visit at the same department and we had a very skillful clinical nurse and an excellent gynecologist (Marjut Rintala) who actually made her PhD on the preliminary results from our cohort. But surprisingly, the families, they were very interested in the topic and also they could all the time get plenty of new information on HPV.

And even they started to have their own discussion via internet that "you don't have to worry about HPV, just go and make a regular check-in." Because these women, they got their pap smears and HPV testing much earlier than anybody else in our country. So they had a very happy feeling to participate in our study.

And actually this study will continue. Now these newborns, they are approximately at the age of 30, and one of our researchers who became a professor at the University of Tampere in gynecology, so she will continue and now will look at what has happened when these tiny children are adults. They have had their own sexual life and maybe they have their own children. Can we find still some indication that the HPV is there in the family, and what has happened with HPV infections which was found in the genital tract and the oral cavity? And all the participants, actually, who had a persistent HPV16 infection, gave them note that you should go and visit your gynecologist or then contact our department in case you want that we make a careful examination, just because of this infection (even though we had finished the study). So I think this might be the main reason.

But the funding was the big problem for us because we started this project without any funding. And we had some support from the university, some being from the hospital, but all this was established in making the laboratory methods, testing them. Having also technicians to work with, that was really problematic because all the gynecologists and myself, we also had our daily duties at the university or at the Department of Gynecology, so none of the seniors had specific time to concentrate on this study as well.

[Sarah Gregory] What further research do you think is needed?

[Stina Syrjänen] I think the most important thing for the whole HPV research is that we should have a method how to calculate papillomavirus. Because only through calculation of the virus, we will get more data: how to classify what is an acute infection, what is a latent infection, what is a chronic infection—like what has been done for many other viruses. Like with herpes viruses, we exactly know when the virus isn't active, when the virus is in the latent state, and when you have a chronic infection. The same is for hepatitis B. Quickly after this problem was solved, it's now a routine when a patient comes with hepatitis B infection, they exactly know that this patient had had the infection but it has been cleared, this person will be a highly transmitting person or then whether it's a chronic infection, which is also (with that virus) a risk factor for liver cancer to come.

And then, when we could, because now we have no good means to say what is a persistent infection. Whether it's like that you have several sequential HPV testing done, and then if two samples are positive, then you have a persistent HPV infection. And then we can always discuss if this is just a reactivation of the old infection what you have got, or is it a new infection coming from the family. And as published, we don't have these categories. It's very difficult to read different papers and to make a final conclusion. The other thing is that the HPV immunity, the time when HPV-evoked immune recognition occurs, is it in early life? Is it later? Because these are the key questions in viral infections. And they are still somehow unsolved questions.

And then finally maybe one that you might have a group of children and adults which are tolerant, so it's like the own body doesn't recognize HPV as a foreigner or foreign antigen. And then there will be no immunity against this virus, and maybe not even the vaccination would help in this situation.

[Sarah Gregory] Your results have several major implications in HPV vaccination programs. You want to tell us briefly about that?

[Stina Syrjänen] Yes. I think even though we are partly speculating, that if a subgroup of children can acquire persistent infection, then the timing of HPV vaccination is important. We are speaking about the prophylactic vaccination, and it should be given before the person has got any HPV infection. However, as I told you earlier, not only we but others have also found that maternal HPV antibodies are transferred with a newborn, which might protect the newborn at early age, but according to common thoughts in this childhood viral infection. So the best option would be that the mother exposes the child with a small (or the fetus with a small) DNA amount, and the infant is born both with the viral antibodies and then viral DNA. However, the adverse situation could be that if the mother has just got their HPV infection during the pregnancy, she doesn't have any HPV antibodies because we need at least six months to develop the IgG antibodies which can then go through the placenta. And then the infant is on its own having the virus. If it's only viral DNA it might not be important, but if there are only viral particles then she has a risk (or he has a risk) to have a chronic HPV infection. But this is speculation, and I think that this is (as you asked) where should we need further research, and immunology is one of the most important aspects.

And we have some evidence from vaccination with hepatitis B, even if totally different virus, but it is known that chronic infection in adults, actually, this infection might heal and might disappear. But if the child....and the chronic infection occurs not frequently if adults will get the hepatitis B infection. But if a child will get a chronic infection, it will lead to liver cancer in 30 years. And now it has beautifully shown that the newborns who have hepatitis B infection which is transmitted by the mother, then vaccination at early age after the delivery will protect these children from liver cancer. And those who were not vaccinated, these children got liver cancer after 30 years. So with children, the hepatitis B infection results frequently to chronic infection, which very seldom happens in adults. And that gives some kind of similarities with HPV, but this is total speculation at the moment.

[Sarah Gregory] So if a person has HPV but doesn’t know it, how does getting the vaccine impact them?

[Stina Syrjänen] First I would say that now when so many young women are vaccinated and they are vaccinated before they become pregnant, so automatically they have much higher antibody levels. And it has been already shown that vaccinated women have a five-fold higher antibody levels, which are transferred to infants as well. So these newborns have a much higher amount of antibodies which can protect them at early childhood. But then we know actually now that HPV, if you have an HPV infection and it was discussed that this vaccination would not help and this discussion is ongoing, but currently HPV vaccines are used in a way which is off-labeled use of vaccine. If a person has a laryngeal papilloma either in early childhood or in adults, so meaning that it's not really, it's not a lesion which becomes malignant but it's a papilloma which is shedding all the time plenty of virus. And some of the infected patients with laryngeal papillomas, they will just get new lesions and they are treated with laser and there will be a scarring of the throat, so they might even die and children might have over 100 operations during their first years. And now when these patients have been vaccinated (and this is with totally off-labeled use of the vaccine), it has been noted that part of the children and adults might develop old papillomas or at least they become a very small one in two years. That would indicate this

autoinoculation, that kind of warty lesion will produce all the time new particles and then these viral particles will infect the mucosa close to the big lesion. And that has been used also in some other studies, and I think the latest that was reported that if a woman has a cervical lesion with severe dysplasia (or so-called high-grade squamous intraepithelial neoplasia), then they use vaccination together with the surgery. And that is the same that during the operation, there might be viral particles which can reinfect the site. But having the vaccination before the operation, the person is protected by new infections which are caused actually by herself.

[Sarah Gregory] What is the most important public health aspect of your study?

[Stina Syrjänen] I think it is important to understand that HPV is not only a sexually acquired infection. And there has been in families where a young child had an HPV-associated lesion in genital tract or even in mouth. There are frequently consultations in hospitals to find whether it's the mother or sexual abuse. And even when we were the first to do HPV genotyping in Finland for our research only, but we got many times samples and calls from hospitals where they have found HPV warty lesions in the mouth and they wanted to know whether it's HPV6 or 11, which was like an indication that it isn't a sexually transmitted lesion. Even we said that HPV is such a stable virus, even if it would make a sequencing, the father and the mother would have exactly the same virus detectable but it would provide no evidence that it is sexually transmitted. There are many other things which are overlooked. But I think this is a very important one, because still it has become a big problem in families if the other partner doesn't know whether there may be any...that kind of contact with the child. And the parents have very small means to convince that this is not true. Even we had the same discussion when you have these famous actors in USA when they were discussing from where did you get this HPV in the mouth or oropharynx. And the only answer would be that we can't make any final decisions based on the HPV detection of HPV6 and 11 in the mouth. You might have got it early in life. And based on our family study, we see that the partners, when we looked at the serology they might have totally different...the husband has plenty of antibodies to different types of some HPVs, but this HPV cannot be found in the female partner. So it looks like they have got their own HPV wart sometime, maybe in early childhood or later in life, but they have also immunity against it or maybe they could transmit it. But that's what I think is also important to know.

And the other thing is that the oral cavity might be one of the first sites of HPV exposure (and the role of mother, what we have already discussed). But mouth is important because then we have saliva; HPV can be brought to tonsils which is a very important site (this lymphoid tissue in the base of the tongue and also in the tonsils) where the immune recognition is made. So, there will be antibodies, not only IgG antibodies against HPV, but also IgA antibodies which is very important antibody in protecting HPV infection in mucosal sites. And what we could also, we could say that HPV types are the same. Even the role of HPV16 is more important in oral infection and also in oral infections of young children. But I think this maybe is time to start to speak only on HPV infection and not always having the label HPV as really only a sexually transmitted disease.

[Sarah Gregory] So tell us about your job. What do you like most about it?

[Stina Syrjänen] I am currently actually retired, but I have the professor emeritus status at the university, which allows the continuation of our research, and research has been really the closest to my heart. I have still PhD students to work with, and we have several results available from

our Finnish family study. But during my earlier duty as the professor and head of oral pathology, so it was not only looking at the biopsies coming from the head and neck region, but it was teaching at the undergraduate and postgraduate level and then hiring PhD students, which we had maybe some 30, I think, during all these years. But also plenty of administration and meetings and committees. And one, which I think was maybe the record for me, that I had to keep for 172 persons at the whole institute to have this employee–corporation negotiation, because at that time there was discussion to close part of the institute. And that was the tough time. And this was the time when actually I had to think something positive and that was the time when I created the plan of our family study, because I thought that when we started to become with a normal routine in our daily job, we will start this study which will be back at the work which belongs to the university. So that's shortly a long history.

[Sarah Gregory] It's been a year since the COVID-19 pandemic began. How has the pandemic impacted your life? And what do you like to do in your free time and have you tried any new hobbies or switched out any since it's been going on so long?

[Stina Syrjänen] Yeah, actually, the COVID-19 changed plenty of things and the first thing would be found in thinking of the laboratory work. So, it was the shortage of all laboratory material of what you were usually wanting to use (the PCR reagents or the pipette stuff and so on), and when wanted to do big-scale DNA/RNA extraction with those raw parts, we couldn't get them because they changed the whole laboratory work. All that kind of action was suspended for COVID-19, and they are still doing. Like sometimes you might still wait six months to get some equipment (laboratory equipment) that you need. And also, in the laboratory, so we have like four people could work together or three people could work together. And that changed, so meaning that plenty of research work has been delayed for maybe one or two years. But otherwise, many professors have said that actually you are back to the time what you had once being as a professor. You had time to think, to read, to discuss on many things, especially if you already have the results then done and you could plan new project, making the application. So, that has had both good and bad sides, thinking of the daily life.

And for me actually, that has been nice because I am not responsible anymore to change all the teaching to happen via internet. So the free time and the hobbies that is like cross-country skiing—last year we got some 500 km in a few months, and now we are trying to do the same—and then much more time to discuss with old friends, and having the music. Listening to classic music is one of my hobbies which I really like.

[Sarah Gregory] Nice.

[Stina Syrjänen] So to be short…

[Sarah Gregory] Well, thank you for taking the time to talk with me today, Dr. Syrjänen.

[Stina Syrjänen] Thank you, and I hope I really could express myself so that you can get something out of this discussion.

[Sarah Gregory] Yes. Very informative, thank you very much. And thanks for joining me out there. You can read the March 2021 article, Oral Human Papillomavirus Infection in Children during the First 6 Years of Life, Finland, online at cdc.gov/eid.

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

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.