Pediatric Grand Rounds-20240920_082941-Meeting Recording

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Kamat, Deepak M started transcription

Kamat, Deepak M 0:28

730 good morning.
Welcome to pediatrician rounds.
Just a quick announcement, the CME code is in the chat box.
We'll keep repeating it and also please fill out the evaluations at the end of the presentation.
We'll try to put the link in the chat chat box if that helps you.
It's my great honor and privilege to introduce this morning's grand round speaker, Doctor Rachel Kazarian, Bogan, who is a Richard E and Pauline.
Lingler professor of Pediatrics and professor of Microbiology and Immunology at India University School of Medicine.
She's division Chief of Adolescent medicine in the Department of Pediatrics and the project director of Indiana University leadership education in adolescent health and Interdisciplinary training program in adolescent and young Adult health.
She's the Co director of the Center for HIV Research and Co, leader of the Cancer Prevention and Control program.
At the Indiana University Simon Comprehensive Cancer Center, the cancer burger attended Johns Hopkins University School of Medicine, where she received her MD in 1999.
She completed her residency in Pediatrics and Fellowship in Adolescent medicine.
And studied at the University of Washington and Seattle Children's Hospital.
She was faculty member there until 2018, when she joined the faculty at Indiana University.
Doctor Kasanova is a physician, physician, scientist, and conduct research on HPV.
Cervical cancer and head and neck cancer in national and International Studies.
Thank you very much for.
Accepting an invitation and the floor is yours.

Katzenellenbogen, Rachel Adria 2:16

You so much.

I'm very excited to talk with you all today about human papilloma virus or HPV, and what I want to do is be able to have a broad discussion about HPV and why it matters in Pediatrics when we think about the life course of our patients.

But really fundamental with that is understanding some of the biology that then leads to understanding the oncology, how the vaccine works in advocacy.

So with that in mind, let me just get my pointer.

So we're gonna talk about first the basic biology of HPV, and there's human papilloma virus.

But there are other papilloma viruses, so there is bovine papilloma virus.

There's cotton tailed rabbit papilloma virus, canine oral papilloma virus, finches get it?

Dolphins get it.

Papilloma viruses have been around for a very, very long time.

We're going to focus on the human form of papilloma viruses.

In order to understand the virus, how the virus infects its host cell and what the two do together.

To support one another, the Natural History of diseases that are caused by HPV and specifically focusing on the cancers, which is my work, and then by understanding the basic biology of HPV infections and their Natural History as they progress to diseases and cancer.

That's what has then driven the evidence behind our clinical screening guidelines.

With that in mind, then it's nice to understand the basic biology of HPV vaccines.

How they only include the viral protein shell, so they're virus like particles.

That function of those vaccines as antibody driven immunity and the data behind the efficacy of those antibodies and protecting against infection in animal to human studies.

But there are a lot of new questions that are out there.

So the context of HIV and immunosuppressed people, so people who are.

Bone marrow transplant recipients. Solid organ.

Transplant recipients. How do we manage their risks of human papilloma virus as people who are consistently immunosuppressed and then also thinking about how do we avoid HPV to begin with and advocacy for that and talking about vaccine

hesitancy and advocacy work. So let's begin.
So the basic biology of HPV, so you need to understand it's a virus.
It's a double stranded circular DNA virus.
Its genome is quite small in comparison to Epstein Barr virus, which is has 100 KBHPVSD NA, is just under 8000 bases in size. The virus is an icosahedron non enveloped virus and this is just.
A pictogram of HPV 16.
Genome HPV 16 is the most common.
HPV type causes about 50% of cervical cancers globally, and HPV expresses genes from 2 main promoters. And those promoters are drive early gene expression and late gene expression, and the early genes are conveniently labeled E for early and those early genes are really important for viral Gen.
Replication gene expression cell cycle disruption to support the viral infection.
And the production of the virus itself.
And then the late genes L1 and L2, again, L for being late are the major and minor capsid proteins that form the shell of the virus. And then just upstream of the two promoters is an LCR or long control region where viral and cellular proteins B.
To help regulate expression tethering of the episomal viral DNA to host.
DNA in order to spread virus.
As cells divide.
So again, HPV, there are a lot of different types of HPV, more than 200 have been numbered and identified, but actually they're probably more than 400.
They just haven't been fully classified and validated.
And a different type is defined on genetic variants.
So having a variation of more than 10% in the DNA sequence homology of the L1, the capsid protein gene is what defines if you have a new type, and so these types are not zero types, they're actually genotypes.
HPV 16 and HPV 18 would be two examples of that, and those are two common high risk HPV types.
Within subtypes within types, there are subtypes, so they don't have at least 10% variation in their DNA, or more than that, but just between one and 10% DNA variation in the L1 gene.
So that would be for example HPV 6A and 6B.
And then their variance where you have less than 1% DNA variation in the L1 gene and those are things such as the HPV 16, European or Asian variants. And those are

now defined more typically as lineages that are sort of ABC and D.
If you're curious about what an HPV looks like, this is a three-dimensional cryo EM reconstruction of an HPV capsid.
And you can look at the comprehensive papilloma virus database and analysis resource sits on the NIH website.
And that has some really lovely annotated and collated information about all papulumovirus.
It's not just HPV.
So when you think about the genetic variations and similarities across HPV types, they cluster into genra alpha, beta, gamma, nu, and MU, and HPV infects stratified squamousothothelium in our bodies, either cutaneous or mucosal.
So beta, gamma, nu and you are all cutaneously, infecting human papilloma viruses, and then the alpha genra of HPV are able to infect cutaneous or mucos.
Stratified is famous epithelium in our bodies and many of the types that can infect mucosa can cause disease, some of which are considered to be low risk, that they're low risk for driving cancer.
And then there are some that are high risk and those are high risk types for cancer.
And they're shown here in red font.

F **Ferre Rivera, Celeste Luisa** 8:37
Hvp.

KA **Katzenellenbogen, Rachel Adria** 8:45
So as I described, HPV infect stratified screen is epithelium and it actually requires full thickness. Stratified squamous epithelium in order to complete its viral life cycle.
So in order for infection to occur either in cutaneous or in mucosal stratified squamous epithelial sites, HPV needs to get in and infect the basal cells of stratified squamous epithelium, so that can happen either with a microabritin so tear affording.
The virus entrance to that basal layer or at transition sites where you go from columnar or monolayer cells.
The stratified squamous epithelium.
And so that would be at the cervical transformation zone. The **** Verge ***** in the oral mucosa, and those are sites where we have HPV associated cancers, which we'll talk about in a little bit.

So when HPV does infect the basal cells of stratified squamous epithelium, it quickly establishes itself and allows for viral genome.
Initial entry and maintenance.
As cells leave the basal layer of stratified squamous epithelium.
Typically, epithelial cells no longer are dividing and instead start to differentiate through the Super, basal or granular. And if you're cutaneous, cornified layers of are stratified spammers.
Epithelium, however, with an active HPV infection, early genes help support viral genome maintenance and also drive cells to proliferate, and we see that even in low risk infections, driving cells to proliferate.
That's why we have a bump.
That's why we have a wart with low risk infections.
Low risk infections in the mucosa causing genital warts or even.
No award on the bottom of our of our foot or on our hands if we're little kids and we're playing on monkey bars.
Those bumps are where cells are growing more typically than they normally would without an HPV infection.
Off of the early promoter, E6 and E7 are really key drivers that are what are driving the disruption in typical regulation of growth, balanced with differentiation. And those are really critical, specifically in high risk HPV infections. But the E1E2E4 and E. 5 genes are also expressed more in the upper layers of stratification.
And then late in the viral life cycle and late in stratified squamous epithelial differentiation.
That signal of true differentiation is what drives the late gene expression expression off of the late promoter, producing the L1 and L2 major and minor capsid proteins.
Those help encapsulate the HPV genomes that haven't just been maintained, but actually amplify a number forming infectious virions, and the viruses released just as stratified squamous epithelial cells.
Slough off and so allow for infection through skin to skin contact, either through a partnership or in sort of self inoculation as well.
So here's another diagram of how HPV infections occur.
So again, in a normal cervical squamous epithelium, epithelial cells normally are growing from the basal cell layer.
And cells stop dividing when they leave that basement membrane and start to differentiate in the parabasis and upper layers of stratified squamous epithelium.

HPV is able to cause an infection through a microabrasion or through that transition. Cell cellular transition at the cervical transformation zone and so HPV infects basal cells.
Allowing for episomal maintenance.
So the HPV DNA remains circularized and just tethers on to cells as they're growing and dividing, allowing HPVDNA to rise with distal movement of these infected cells, ultimately establishing a viral assembly in the upper layers of stratified squamous epithelium and creat.
New infectious virus that can infect either still in regional tissues or to other partners.
And interestingly, because HPV dysregulates how a cell is normally working, so driving them to continue to divide even when they normally would not, also having them ignore signals that would alert the body to an infection or alert the body that this cell really should no longer be Div.
And should be going through either cellular senescence or cellular apoptosis.
That dysregulation in those cells can also cause some stochastic events, which actually gets HPVDNA to become integrated into the host cell.
And when that happens, that's a dead end for the virus. The virus needs to have episomal DNA to be encapsulated in the L1 and L2 proteins in order to create infectious virions.
There's no time, unlike HIV, where the DNA should integrate into the host genome.
And so by integrating that becomes a dead end to the cells.
But it actually drives further expression of some key genes in HPV.
And allows cells to continue to divide when they're ignoring these signals of apoptosis.
Cellulose. In essence, the DNA damage that's occurring and also inducing angiogenesis.
So drawing blood vessels in and allowing the cells actually to invade.
So in the normal cervix, if HPV causes an initial infection that could be detected on a pap smear by seeing atypical cells, squamous cells of undetermined significance or low grade squamous intraepithelial lesions. And so there's going to be minor cytologic abnormalities that can be seen on a P.
Smear if someone were to have a biopsy, this typically would look at look like can one or two so.
That is important to understand, but really, when we think about an active infection, our bodies very often are able to clear that. And so over time the cervix can become

typical again, and HPV can be cleared. If you have a persistent infection, there can be progression beyond these.
Sort of states that we now really understand are a reflection of active infection and can drive a precancerous lesion.
On Pap smear this most often it correlates with a high grade screen epithelial lesion. Or cin two or three.
And then there's also carcinoma in Cyt 2 and ultimately invasion that can be. Aggressive cancer.
This is a biopsy of a HPV positive person.
Who, if you did a pap smear, would look typical for low grade squamous epithelial lesions where you're looking at exfoliated cervical cells and identifying occasional cells that look atypical and what you can see here. This is the basal layer of stratified squamous epithelium.
Where there's a lot of continued growth and differentiation.
That's happening before the cells really start to differentiate in the upper layers of stratified spamase epithelium cin one shows typically cellular atypia in the bottom third of full thickness histologic slides of cervical tissue. But the upper 2/3 are typically normal.
When you look at something that would be typically associated with a high grade S IL or CIN 2 on biopsy, you can see that there are abnormal cells abnormal meaning these cells normally would not be.
Growing and dividing up into these upper 2/3 of the layer of stratified stratified squamous epithelium of the cervix.
High grade would also be seen in this case, where there's carcinoma in situ with full thickness abnormalities, including nuclei. Even being seen in the upper most layers of this cervical biopsy and ultimately cancer occurs when you have invasion through that basement membrane and leading to metastases and INV.
Regionally as well.
So in a diagram form, typically a low grade interepithial lesion or CIN one, you have abnormal expression of some of these HPV genes driving further growth in layers where cells normally would be only differentiating and you still are able to have an infection that might be produced.
However, as you progress to these more aggressive forms of HPV infection.
You can see that the early genes are expressed throughout the full thickness of stratified squamous epithelium of the cervix.

And really, you lose those late gene products.
So ultimately you don't produce any virions at this point, and instead you develop cancer.
And with that, the inactivation of cell cycle checkpoint where cells would recognize that they need to stop growing, there's a blockage of apoptosis and an induction of telomerase.
When HPV DNA in cervical cancer is still detected for the most part in cervical cancer, HPVDNA in those cancers has become integrated.
And most often.
The integration occurs where you lose expression of the E1 or E2 genes, especially the E2 gene tends to be.
Disrupted and E2 functions in a couple ways it drives.
HPV DNA replication.
With E1 and it actually also dampens the expression of the E6 and E7 genes. These two viral oncogenes, the cells, the the viral genes that have functions at the cellular level to drive growth, block differentiation, ignore signals of apoptosis, and so by losing the E.
2 gene when the HPD DNA opens and integrates into the host cell, you actually have a greater expression of E6 and E7.
More typically, in cervical cancers and so that.
Further accelerates the cellular changes that can drive cancer development and progression.
Some common pathways that are a part of all cancers, whether they're HPV related, infection related or non infection related.
And these are just some of them.
So sustaining proliferative signalling, evading growth factor suppressors, and activating invasion metastases, enabling replicative immortality, inducing angiogenesis and resisting cell death.
And what we know is that these high risk HPV.
There is 6 and E.
7 genes are specific enough to actually affect all of these pathways to drive cancer development and progression.
So my work has really focused on the most common high risk HPV type, HPV 16 and one of its two oncogenes, HP VE 6.
And we found that this protein, we know that the E6 and E7 proteins actually have no

enzymatic activity, as at all, they have to partner with other cellular proteins in order to drive dysregulation of typical.
Cell pathways that are normally.
Regulating how a keratin site is functioning.
And when HPV 16 infect cells, we know that E6 partners with a number of cellular proteins.
One of which is a protein called NFX 1123, NFX 1123 is 123 kilodaltons in size, and we know that it interacts with HPV 16 E 6 in its central domain. Nfx 1123 has RNA binding and.
RNA processing protein interacting capabilities through its n-terminal Pam 2 motif and through its C terminal R3H.
Domain it also has E3 ubiquitin ligase functions where it can find ubiquitin Y DS2 proteins to drive their degradation and also has eight additional zinc fingers.
And with this, we found that NFX 1123, again it is a normal protein that's found in cervical tissue and other epithelial.
Cell lines. If you use them and it's normally expressed in the cervix and actually it's expression increases.
As cells are differentiating in the normal sort of X so it can be found throughout stratified squamous epithelium, but its expression is greater in these upper differentiation differentiated layers of the cervix. However with disease. So again thinking about cellular dysplasia but not frank cancer.
So cin two, you can see that the expression of NFX 1123 has further increased and in squamous cell carcinoma of the cervix, you can see that there's high levels of NFX. 23 we've done quantification of that comparing normal cervical tissues to cervical cancers.
So carcinoma and cyto moderately to different poorly differentiated squamous cell carcinomas and ultimately to invasive squamous cell carcinoma. And the expression level of NFX, 1/1/23 at the protein level is higher than what can be found typically in normal cervical tissues.
And this is just an example of some of that in a histochemistry studies that we did.
So NFX 123 is a protein that interacts with E6.
It appears to have greater expression in in the process of HPV associated cervical cancers, but its role in differentiation. We wanted to understand how that could be happening because typically we think about if a cell is differentiating, it's not growing and if a cell is growing, it's not.

Differentiating and what we have found is that in the context of cervical cancer development and progression.
That cells appear to be doing both.
Growing and dividing and differentiating, and we know that for a cell to support an HPV infection, it has to be growing and dividing, but it also needs to differentiate to trigger HPVDNA amplification in number and also late gene expression to form that infect.
Virion and So what we found is that since NFX 1123 appears to have greater expression.
During differentiation and actually participates in cellular differentiation as well.
That when you have higher expression of NFX moment, 23 in a cell and so this is a flag tag form of the protein of interest versus an anti vector control and you overexpress it and then drive differentiation one of the ways that we drive differentiation in my.
Lab is actually taking care tenocytes and having them actually.
Not attached to a plate, but actually in suspension with methylcellulose.
Almost mimicking them coming off of the basement membrane and being lifted off of the base of the layer to be super basilar and so triggering differentiation and so with cellular growth in a differentiation. Millie, you with higher expression of NFX 123 there's a typical activation of.
Expression of those late genes that form the viral capsid.
That's further augmented. If you have more NFX moment, 23 to begin with and this happens at the RNA level and this also happens at the protein level.
So again, keratinocytes that are being suspended in methylcellulose and have greater expression of NFX, 123 to begin with are able to produce much more L1 protein.
And so that might actually be an ideal way for a cell to support an HPV infection, and really, a persistent HPV infection is what is the most.
Common clinical risk factor that can be tracked by a a physician for risk of developing cancer.
We know that in this balance of differentiation with more NFX 123, these cells grow better. So that balance where there's typically a separation between growth and differentiation.
This appears to be merged in our cells, and so human foreskin keratinocytes, which we collect from neonatal circumcisions that otherwise would be considered biohazard, were able to grow those primary care tanocytes in culture.

And when we over express NFX, 1123, there's no real difference in their growth.
Only in the context of HPV 16 E 6 is coexpression.
Do we see that these cells actually grow faster and for longer in culture when compared to even cells that have one of the two oncogenes of HPV HPV16E6 by themselves? So the host cell having greater expression of NFX 1120?
Three helps support.
Improved growth, which might be important for either early stages of an HPV infection.
Or these latter steps in dysplasia and cancer.
We've done some modelling of how the NFX 1123 protein might look in three dimensions and then mapped what drugs might interact with NFX 123 and could be functioning as.
A way to target this protein so that it works less well or disrupts other protein protein partnerships that are important.
And so we have a three-dimensional modeling here of NFX woman, 23 and then interacting with three drugs.
Robotn R428 and ketoconazole and what we found is that all of these proteins, all of these drugs interact with our protein of interest.
Nfx, 1123 and do actually affect its functionality, and we'll focus just specifically on robot.
So we've taken in this study HPV 16 positive cervical cancer cell lines and here we used see how which is an HPV 16 positive cervical cancer cell line.
And we did a study looking at cellular migration plating cells on one side of a trans well, stimulating them to cross through the trans well to come on the other side with some chemotactic and growth factors and you're able to see that these cervical cancer cells are able.
Migrate through the transfer typically, but when you treat with increasing doses of ropaton, you have less cell migration. In this transwell assay you also have less cell migration when you think about wound healing.
And so see how cells can be grown to full confluency on a monolayer culture in tissue culture. And then you scrape a line through those cells and follow how quickly they're able to.
Migrate and heal that wound.
But if you treat these cells with ropaton again with increasing doses, they have slower wound healing and that can be quantified.

So it's important to take all of that information in mind when you think about how HPV can be causing cancers and thinking about both cervical cancer, which is what really defines an HPV type 2B, high risk or low risk and all the other types of cancers that.
Occur with HPV as well, so globally.
Cancer incidence typically is most often found in low and middle income countries. About 85% of cervical cancers are in those countries, and a large majority is in sub-Saharan Africa.
But HPV associated cancers incidence rates also can be found in other countries, including ours, driven by other types of HPV associated cancers, cervical cancer, as I said, is the most common.
One for us to consider is the 4th most common cancer in women worldwide.
There's also vaginal cancer, vulvar cancer, **** cancer and penile cancer and head neck cancers is a type of cancer that's increasingly common in our country as well.
**** cancer is more commonly found in women than men, most likely due to auto inoculation from the genital tract to the **** verge and head neck cancer.
For a minority of HPV, associated head neck cancers used to be a minority.
But now are a majority of head neck drivers of head neck cancers in in many countries, including ours, and I think it's really important to think that to recognize that nearly 5% of all cancers worldwide are attributable to HPV. And when we think about infection associated can.
HPV causes a third of all of those cancers.
So.
HPV is not a great thing to have.
So what are the ways we can prevent HPV infections and how do you avoid the ultimate outcome of an HPV infection?
Which would be an HPV associated cancer.
So the first thing is for people who may have been exposed to screen for and treat for any persistent evidence of clinical disease.
Some people with the cervix that's doing cereal pap smears, where you're looking for abnormal cells and cytology.
For places where Cytologic evaluation of cells.
Challenging visual inspection can be done as well.
So you do visual inspection by using dilute acetic acid, which is basically vinegar. It has it drives the cervical tissue to sort of contract and you can see differences in

regions of the cervix that may be infected with HPV.
You can biopsy at those points to determine what may be happening at those sites or.
Specifically sort of screen and treat with a removal of those.
Regions in real time.
Since we understand the cervical cancer is 99.9% caused by HPV, you can also start with HPV DNA testing and increasingly, in some countries HPV DNA testing, including in the US is an is a way to be looking for the infection that's driving.
The cellular atypia.
The histologic atypia in cancers.
The second thing to do is to decrease your exposure to HPV so you can do that by using condoms consistently.
Male circumcision decreases risk of infection and spread.
In female and male partnerships, and then also you can avoid being exposed to HPV by not having another sexually transmitted infection.
Then the last thing is you can vaccinate against HPV to prevent infection from an exposure, and we'll talk about the components of the vaccine.
But really, you're avoiding the cancer as part of HPV.
So those high risk E6 and E7 oncogenes?
By recognizing that HPV is a driver of dysplasia and cancer, and typically that takes years to occur.
Our current guidelines are based on our knowledge of this Natural History of HPV and HPV biology.
So the asccp or the American Society for Cytology and Cytopathology has an app that's extraordinarily helpful and it's updated when their changes to the regulations and recommendations.
So you can input the person's age their.
Current evaluation will kind of follow up.
They should have, etcetera.
So it's very nice when we think about.
Someone who does HPVDNA testing as their primary screen.
There's really strong negative predictive value of an HPV negative test. If you're HPV negative, the chances of you developing cervical cancer in the next five years is extraordinarily low. As we think about Natural History with someone who has a typical immune system.

It's weekly positive in its predictive value. If you have an HPV positive test, especially if you're young, because very often those HPV infections can clear.
And that it's important to also know that the instance rates of cervical cancer are exceedingly rare in women under the age of 25.
We do recommend in the United States at this point to start screening at the age of 21 and there's really a lot of watchful waiting when you're younger with any symptomatic change, recognizing that those likely reflect an active infection that could be cleared by the body and.
So because of that, HPDDNA testing is not included in HPV or cervical cancer screening guidelines until someone is at least 30.
When you think about HPV associated cancers, what are the screening guidelines for other cancers?
There are none.
So there's no screening for other INTERGENITAL guidelines for men.
No screening guidelines for oral disease and unfortunately head neck cancers are on the rise.
So if you look at HPV prevalence in the oral cavity.
In men versus women and correlate that with a number of lifetime sexual partners that they've had.
What you can see is that women have HPV DNA that can be detected in the oral cavity, but that typically plateaus at around 2 to 3%.
However, for men this can increase up to about 10% prevalence and increases.
Well up when people have increasing numbers of lifetime partners.
So the HPVDNA prevalence in the male oral cavity is much higher than females.
And that's also reflected in oral pharyngeal cancers in men versus women.
So the ratio really is.
At this point, about four to one or five to one, men versus women and since 2010.
Head and neck cancers have outstripped actually 2012, I believe, have outstripped cervical cancers in the United States.
The way to avoid HPV infections by decreasing exposure.
This is before vaccination.
We have data on this information, so HPV is a very common sexually transmitted infection.
It is the most common sexually transmitted infection and if you look at incident infection with the first partner, if you're a woman, 28% of people before vaccination.

Will have become HPV infected within the first year and half of women by the third year of their first partnership.
And then if we look at even younger girls, so girls, this was a part of the NHIN study that were 14 to 19 years old and stating that they initiated sex within one year or at least two years ago. 22.5% of those girls 4.
To 19 were HPV positive.
Again, this is data. Before HPV vaccination had really rolled out and at least three years prior. A third of these girls participating.
Of these girls, when they stood that they had had one lifetime partner, they were HPV +16.4% of the time.
And at least three lifetime partners, 41.2%.
So HPV is almost like voting happens early and often.
So there really is a lot of HPV that.
Can occur early again.
That's why we don't necessarily do aggressive HPV screening in people under the age of 21 and don't include HPV testing until 30.
Because many of these infections can clear and none of these guidelines and recommendations include any sort of triaging of people based on their HPV vaccination status.
But the prevalence is extraordinarily high in people who are unvaccinated.
Using condoms consistently can help.
So in a study that was published in the New England Journal, if you use condoms 100% of the time as a as a woman with receptive vaginal sex, HPV infection was reduced by 70%. If condoms were used all of the time.
So vaccination really is incredibly powerful when we think about.
Protection from disease.
Prevention of disease and so the basic biology behind an HPV vaccine is mounting an antibody, and these antibodies are mounted against a natural infection with HPV after exposure.
And these antibodies are typically protective against future infections.
But both in natural infections and in the vaccination.
The antibodies that are produced are HPV type specific and that's because when we think about.
The the viruses.
I'll show you a model that the external surface of HPV has regions of the virus that

are unique to that type.
Again, remember I told you that different types have different variations in the L1 protein at the DNA level that manifests in different protein structures.
On the outside of the HPV virion.
And so those differences are what the antibodies respond to.
And so an antibody to HPV 16 protects against HPV 16, but it doesn't protect very well against HPV 18.
Because we know that antibodies are produced naturally against HPV that are type specific, the vaccine then was developed to exploit that.
So the L1 protein, which is the major capsid protein that helps form the shell of HPV, can be produced in yeast cells. And when that protein is produced and allowed to sit. It actually self assembles into.
Noninfectious virus like particle or capsid that looks to the immune system nearly identical to a natural HPV infection.
However, this virus like particle is only the L1 protein.
It does not contain any HPV DNA and so as a part of that it does not contain the oncogenes to which HPV drives cancer.
And so in no way could anyone get cancer from an HPV vaccine.
It only has the L1 protein as a part of it.
We also know that HPV protects itself from infection by really completing its full viral life cycle in stratified chromosomes.
It has no time that it has hematologic or lymphatic spread and it actually also decreases both the innate and adaptive immune responses to a viral infection during its infection.
The HPV vaccine is given intramuscularly and so it's putting these virus like particles, which actually are very antigenic right into the blood system. So the body responds to this right away and mouse, really a huge amount of antibodies, you know, log fold increase in comparison to natural anti.
Production, so the antibody response to HPV vaccination.
Is extremely robust and again does not contain any of the E637 genes as a part of it.
So here is a structure of the L1 capsid forming this pentamer which looks star like in this projection.
This is it on the side and what you can see is that there's some very conserved regions across all HPV types that allow for the L1 proteins to self assemble into this capsid structure.

But the unique parts.
Of an L1.
Type genotype are on the external facing.
Loops of this caps mirror.
So this is what our antibodies are responding to that are unique type by type.
And as proof of the vaccine driving an antibody response, there were studies in animals where virus, like particles were used to immunize a cotton tail rabbit with papilloma virus, canine oral papilloma virus and dogs and bovine papilloma viruses and cows.
So they were exposed to a virus like particles and then after immunization, Sero was removed from these immunized animals.
And placed into animals that had not been immunized.
And then they were challenged with a homologous papilloma virus type and what they found is that the sera which has antibodies.
Protects them from this challenge from a homologous human or a homologous papilloma virus type. So again.
The antibodies is what drives prevention of HPV infection in humans as well.
So of the vaccines that have been.
Tested and approved.
There was initial approval for HPV vaccination for girls in 2003, nine to 26 years old, and boys in 2009 as a three dose series.
There've been three different vaccines that have been produced, only one of which is now distributed in the United States since 2016.
So there's a nine valent vaccine. This 9 valent vaccine includes 2 low risk types.
HPV6 and HPV11 that cause genital warts and external genital lesions.
These are also associated with recurrent respiratory papillomatosis.
And then seven high risk types that are associated with about 85% of cervical cancer.
Globally.
Antibody response to the virus, like particles in HPV vaccines, are extremely robust, and so the initial studies looking at a three dose series have been then followed up to determine if two doses is adequate and what people have found is in A2 dose series where you receive.
One dose at times zero and then a second dose 6 to 12 months later. You have non inferior antibody responses, in fact excellent.
And.

If if you're now are.
Under the age of 15, you can receive 2 doses and that is a completed series for people. If you're 15 years and older, they still recommend a three dose series in the United States where you get one shot and then one one to two months later and then.
1-6 months later.
The HPV vaccine has also now been approved to extended age ranges to 45 years old, with shared decision making.
There's been some really great data looking at how well just one dose of the HPV vaccine may work for people.
And there's been strong efficacy studies in 15 to 20 year old women showing 97% efficacy with a single dose of vaccination and the WH OS Strategic advisory group for experts on immunizations in 2022 looked at two doses versus 1 dose and stated that one.
One or two doses for girls or women that are 9 to 20 years old would be recommended, and then a second dose within six months for women who are older than 21.
When reflecting back in the United States, it's important to remember that.
A vaccine only works when it's been given, so a vaccine on the shelf has 0% efficacy.
A vaccine that's been given to a person can lead to protection and in the United States, what you can see is that the HPV vaccine.
Rates shown here in the blue dotted line had a a reduction in administration for people who are born in 2007 and 2008.
When compared to other vaccines that typically are given at the 11 to 12 year old visit.
And so this reduction in HPV vaccinations needs to be made-up for.
It's also, in my mind, quite compelling that three vaccines that should be given at the same.
At the same visit that there's one that has less uptake and when we think about ways to protect people, to be healthy adults, HPV vaccination is really critical.
So with that, we really need to counter vaccine hesitancy.
Concern that a vaccine is somehow less safe.
Than working to try to avoid infection or having a natural infection that somehow a natural infection is more natural, more typical, more healthy. We definitely know for HPV, the antibody response to vaccination is much better than being exposed.

And when you're exposed, you're exposed to the whole HPV genome, including the high risk genes that can be incorporated into your cellular DNA and be there permanently.
So we really need to advocate for the value of vaccination as a way to lead a healthy adult life.
And we need to leverage some known interventions that work well, so tailored messages to improve intent to vaccinate children. When we think about people who are vaccine hesitant, providing reminders both for families and for providers.
And making sure that that's consistent across your whole team from scheduling appointments, checking in administration, etcetera and making declarative statements.
Wording is very important. The statement that your child will receive 3 vaccinations today.
Versus your child will receive 3 vaccinations today, two of which are important, and 1:00 you could consider.
There are three vaccinations, one of which is may be optional for you.
Those types of things, really.
Drive some concern for people when we think about.
Why there should be any ranking in order of what types of vaccines need to happen?
I think parents of young children, babies are concerned about sort of the number of needles going in as a demonstration of the number of sort of overwhelming and immune system.
That's new, but I think we also recognize that for us it's the number of antigens that are in a vaccine that are more important than the number of needles.
And this is a single antigen for each HPV type.
So it's really a specific way to protect against high risk and low risk HPV infections.
And our bodies are exposed to millions and millions of viruses and bacteria, and studies have shown that vaccination is, you know, I believe it's point 1% of all of the microbes that.
We're exposed to on a daily basis.
It's also important to consider high risk groups.
So HIV both domestically and internationally places people at increased risk of cervical cancer development and progression as well as risk of other HPV associated cancers and people who are transplant or immunosuppressed patients are also people to really consider.

There have been studies looking at cancer survivors and people who've received, for example, a bone marrow transplant.
One year out, only 25% of people who've received a bone marrow transplant had been vaccinated against HPV.
And when you think about high risk patients who've received a huge amount of chemotherapies, perhaps irradiation that can cause DNA damage and then being infected with ADNA virus, that drive cells to ignore signals of DNA damage, apoptosis or other abnormalities, places, people who've been cancer survivors at at.
Increased risk as well.
And people who are immunosuppressed, it's very important to make sure that they're protected.
So with that, I just want to end by sort of pointing out my happy place.
So I am a physician. I love seeing patients, but I also really enjoy doing basic science research and really understanding the fundamental mechanisms by which HPV infection is supported and driving clinical disease and the ways that we can intervene to help protect people against disease in the future.
So thank you very much.

Kamat, Deepak M 49:39
Thank you, Katherine Logan, for that wonderful, wonderful presentation on biology, oncology of actionology and advocacy on HPV.
Let's see if anybody has questions and comments for you.
I'm monitoring the chat box.

Williams, Janet F (Dr.) 49:53
Deepak, this is Janet.
I have a question.

Kamat, Deepak M 49:57
So go ahead please.

Williams, Janet F (Dr.) 49:58
What? What is the recommendation for?
Younger children, who at between 2003 and 2016 got a two or three valent vaccine and now are they're, you know, older.

And is it recommended that they get the forgot what it is 6 valent or or 9 valent vaccine?

Katzenellenbogen, Rachel Adria 50:28
Good question. Right now it is not recommended to reimmunize patients.
So if you received the bivalent or the quadrivalent that is where vaccination would stop.
I will tell you my own story as a parent.
So I'm a parent of fraternal Boy Girl twins, and I had my children vaccinated at the age of nine, with the quadrivalent vaccine again.
Some of the studies looking at 3 dose versus 2 dose versus 1 dose, we definitely see that antibody responses are better the younger you are when you start your, your vaccination and those antibodies sort of drift down but then remain at a higher level if you are vacc.
Early so my kids were vaccinated at 9:00, and then the 9 valent vaccine came out with A2 dose series and I had them revaccinated.
So my kids have received 5 vaccinations against HPV.
And that was my own choice as a parent and also as a researcher.
But it is not recommended.
That there be revaccination at this point.
Nor is there a recommendation that we alter our clinical screening guidelines based on vaccination history at this point in the US.

Kamat, Deepak M 51:39
There's a question in the chat box in making HPV vaccine.
Is the vaccine exposed to any animal cellular elements? Some hesitancy related to animal retroviruses?

Katzenellenbogen, Rachel Adria 51:52
The the vaccine.
That's the 9 valent vaccine is produced in yeast, so it's.
It's just in yeast, it's not in animals.

Kamat, Deepak M 52:09
Any other question comments.

Katzenellenbogen, Rachel Adria 52:26
How much resistance people feel?
To HPV vaccination versus other common childhood vaccinations in their patient cohorts.

Williams, Janet F (Dr.) 52:45
I think it's up there with the flu vaccine.
The resistance rates and.
It's not super high, but of of the vaccines, those are the top 2.

Katzenellenbogen, Rachel Adria 53:02
Think you know there's some just in thinking about?
Ways to 1st you know query what are the concerns.
What have they heard?
What do they understand is really important before.
Sort of giving.
Batch based counseling. I think another thing to know is you know hundreds of millions of doses of the HPV vaccine have been given globally and we understand that it is safe.
So you know, with that in mind, when we think about a woman dying of cervical cancer in the prime of her life leaving her children.
Without a parent is something that is really striking when we think about ways that we really can protect against these.

Kamat, Deepak M 53:49
There's a question in the chat box how you compare the different manufacturers in the market for HPV vaccine.

Barton, Theresa 53:58
Play.

Katzenellenbogen, Rachel Adria 53:58
The nonviolent vaccine is produced by Merck, and so that is one company.
There are a few other the the bivalent vaccine was produced by Glasgow Smith Kline,

but that's no longer.
Offered on the vaccine for children formulary in the United States.
There are other vaccines that are being produced in other countries that appear to have quite strong protections, one of which has been produced in China and actually has not grown in yeast but is grown in bacteria that appears to be very effective as well, and growing bacteria is.
Growing yeast, so when we think about cost in production, that's that's very helpful.
There also are other vaccines that are in development but are not fully through their clinical trials or FDA approved at all.
So I told you that these vaccines are against the L1 protein that major capsid protein that forms that outer shell of the virus.
There's some vaccines that are being produced against the L2 protein.
The L2 protein is also an important structural protein that helps tether the HPDDNA inside the virus to that outer shell.
And it appears that the L2 protein when you make antibodies against that, it has actually broad and not type specific protection.
And so those are sort of new generations of vaccines that are being produced right now study.

Kamat, Deepak M 55:22
So Barton, go ahead and ask your question please.

Barton, Theresa 55:26
Yeah, I was just gonna make maybe a comment just regarding the the hesitancy that in my experience, you know unlike some other vaccines that the issues about like the parent, the issues that parents have raised with me have not usually been regarding, you know safety or side effects.
Or things like that.
But really is more kind of based in the.
Probably kind of puritanical roots of like my child. Not ready. They're not going to be having sex, and therefore they're not going to be getting that virus.
And I think that one of the one of the, the the best tools or the best you know little factoids to to help parents with that is is the you know relative effectiveness of the antibody response when given early as opposed to when given later.
You know, and and touting it like this is this is for preventing cancer.

Like, why wouldn't you want to prevent your child from having cancer eventually, and you have a better a better opportunity when they're a little bit younger to do that.

Katzenellenbogen, Rachel Adria 56:32
I absolutely echo that.
I think the other evidence that's really profound about an early vaccination still leading to protection is in the, quote UN quote older women still very young in my mind, who participated in these initial clinical studies.
They continue to be tracked to see if they've had any breakthrough bleeding that not breakthrough infection that would lead to needing a booster shot.
So those women are almost 20 years out now.
If not 20 years out now and they have not had.
Breakthrough infections and so if we think about as you're describing the earlier age driving higher antibody response to the vaccination and that antibody response being maintained, really you're vaccinating now to protect the later and that protection is still maintained and is robust. And I think that that's somet.
Really helpful.
You know, we don't put on a seat belt planning on having an accident. We put on a seat belt in case we have an accident. And so this is functioning like a seat belt too.


Kamat, Deepak M 57:33
Another question in the chat box, is there a difference in antibody response if a child is vaccinated at age 9 years versus age 11 to 12 years?

Katzenellenbogen, Rachel Adria 57:45
Age split out nine, split out nine to 15 first versus 16 to 26 in the initial studies. And then they've done more parsing looking at 11 to 15 and 9:00 to 11:00.
The antibody responses to the younger you are, the better it is so. So 9 year olds are are on average better than 11, better than 15. Better than 26, yeah.


Kamat, Deepak M 58:09
Thank you.
Any other questions?
Comments doctor Barton.
You have another question or?

Barton, Theresa 58:15

Oh, sorry, I I just left my hand up accident.

Kamat, Deepak M 58:18

Any other questions or comments?

I don't see any and it's almost 8:30 to some of us need to run to the clinic.

So doctor, Kaiser Morgan, thank you very much for that fascinating presentation. And thank you for accepting our invitation.

KA

Katzenellenbogen, Rachel Adria 58:35

Yes.

Kamat, Deepak M 58:39

I know you are very busy.

And still here you could teach us.

So thank you all for attending this morning's GAIL rounds.

I would conclude have a wonderful Friday and a wonderful weekend.

Thank you again.

KA

Katzenellenbogen, Rachel Adria 58:51

Thank you very much everyone.

Williams, Janet F (Dr.) 58:53

And four, 7346.

Kamat, Deepak M stopped transcription