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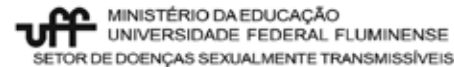
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## ***Reflexão sobre o Futuro da Abordagem das DST Frente ao Avanço Tecnológico***

Um dos maiores desafios para o exercício da medicina contemporânea é a adaptação contínua aos modelos de financiamento da saúde, frequentemente nos obrigando a um distanciamento perigoso dos princípios hipocráticos que regem nossa atuação no cuidado do paciente. O resultado desta equação é uma dualidade flagrante entre o exercício assistencial de qualidade e as condições para que ele possa ser efetivado. Diria que, na atualidade, o profissional de saúde em nosso país é um “equilibrista de princípios”, pois tem a noção clara da responsabilidade de atender às necessidades da população no campo da saúde, mas enfrenta limitações que se projetam e, eventualmente, impactam negativamente sobre a qualidade do nosso trabalho. O atendimento de pessoas portadoras de doenças sexualmente transmissíveis (DST) é um exemplo claro desta dualidade. Sabemos das limitações do atendimento baseado apenas nas informações clínicas traduzidas por sinais e sintomas, mas a inacessibilidade aos exames confirmatórios nos transforma em pensionistas deste atraso assistencial. Curiosamente, esta flagrante limitação tecnológica no atendimento de pessoas portadoras de DST não atinge apenas os pacientes que dependem do Sistema Único de Saúde (SUS), mas também aqueles atendidos em convênios e até da clínica privada. Por mais que se negue esta prática nos debates públicos, sabe-se que na maioria dos atendimentos fora do SUS, o diagnóstico das DST ainda é baseado apenas em sinais e sintomas ou utilizando técnicas consideradas ultrapassadas em países tecnologicamente mais preparados.

Em nosso meio, a falta crônica de recursos no atendimento de pessoas portadoras de DST alimentou a inércia do progresso no tocante à absorção da tecnologia disponível atualmente. Nos países onde o recurso tecnológico é mais facilmente acessado, vive-se a era do diagnóstico baseado em biologia molecular, realidade ainda distante para nossa população. Eventualmente, algum avanço pode estar disponível para alguns pacientes de melhor poder aquisitivo, mas se não está disponível para todos não há como falar em disponibilidade democraticamente aceitável. Infelizmente, a realidade atual é desconfortável, demandando disposição de todos da área da saúde para interferir e mudar os rumos do futuro no atendimento de pessoas com alguma DST. Que este desconforto seja a alavanca para as mudanças necessárias, fazendo com que nossos sentimentos de cidadania despertem deste longo sono, eventualmente alimentado pelo desalento dos profissionais da área da saúde que atuam no combate às DST.

Algumas vezes me surpreendo pensando e procurando resposta para explicar a resistência mal dissimulada aos testes de diagnóstico rápido das DST. Hoje, já estão disponíveis no mercado internacional testes com excelentes escores de *performance* (precisamos ser criteriosos na escolha) e sua aquisição poderia auxiliar objetivamente no controle de várias DST.

Como falar da infecção por *Chlamydia trachomatis* sem a disposição de investimento (recursos pessoais e tecnológicos) em diagnóstico baseado em biologia molecular? Nesta mesma linha de raciocínio lembra-se do diagnóstico moderno das infecções causadas por *Trichomonas vaginalis* e *Neisseria gonorrhoeae*, entre outras. Hoje, as técnicas de biologia molecular atingiram tal desenvolvimento e praticidade que, dificilmente, teremos argumentos fiáveis para não as utilizarmos no futuro.

No contexto do meu otimismo pragmático para a incorporação tecnológica no atendimento de pessoas portadoras de DST no futuro, antevejo que esta medida dará lastro para uma evolução extraordinária na qualidade da assistência. Esta é a minha ferramenta de convencimento às autoridades de mando na saúde de nosso país. Mas, de novo o espectro da dualidade aflora! Como posso falar em diagnóstico automatizado da sífilis ou isolamento do *Treponema pallidum* das lesões utilizando tecnologia de replicação do DNA se ainda temos gestantes que dão à luz sem um único exame de VDRL? Vejo também que é cada vez mais raro encontrarmos laboratórios que executem a técnica de identificação do *Treponema* em campo escuro. Esquecemos o “antigo” e não criamos condições de absorver o novo! Resultado? Diagnósticos e tratamentos equivocados. Mas vamos ser práticos. Objetivamente, penso que se não nos apartarmos de nossa dualidade atávica, jamais chegaremos ao progresso! Podemos praticar nossas atividades de cuidado às pessoas portadoras de alguma DST com o que temos disponível, mas jamais podemos deixar de ter nossa visão no que há de melhor para o paciente sob nossos cuidados. Será que já não é hora de um posicionamento mais ativo de nossa parte?

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## ***Reflection on the Future of STD Approach Towards the Technological Progress***

One of the biggest challenges to practice contemporary medicine is the continuous adaptation to the health financing models, often forcing us a dangerous detachment of the Hippocratic principles that rule our activities in the patient's care. The result of this equation is a glaring duality between the quality care exercise and the conditions to accomplish it. Nowadays, I would say that the health professional in our country is an "acrobat of principles", since he has a clear notion of his responsibility to meet the population needs in the health field, but otherwise faces clear limitations, which eventually impacts negatively on the quality of his work. The care of people with sexually transmitted diseases (STD) is a clear example of this duality. We are aware of care limitations based only on clinical information shown by signs and symptoms, but the inaccessibility of confirmatory tests make of us hostages of this ancient politic aspect of our health care system.

Interestingly, this flagrant technological care limitation to people with STD reaches not only patients who depend on the Unified Health System (SUS), but also those covered by health insurance and even private clinic. Although this practice is denied during public debates, it is known that in most of the assistance outside SUS, STD diagnosis is only based either in signs and symptoms or using techniques considered outdated in more technologically prepared countries.

In our area, the chronic lack of resources caring people with STD has fuelled the inertia of progress regarding the absorption of currently available technology. In countries where access to technology is more easily accessed, the health professionals are living in an era of diagnosis based on molecular biology, a reality still distant to our Brazilian reality. Eventually, some progress might be available for some patients with a higher income, but if it is not available for all, there is no condition to talk about availability in an acceptable democratically way. Unfortunately, the current reality is uncomfortable, requiring disposition of all people involved in health care to intervene and change the course of the future in the setting of care for people with any STD. May this discomfort could be the lever for necessary changes, awaking our citizenship feelings from this long sleep, possibly nourished by the dismay of health care professionals who fight against STD.

Sometimes I catch myself thinking and looking for answers to explain the poorly disguised resistance against the rapid STD diag-

nostic tests. Today, there are tests already available in the international market with excellent performance scores (we need to be careful about the choice) and its acquisition could objectively helps in controlling several STD.

How can we talk about the *Chlamydia trachomatis* infection without the provision of investment (personal and technological resources) in diagnosis based on in molecular biology? Considering this same way of thought, we can recall the modern diagnosis of infections caused by *Trichomonas vaginalis* and *Neisseria gonorrhoeae*, among others. Nowadays, the molecular biology techniques have reached such a development and practicality that we shall hardly have reliable arguments not to use them, now and in the future.

In the context of my pragmatic optimism concerning the incorporation of technology to care people with STD in the future, I foresee that this change of paradigm will provide a solid base to an extraordinary evolution on this care quality. This is the persuasion tool that I address to the health authorities of our country. But again, the duality spectrum emerges! How can I talk about automated diagnosis of syphilis or isolation of *Treponema pallidum* lesions using DNA replication technology if we still have pregnant women giving birth without a single VDRL test? I also see that laboratories testing the technique of *Treponema* identification in dark field are increasingly rare to find. We forget the "old" and did not create conditions to absorb the "new"! What is the result of this crazy equation? Wrong diagnoses and treatments! But, let us be practical. Objectively, I consider that if we not detaching from our atavistic duality, we never will find the real progress! We can practice our care activities to people with any STD using what we have available, but we must never abandon our vision of what is the best possibility for the patient under our care. Isn't it already time for a more active position of our part?

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# PERFIL CITOPATOLÓGICO DE MULHERES ATENDIDAS NAS UNIDADES BÁSICAS DO MUNICÍPIO DE URUGUAIANA, RS

## CYTOPATHOLOGICAL PROFILE OF WOMEN MET IN THE BASIC UNITS OF THE MUNICIPALITY OF URUGUAIANA, RS

Deise Jaqueline Ströher<sup>1</sup>, Thais DB Aramburu<sup>2</sup>, Marta Aurora S Abad<sup>3</sup>, Vinicius T Nunes<sup>4</sup>, Vanusa Manfredini<sup>5</sup>

### RESUMO

**Introdução:** o câncer do colo de útero tem sido apontado como o terceiro tipo de câncer mais comum entre as mulheres e sua relação com a infecção por papilomavírus humano (HPV) é bem estabelecida. **Objetivo:** conhecer o perfil citopatológico de mulheres atendidas nas Unidades Básicas de Saúde do município de Uruguaiiana, RS. **Métodos:** análise retrospectiva de corte transversal e descritivo dos laudos de exames citopatológicos de pacientes que realizaram a citopatologia ginecológica (Papanicolaou) e respectivos prontuários, emitidos entre os anos de 2003 e 2011. Foram selecionadas as variáveis referentes à idade e a alteração citopatológica e classificadas segundo Bethesda, 2001. **Resultados:** da totalidade de laudos de exames citopatológicos analisados, 15,5% possuem alguma alteração celular e a que apresentou maior prevalência foi a atipia de células escamosas de significado indeterminado (ASC-US), com 50,28%, seguida das lesões intraepiteliais de baixo grau (LIEBG), com 35,45%. Em ambos os casos as mulheres com idade inferior a 25 anos foram as que apresentaram maior prevalência. Cerca de 13% das pacientes apresentaram infecção pelo HPV e a maior prevalência foi observada na faixa etária inferior a 25 anos (47,84%). **Conclusão:** a faixa etária de maior prevalência de lesões cervicais está em mulheres com idade inferior a 25 anos e muitas das alterações celulares estão associadas à infecção pelo HPV. Salienta-se, portanto, a necessidade de políticas de rastreamento de lesões cervicais em mulheres nesta faixa etária, evitando assim a progressão das lesões que evoluem ao câncer.

**Palavras-chave:** câncer do colo de útero, Papanicolaou, papilomavírus humano, HPV, DST

### ABSTRACT

**Introduction:** cancer of the cervix has been named as the third most common type of cancer among women and its relation to infection by human papillomavirus (HPV) is well established. **Objective:** cytopathologic know the profile of women attending the Basic Health Units in the municipality of Uruguaiiana, RS. **Methods:** retrospective analysis of cross-sectional and descriptive the reports of cytopathology from patients who underwent gynecologic cytology (Papanicolaou) and their medical records, issued between the years 2003 and 2011. We selected the variables related to age and change and cytopathological sorted by Bethesda, 2001. **Results:** of all reports of reports of cytopathology analyzed, 15.5% have a cell phone and some change with the highest prevalence was atypical squamous cells of undetermined significance (ASC-US), with 50.28%, followed by low-grade intraepithelial lesions (LSIL), with 35.45%. In both cases, women younger than 25 years showed the highest prevalence. About 13% of patients had HPV infection and the highest prevalence was observed in the age group below 25 years (47.84%). **Conclusion:** the age group with the highest prevalence of cervical lesions in women is under the age of 25 years and many of the cellular changes associated with HPV infection. It is noteworthy, therefore, the need for political screening of cervical lesions in women in this age group, thus preventing the progression of lesions that evolve to cancer.

**Keywords:** cervical cancer, Papanicolaou, human papillomavirus, HPV, STD

## INTRODUÇÃO

O câncer do colo do útero é um importante problema de saúde pública no mundo. As mais recentes estimativas mundiais apontaram 529 mil casos novos desse câncer em mulheres para o ano de 2008, configurando-se o terceiro tipo de câncer mais comum entre as mulheres. Sua incidência é cerca de duas vezes maior em países menos desenvolvidos, quando comparada aos países mais desenvolvidos. Para o Brasil, as estimativas do Ministério da Saúde, no ano de 2012, esperam 17.540 casos novos de câncer do colo do útero, com um risco estimado de 17 casos a cada 100 mil mulheres<sup>(1)</sup>.

A incidência do câncer do colo do útero manifesta-se a partir da faixa etária de 20 a 29 anos, aumentando seu risco rapidamente até

atingir o pico etário entre 50 e 60 anos. Com exceção do câncer da pele não melanoma, esse tumor é o que apresenta maior potencial de prevenção e cura quando diagnosticado precocemente<sup>(1)</sup>.

A relação entre o câncer cervical e infecção por papilomavírus humano (HPV) é bem estabelecida. O material genético, ou seja, o DNA do HPV de alto risco é detectado na maioria dos espécimes (92,9% a 99,7%) de câncer cervical invasivo<sup>(2,3)</sup>.

São conhecidos, atualmente, mais de 100 tipos diferentes de HPV e cerca de 20 destes possuem tropismo pelo epitélio escamoso da região anogenital (colo, vulva, perineo, região perianal e anal)<sup>(4)</sup>. A Organização Mundial da Saúde (OMS), em parceria com a *International Agency for Research on Cancer* (IARC), identificou os tipos 16 e 18 como os principais agentes etiológicos do câncer de colo uterino<sup>(5)</sup>. Estima-se que, aproximadamente, 75-80% da população feminina será infectada até completar a idade de 50 anos<sup>(6)</sup>.

Além de aspectos relacionados à própria infecção pelo HPV (tipo e carga viral, infecção única ou múltipla), outros fatores como alta paridade, uso prolongado de contraceptivos orais e tabagismo parecem influenciar os mecanismos ainda incertos que determinam a regressão ou a persistência da infecção e também a progressão para lesões precursoras ou câncer. A idade também interfere nesse processo, sendo que a maioria das infecções por HPV em mulheres com menos de 30 anos regride espontaneamente, ao passo que, acima dessa idade, a persistência é mais frequente<sup>(1,7)</sup>.

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Entretanto, uma pequena fração de mulheres apresenta persistência da infecção, provavelmente por falha de mecanismos imunológicos, o que pode provocar alteração no epitélio cervical e transformação maligna. As mulheres que apresentam infecção persistente por tipos virais de alto risco do HPV são consideradas o verdadeiro grupo de risco para o desenvolvimento do câncer cervical<sup>(2)</sup>.

O exame de prevenção do câncer do colo uterino, cujos primórdios no Brasil datam da década de 1940, foi implantado na rede pública em 1999 e compõe atualmente a Política Nacional de Atenção Oncológica, sob responsabilidade do Instituto Nacional do Câncer José Alencar Gomes da Silva (INCA). Sua finalidade consiste na detecção precoce da neoplasia invasora e suas lesões precursoras por meio da análise citológica periódica do esfregaço obtido pela coleta utilizando a técnica de Papanicolaou. Dados estatísticos revelam que o rastreamento efetivo consegue reduzir a incidência de formas invasoras do câncer de colo em até 91%. Porém, a incidência da doença mantém-se como uma das mais altas entre as neoplasias malignas que ocorrem em mulheres brasileiras<sup>(8)</sup>.

Sabendo que o câncer cervical é uma doença passível de prevenção através da detecção precoce e do tratamento das lesões precursoras, se faz necessário o rastreamento de alterações cervicovaginais ainda em adolescentes e mulheres jovens.

## OBJETIVO

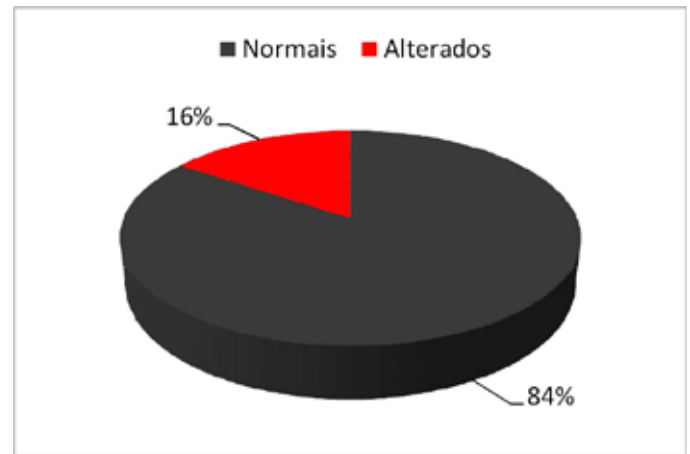
Conhecer o perfil citopatológico de mulheres atendidas nas Unidades Básicas de Saúde do município de Uruguaiana, RS.

## MÉTODOS

Trata-se de um estudo retrospectivo de corte transversal e descritivo, no qual foram analisados 12.644 laudos de exames citopatológicos de pacientes que realizaram a citopatologia ginecológica (Papanicolaou) e respectivos prontuários nas Unidades Básicas de Saúde do município de Uruguaiana, RS, no período de 2003 a 2011. Os esfregaços cervicovaginais foram encaminhados para o Laboratório Central de Saúde Pública (LACEN) localizado em Porto Alegre, RS. Os critérios de inclusão no estudo foram preenchimento da idade das pacientes e o resultado do exame citopatológico. A análise dos dados não contempla laudos repetidos.

As alterações citopatológicas foram classificadas segundo Bethesda, 2001<sup>(9)</sup> e agrupadas em: atipias de significado indeterminado de células escamosas e glandulares (ASC-US/AGUS); lesões intraepiteliais de baixo grau (LIEBG), que incluem NIC I; lesões intraepiteliais de alto grau (LIEAG), que incluem NIC II e NIC III e câncer para carcinoma escamoso invasivo. Foram selecionadas as variáveis referentes à idade e a alteração citopatológica. Para a análise dos resultados, as pacientes foram classificadas de acordo com a faixa etária (inferior a 25; 26-35; 36-45; 46-55; 56-65; mais de 65 anos) e os dados foram plotados no programa Microsoft Office Excel e posteriormente analisados pelo programa GraphPad Prisma, expressos em porcentagem.

O presente estudo foi autorizado pelo atual secretário de saúde do município de Uruguaiana e aprovado pelo Comitê de Ética e Pesquisa (CEP) da Universidade Federal do Pampa (UNIPAMPA) sob o número URU47/11.



**Figura 1** – Percentual de laudos citopatológicos normais e alterados de pacientes que realizaram a citopatologia ginecológica em Unidades Básicas de Saúde do município de Uruguaiana, RS, no período de 2003 a 2011.

## RESULTADOS

Dos 12.644 laudos de exames citopatológicos analisados, 1.963 (15,5%) possuem alguma alteração celular, conforme observado na **Figura 1**. Dentre as alterações celulares observadas nos laudos citopatológicos, a que apresentou maior prevalência foi a atipia de células escamosas de significado indeterminado (ASC-US), com 50,28%, seguida das lesões intraepiteliais de baixo grau (LIEBG), com 35,45%. Em ambos os casos as mulheres com idade inferior a 25 anos foram as que apresentaram maior prevalência (**Tabela 1**).

Da totalidade dos laudos analisados, 255 pacientes apresentaram lesões cervicais associadas ao papilomavírus humano (HPV) e a maior prevalência foi observada na faixa etária inferior a 25 anos (47,84%) e decresce após essa idade, conforme apresentado na **Tabela 2**.

## DISCUSSÃO

A incidência do câncer do colo de útero vem aumentando consideravelmente em diversas regiões do Brasil em mulheres jovens e está, na maioria das vezes, associada à infecção pelo HPV<sup>(1)</sup>.

No presente estudo, a média de idade das pacientes com alterações citopatológicas foi de 33,37 anos. A faixa etária que apresentou maior número de alterações celulares foi inferior a 25 anos, representando 607 (30,92%) pacientes, seguida da faixa etária de 26-35 anos com 571 (29,08%) pacientes.

Em relação aos laudos com alterações citológicas, foi observado predomínio das atipias de significado indeterminado (ASC-US) e lesões intraepiteliais de baixo grau (LIEBG), representando respectivamente 987 (50,28%) e 696 (35,45%) pacientes. Essas alterações foram mais prevalentes nas mulheres mais jovens, com maior número de casos em pacientes com menos de 25 anos. De acordo com dados da literatura, a atipia escamosa de significado indeterminado é a mais comum anormalidade epitelial diagnosticada nos esfregaços corados pelo método de Papanicolaou e representam até 10% dos resultados processados nos laboratórios de citologia<sup>(10,11)</sup>.

Um estudo realizado por Prado *et al.*<sup>(12)</sup> rastreou pacientes com resultados colpocitológicos de ASCUS/AGC, LSIL e HSIL, entre

**Tabela 1** – Prevalência de exames citopatológicos de colo de útero com alterações, de acordo com a faixa etária e atipias celulares

Faixa Etária	Alterações Celulares					
	ASC-US <sup>a</sup>	ASC-H <sup>b</sup>	AGUS <sup>c</sup>	LIE BG <sup>d</sup>	LIE AG <sup>e</sup>	CEI <sup>f</sup>
Inferior a 25 anos	293 (29,68%)	1 (33,3%)	10 (9,61%)	281 (40,37%)	22 (14,56%)	0
26-35 anos	280 (28,36%)	1 (33,3%)	14 (13,46%)	216 (31,03%)	56 (37,0%)	4 (18,18%)
36-45 anos	237 (24,01%)	0	38 (36,53%)	145 (20,83%)	50 (33,11%)	11 (50,0%)
46-55 anos	133 (13,47%)	1 (33,3%)	34 (32,70%)	45 (6,46%)	18 (11,92%)	4 (18,18%)
56-65 anos	30 (3,03%)	0	6 (5,77%)	5 (0,72%)	3 (1,98%)	1 (4,54%)
Mais de 65 anos	14 (1,41%)	0	2 (1,92%)	4 (0,57%)	2 (1,32%)	2 (9,09%)
Total	987 (50,28%)	3 (0,15%)	104 (5,29%)	696 (35,45%)	151 (7,6%)	22 (1,12%)

<sup>a</sup> atipias de significado indeterminado de células escamosas; <sup>b</sup> células escamosas atípicas que não permitem excluir uma lesão de alto grau; <sup>c</sup> atipias de significado indeterminado de células glandulares; <sup>d</sup> lesão intraepitelial de baixo grau; <sup>e</sup> lesão intraepitelial de alto grau; <sup>f</sup> carcinoma escamoso invasivo.

**Tabela 2** – Percentual de laudos citopatológicos de pacientes portadoras de lesões cervicais por HPV, de acordo com a faixa etária

Faixa Etária	Número de Pacientes
Inferior a 25 anos	122 (47,84%)
26-35 anos	77(30,20%)
36-45 anos	47(18,43%)
46-55 anos	7(2,74%)
56-65 anos	1(0,39%)
Mais de 65 anos	1(0,39%)
Total (100%)	255

2007 a 2008, no setor público da cidade de Rio Branco no Acre, e encontrou resultados colpocitológicos de ASCUS/AGC, LSIL e HSIL, 18,2% (n = 154) apresentaram lesão intraepitelial de baixo grau (LSIL), 13,2% (n = 112) lesão intraepitelial de alto grau (HSIL), 66,5% (n = 563) atipias de significado indeterminado (ASCUS/AGC) e 2,0% (n = 17) tinham câncer.

Acredita-se que o alto número de diagnósticos de ASC-US encontrado em nosso estudo seja um meio de escape para as dificuldades diagnósticas, provavelmente, fruto de erros na coleta e leitura das lâminas citológicas e pelas limitações dos serviços públicos de saúde. Para diminuir os fatores que geram este abuso, deve-se garantir a acuidade diagnóstica do teste de Papanicolaou com atividades de controle de qualidade, permitindo êxito na detecção precoce e no tratamento das lesões cervicais<sup>(13)</sup>.

Pereira *et al.*<sup>(14)</sup> avaliaram o desempenho dos laboratórios da rede pública do estado de São Paulo envolvidos no Monitoramento Externo de Qualidade (MEQ) e a aplicabilidade deste método de controle de qualidade no Sistema Único de Saúde (SUS). Dos 67.954 casos analisados no período entre 2000 e 2004, houve discordância diagnóstica em 9.641 (14,2%) casos. O total de alterações epiteliais atípicas observadas no período estudado foi de 21,5%, distribuídas nas categorias ASCUS/AGUS, 8,8%, LSIL, 9,1%; HSIL, 3,2%; e lesões invasivas, 0,4%. O percentual de discordância na categoria diagnóstica ASCUS/AGUS, em 2000, foi de 32,3%, com redução para 19,2% em 2004. O mesmo ocorreu com os diagnósticos de LSIL, HSIL e lesões invasivas com valores respectivos de 20,6%, para 6,3%, 27,1% para 10,6% e 31,7% para 11,5%.

As avaliações do MEQ podem ser usadas pelos laboratórios a Rede Pública para implantação de estratégias de controle interno de qualidade e aprimoramento das preparações técnicas, através de treinamento em colheita, fixação e coloração das amostras, resultando assim, na redução das taxas de resultados falso-negativos e falso-positivos, além da garantia de qualidade dos laboratórios que prestam serviços ao Sistema Único de Saúde<sup>(14)</sup>.

Um estudo realizado com 230 casos de pacientes apresentando lesões cervicais de baixo grau a carcinoma cervical escamoso apontou que 20,7% dessas lesões regrediram espontaneamente, 48,9% persistiram e 30,4% progrediram, corroborando outras afirmações da literatura que tendem a apontar um índice de remissão espontânea das lesões em torno de 30%<sup>(15)</sup>.

Segundo Bezerra *et al.*,<sup>(16)</sup> a incidência do câncer de colo de útero ocorre em mulheres com idades entre 40 e 60 anos, sendo menos frequente antes dos 30 anos, o que se deve ao longo período da evolução da infecção inicial pelo HPV até o aparecimento do câncer. Em nosso estudo, a faixa etária com maior número de casos de câncer de colo de útero é de 36 a 45 anos, com 11 casos. Porém, os autores comentam que esse quadro vem se modificando aos poucos e o aparecimento de lesões precursoras está ocorrendo cada vez mais precocemente, devido à iniciação cada vez mais antecipada da atividade sexual associada aos demais fatores de risco.

A prevalência de lesões cervicais por HPV observadas nesse estudo foi de 13% (255 pacientes). Segundo Rama *et al.*<sup>(17)</sup>, as maiores prevalências de HPV são encontradas em mulheres abaixo dos 25 anos, com progressivo declínio linear após esta idade, devido à elevação da idade resultar em mudanças dos hábitos sexuais, tornando as mulheres menos expostas. Este achado corrobora com os resultados deste estudo, onde a faixa etária com maior prevalência de lesões cervicais por HPV é inferior a 25 anos (47,84%).

Das lesões cervicais por HPV, 177 estão associadas a lesões intraepiteliais de baixo grau (LIEBG) e 78 a atipias de células escamosas de significado indeterminado (ASC-US). As infecções associadas ao HPV em mulheres jovens têm sido relacionadas a fatores como múltiplos parceiros sexuais, idade, início precoce da atividade sexual, fumo e uso de anticoncepcional oral<sup>(18)</sup>.

Salienta-se a necessidade de políticas de rastreamento de lesões cervicais em mulheres nesta faixa etária, evitando assim



a progressão das lesões que evoluem ao câncer, uma vez que 14,56% de LIE de alto grau ocorreram em mulheres com menos de 25 anos de idade.

## CONCLUSÃO

A faixa etária de maior prevalência de lesões cervicais está em mulheres com idade inferior a 25 anos e muitas das alterações celulares estão associadas à infecção pelo HPV. Cerca de metade das mulheres com colpocitologia alterada apresentava ASC-US.

## Conflito de interesses

Não há conflito de interesses a declarar.

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# CONHECIMENTO SOBRE DST ENTRE POLICIAIS MILITARES DO 10º BPM DO ESTADO DO RIO DE JANEIRO

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## RESUMO

**Introdução:** as DST são um sério problema de saúde pública, causando várias complicações, como infertilidade, câncer de colo de útero, câncer de pênis, além de vários problemas psicossociais. **Objetivo:** verificar o conhecimento de DST e fatores de risco para aquisição de DST entre policiais militares do 10º Batalhão de Polícia Militar do Estado do Rio de Janeiro (10º BPM-RJ). **Métodos:** estudo epidemiológico com delineamento transversal com aplicação de questionário autoaplicável, individual e anônimo. População-alvo: policiais militares do 10º BPM, situado em Barra do Pirai, RJ. O questionário foi constituído de 24 perguntas que abordavam dados sociodemográficos (como idade, sexo, estado civil, patente) e de comportamento sexual/práticas de risco (tipo de parceria, práticas sexuais, uso de preservativo, número de parceiros, frequência das relações, uso de bebidas alcoólicas, drogas ilícitas). **Resultados:** de 600 questionários distribuídos para um efetivo de 771 policiais militares na ativa, 313 foram respondidos, sendo 291 incluídos para análise. A média de idade foi de 36,9 anos, 76,64% eram casados, 89,7% conhecem as DST, 94,5% sabem como se previne DST, 90,37% já tiveram DST, 13,05% já tiveram DST, 95,88% utilizam contraceptivo, 22,68% tiveram mais de 41 parceiros sexuais na vida, 40% tiveram mais de dois parceiros sexuais no último ano, sendo que 14,42% tiveram mais de seis parceiros sexuais nos últimos 12 meses, 23% possuem relação extraconjugal, cerca de 13% relataram relação sexual com profissionais do sexo, 9,27% informaram relação sexual em grupo, 6,19% usam bebidas alcoólicas durante a relação sexual, 4% informaram atividade sexual com pessoa do mesmo sexo, 45,36% possuem duas a três relações sexuais por semana, 71,14% fazem sexo oral e 34,02% fazem sexo anal. **Conclusão:** policiais militares do 10º BPM apresentam alto conhecimento sobre DST e existe considerável risco para a aquisição de DST pelos PM do 10º BPM-RJ, pois muitos não usam preservativos, possuem parceria sexual múltipla, têm relação sexual extraconjugal, fazem sexo em grupo e praticam relação sexual com profissionais do sexo.

**Palavras-chave:** DST, educação, policiais militares, 10º BPM-RJ

## INTRODUÇÃO

As doenças sexualmente transmissíveis (DST) representam um problema de saúde pública, principalmente em países em desenvolvimento<sup>(1)</sup>. No estudo da sexualidade, é necessária a investigação das práticas de risco e a prevalência de infecções por transmissão sexual. Tal relação é atribuída pela morbimortalidade decorrente deste tipo de infecção, especialmente do HIV/aids<sup>(2)</sup>.

Muitos fatores contribuem para a atual situação do mundo frente às DST, por exemplo, falta de informação/educação sexual, idade precoce do início da atividade sexual, baixa renda e baixa escolaridade, falta de uso consistente de preservativos, multiplicidade de parceiros, relações com profissionais do sexo, uso de bebidas alcoólicas e alucinógenas durante práticas sexuais, entre outros. Em um país como o Brasil, em que os recursos financeiros para saúde e educação ainda são restritos e, muitas das vezes, mal aproveitados, a solução nem sempre está na implementação de técnicas avançadas, e sim na medicina preventiva.

As DST são consideradas de alta morbidade e trazem consequências sérias, como infertilidade, doenças neonatais, gravidez ectópica, mutilações em genitais, cânceres e até mesmo a morte, além do forte fator predisponente para uma contaminação pelo HIV/aids<sup>(3)</sup>. Costa & Germano<sup>(4)</sup> citando Carrara, autor de impor-

tante publicação sobre a história da sífilis no Brasil, relatam-nos: “Em 1873, um ministro da Guerra do Império, o médico João José de Oliveira Junqueira, reconhecia a sífilis como a doença mais comum entre os soldados. Em 1883, ele garantia não existir nenhum soldado que não tivesse tido mais de um internamento por doença venérea.

No 1º Congresso Sul-Americano de Dermatologia e Sifilografia, em 1918, o médico militar Júlio Porto Carrero atenta para o “crescimento da incidência de doenças venéreas nas forças armadas”. Os mesmos autores, Costa & Germano<sup>(4)</sup>, ainda afirmam que “a posição social conferida aos policiais militares coloca-os em uma situação de destaque, sendo simbolizada pela farda. Seria para as mulheres um exemplo de masculinidade e fortaleza, portanto, de homem ideal”. É claro que a posição de militar, farda, masculinidade e homem ideal não se aplica para todas as mulheres de todas as classes sociais.

É importante identificar o conhecimento sobre DST e riscos para DST entre policiais militares do estado do Rio de Janeiro, a fim de traçar estratégias para melhorar a saúde dos militares e de seus familiares. Assim, após analisar os dados de conhecimento sobre educação em saúde em DST entre policiais militares, será possível delinear propostas para atividades que aumentem os conhecimentos sobre DST e práticas de sexo seguro nesta população.

É esperado, então, que os policiais militares estendam os conhecimentos aprendidos aos seus familiares. Com isso, esperamos contribuir para melhorar a saúde dos policiais militares envolvidos na pesquisa, bem como a de suas famílias.

## OBJETIVO

Verificar o conhecimento de DST e fatores de risco para aquisição de DST entre policiais militares lotados no 10º Batalhão de Polícia Militar do Estado do Rio de Janeiro (10º BPM-RJ).

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Este artigo foi apresentado e aprovado por comissão de avaliação específica, como requisito final do Curso de Aperfeiçoamento de Oficiais na Polícia Militar do Estado do Rio de Janeiro.

## MÉTODOS

Foi realizada reunião com o comandante do 10º BPM-RJ para a apresentação do projeto e a posterior distribuição dos questionários e das urnas lacradas, para cada companhia. O 10º BPM-RJ está situado no município de Barra do Pirai, RJ e é composto de cinco companhias (Barra do Pirai, Vassouras, Paty do Alferes, Valença e Pirai) e do Pelotão de Comando e Serviço (PCSV).

Os comandantes de cada companhia receberam informações sobre esta pesquisa para a participação voluntária e totalmente não identificável dos PM de suas companhias. Os questionários e as urnas ficaram disponíveis na secretaria de cada corporação militar.

O questionário autoaplicável foi constituído de 24 perguntas que abordavam dados sociodemográficos (como idade, sexo, estado civil, patente) e de comportamento sexual/práticas de risco (identidade sexual declarada, tipo de parceria, práticas sexuais, número de parceiros e frequência das relações).

Não utilizamos o termo de consentimento livre e esclarecido (TCLE) porque, se fosse usado, de alguma maneira, poderia identificar os sujeitos de um grupo de pesquisa, especialmente dos oficiais superiores, pois esse grupo tem contingente muito menor que o de praça. Assim, procuramos maior adesão, uma vez que, desta forma, o estudo não dá chance para a identificação.

Tipo de estudo: estudo epidemiológico com delineamento transversal com a aplicação de questionário autoaplicável, individual e anônimo.

População-alvo: policiais militares, praças (soldado, cabo, 3º sargento, 2º sargento, 1º sargento, subtenente) e oficiais (cadete, aspirante, 2º tenente, 1º tenente, capitão, major, tenente-coronel e coronel) masculinos e femininos do 10º BPM-RJ, situado em Barra do Pirai.

Ao todo, o efetivo é composto de 771 policiais militares e foram disponibilizados 600 questionários para todo o contingente, por considerarmos que vários PM estão, no momento, afastados de suas atividades por motivos diversos (licença médica, férias).

Local do estudo: 10º BPM-RJ situado em Barra do Pirai, RJ e as suas companhias.

Crítérios de inclusão: Preenchimento correto do questionário autoaplicável e colocação em urna lacrada e sem identificação.

Crítérios de exclusão: Não preenchimento do questionário ou preenchimento de menos de 50% do mesmo.

Época do estudo: Os questionários foram distribuídos e coletados nos meses de setembro e outubro de 2012.

Análise estatística: Frequência simples.

## RESULTADOS

Do total de 600 questionários disponibilizados, recebemos 313 questionários. Todavia, foram incluídos 291 (92,97%) questionários devidamente preenchidos para serem analisados.

Quanto ao sexo dos sujeitos de pesquisa, 21 (7,21%) eram mulheres e 269 (92,44%) eram homens. Apenas em um questionário (0,35%) esta questão não foi respondida.

A média de idade dos PM foi 36,9 anos, sendo 21 anos a menor idade relatada e 58 anos a maior. Quanto ao estado civil, os resultados estão na **Tabela 1**.

**Tabela 1.** Estado civil – PM – 10º BPM-RJ, 2012

Estado Civil	N (%)
Solteiro	50 (17,19%)
Casado	223 (76,64%)
Divorciado	12 (4,13%)
Viúvo	3 (1,03%)
Não respondeu	3 (1,03%)

Sobre patentes, encontramos que dez (3,5%) eram oficiais e 273 (93,81%) eram praças. Dos praças, 60 (20,62%) declararam que tinham curso superior. Considerando que os números de pessoas do sexo feminino e de oficiais são sensivelmente menores que os de pessoas do sexo masculino e de praças, apresentaremos os demais resultados de forma conjunta.

Nas **Tabelas 2 a 9** apresentamos os principais resultados das perguntas do nosso questionário.

Dos 38 PM que relataram ter tido DST, as doenças citadas foram: sífilis (4/10,52%), gonorreia (19/50%), verruga genital/HPV (8/21,05%) e herpes genital (8/21,05%).

**Tabela 2.** Conhece DST, previne DST, tem medo de DST, teve aula de DST, teve DST, usa preservativo, usa contraceptivo, PM – 10º BPM-RJ, 2012

Pergunta	Sim N (%)	Não N (%)
Conhece DST	261 (89,7%)	30 (10,3%)
Sabe prevenir DST	275 (94,5%)	16 (5,5%)
Tem medo de pegar DST	210 (72,16%)	81 (27,84%)
Teve aula de DST	263 (90,37%)	28 (9,63%)
Já teve DST	38 (13,05%)	253 (86,95%)
Usa preservativo	117 (40,20%)	174 (59,79%)
Usa contraceptivo	279 (95,88%)	12 (4,12%)

**Tabela 3.** Número de parceiros sexuais na vida, PM – 10º BPM-RJ, 2012

Número de Parceiros Sexuais	N (%)
1-5	64 (21,99%)
6-10	35 (12,02%)
11-20	59 (20,28%)
21-40	57 (19,59%)
41 ou mais	66 (22,68%)
Não informado	10 (3,44%)

**Tabela 4.** Número de parceiros sexuais no último ano, PM – 10º BPM-RJ, 2012

Número de Parceiros Sexuais	N (%)
Nenhum	7 (2,41%)
1	163 (56,01%)
2-5	75 (25,77%)
6-10	19 (6,52%)
11 ou mais	23 (7,90%)
Não informado	4 (1,37%)

**Tabela 5.** Frequência de relações sexuais por semana, PM – 10º BPM-RJ, 2012

Número de Relações Sexuais por Semana	N (%)
Nenhum	8 (2,75%)
1	18 (6,19%)
2-3	132 (45,36%)
4-5	97 (33,33%)
6 ou mais	34 (11,69%)
Não informado	2 (0,69%)

**Tabela 6.** Modelo de sexo, número de parceiros sexuais, PM – 10º BPM-RJ, 2012

Modelo de Parceria Sexual	N (%)
Única	211 (72,50%)
Múltipla	72 (24,75%)
Sem relação sexual no momento	8 (2,75%)

**Tabela 7.** Tipo de relação sexual, local anatômico, PM – 10º BPM-RJ, 2012

Local Anatômico de Relação Sexual	N (%)
<b>Vaginal</b>	
Sim	218 (74,92%)
Não	65 (22,34%)
Fez no passado	8 (2,7%)
<b>Oral</b>	
Sim	207 (71,14%)
Não	77 (26,46%)
Fez no passado	7 (2,41%)
<b>Anal</b>	
Sim	99 (34,02%)
Não	192 (65,98%)
Fez no passado	6 (1,03%)

**Tabela 8.** Relação sexual extraconjugal, em grupo e com pessoas do mesmo sexo, PM – 10º BPM-RJ, 2012

Relação Sexual Extraconjugal, em Grupo e com Pessoa do Mesmo Sexo	N (%)
<b>Extraconjugal</b>	
Sim	68 (23,37%)
Não	223 (76,63%)
Já no passado	29 (9,97%)
<b>Em grupo</b>	
Sim	19 (6,52%)
Não	272 (93,47%)
Já no passado	8 (2,75%)
<b>Com pessoa do mesmo sexo</b>	
Sim	9 (3,09%)
Não	282 (96,91%)
Já no passado	3 (1,03%)

## DISCUSSÃO

Embora muitos estudos sobre sexualidade, conhecimento e fatores de risco para a aquisição de DST existam na literatura médi-

**Tabela 9.** Uso de bebidas alcoólicas e drogas, PM – 10º BPM-RJ, 2012

Bebidas Alcoólicas e Drogas Ilícitas	N (%)
<b>Álcool</b>	
Sim	18 (6,19%)
Não	273 (93,81%)
Já no passado	23 (7,90%)
<b>Drogas ilícitas</b>	
Sim*	5 (1,72%)
Não	286 (98,28%)
Já no passado**	1 (0,35%)

\*Um caso de LSD, um de maconha, um de cocaína e êxtase, um de maconha e cocaína.

\*\*Um caso de cocaína e LSD.

ca, infelizmente poucos são sobre PM<sup>(5-7)</sup>. Na nossa amostra de 600 questionários disponibilizados, recebemos devidamente preenchidos 291, ou seja, 48,5%. Consideramos que para uma pesquisa envolvendo sexualidade, comportamentos e vulnerabilidades entre policiais militares, o retorno foi altamente satisfatório.

Todavia, de 313 questionários devolvidos, recebemos 22 (7,02%) questionários incompletos e uns poucos com comentários impróprios para serem analisados. Avaliamos que um contingente pequeno de PM do 10º BPM-RJ ainda carece de atenção para a seriedade de estudos como este.

Em estudo também usando questionário e risco de DST, Pinheiro *et al.*<sup>(5)</sup> trabalhando com 450 PM de Santa Catarina, obtiveram um contingente de 193 (42,89%) questionários devidamente preenchidos.

Como já dito anteriormente, não fizemos a análise por sexo. Todavia, destacamos que o percentual de mulheres no 10º BPM-RJ é de 7,21% e, segundo dados encontrados na publicação de D’Araujo<sup>(8)</sup>, esta taxa é maior do que as encontradas em forças armadas dos seguintes países, no início de 2001: Alemanha (2,8%), Dinamarca (5,0%), Espanha (5,8%), Grécia (3,8%), Itália (0,1%) e Noruega (3,2%).

A participação feminina nas PM do Brasil, em 2003 era: Rio de Janeiro (4%), São Paulo (9,7%), Minas Gerais (6,6%), Bahia (12,1%), Espírito Santo (7,5%), Rio Grande do Sul (5,7%), Amazonas (8,6%), Pará (13,4%), Pernambuco (3,3%), Ceará (1,5%), Tocantins (7,4%), Distrito Federal (4,7%)<sup>(9)</sup>.

A média de idade foi de 36,9 anos, sendo a menor idade declarada 21 anos e a maior, 58 anos. No estudo de Pinheiro *et al.*<sup>(5)</sup>, a média de idade foi praticamente igual, 36,7 anos. Todavia, a menor idade foi de 17 anos e a maior, de 65 anos. Dos 291 sujeitos de pesquisa, 223 (76,64%) declaram-se casados/vivendo com companheiro(a). Pinheiro *et al.*<sup>(5)</sup> informaram que este percentual foi de 62,7%.

Os PM deste estudo apresentam alto índice de conhecimento sobre as DST, pois 90% deles relataram conhecer alguma DST. Entretanto, ressaltamos que a própria autora já proferiu inúmeras palestras sobre esse tema, nos últimos 5 anos, no 10º BPM-RJ. Assim, acreditamos que isso possa ter alterado, para mais, o conhecimento sobre as DST. Outrossim, 10% dos pesquisados afirmam que não conhecem DST, o que mostra a necessidade de mais abordagem do assunto. Infelizmente, não encontramos artigo similar para a comparação.

No nosso estudo, 13,05% (38/291) dos PM relataram ter tido DST no passado. Destes, 50% alegaram passado de gonorreia, 21,05% de herpes, 21,05% de condiloma acuminado/HPV e 10,52% de sífilis.

Pizzol<sup>(10)</sup> trabalhando uma população de 1.745 atendimentos no ambulatório de dermatologia do Hospital da PM do Espírito Santo, em Vitória, encontrou 178 (10,2%) casos de DST, sendo 34,83% de uretrites não gonocócicas.

Pinheiro *et al.*<sup>(5)</sup> em 2011, após aplicarem questionário para PM do município de Ponta Grossa, Paraná, identificaram que 34 policiais (17,61%) possuem história pregressa de DST. Como no nosso estudo, a maior parte alegou ter tido gonorreia, seguida de HPV, herpes e sífilis. Destacamos que nenhum PM informou ter infecção por HIV.

Na nossa investigação, 59,79% (174/291) afirmaram que não usam preservativo nas relações sexuais. Na publicação de Pinheiro *et al.*<sup>(5)</sup> esse número foi de 146/193 (75,64%). No nosso material, 12/291 (4,12%) informaram o não uso de contraceptivo. Neste mesmo tema, Pinheiro *et al.*<sup>(5)</sup> citam resultado bem diferente do nosso, ou seja, 29,5%. No quesito número de parceiros por ano, os nossos resultados são bem similares aos números de Pinheiro *et al.*<sup>(5)</sup>. Comparando os nossos achados quanto aos itens número de parceiros sexuais no último ano, número de relações sexuais por semana, prática de sexo vaginal, anal, relação extraconjugal, relação com pessoas do mesmo sexo e relação com profissionais do sexo, observamos também a similaridade.

Cerca 10% dos PM de nossa investigação informaram relação sexual em grupo. Infelizmente, não encontramos qualquer publicação para comparar com os nossos números. Entretanto, vale dizer que essa é tradicionalmente considerada uma prática de alto risco para a aquisição de DST.

Encontramos informações de que 5/291 = 1,72% dos PM do 10º BPM que responderam ao questionário usam drogas ilícitas (maconha, LSD, cocaína, êxtase) 2 horas antes ou durante o relacionamento sexual. Pinheiro *et al.*<sup>(5)</sup> mostraram o consumo de drogas por 27,46% (53/193) policiais militares do Paraná. Todavia, a pergunta era geral e não explicitamente vinculada à relação sexual. No nosso estudo, 18/291 = 6,11% dos PM consomem álcool antes (2 horas) ou durante a relação sexual. Silveira<sup>(11)</sup>, estudando militares bombeiros de Florianópolis, Santa Catarina, mostrou que o consumo de álcool entre esses militares é baixo, em torno de 12%. Na investigação de Pinheiro *et al.*<sup>(5)</sup>, a pergunta sobre consumo de álcool era de forma geral e não relacionada diretamente com a relação sexual. O número encontrado pela autora foi 131/193 (67,87%).

Não temos como afirmar se os PM do 10º BPM-RJ usam menos drogas e bebidas alcoólicas que os PM de Ponta Grossa-PR, uma vez que as perguntas foram elaboradas de modos diferentes. Mesmo considerando que os nossos números sejam pequenos, o ideal é que profissionais militares tenham consumo zero de drogas ilícitas.

Embora tenhamos trabalhado com um tema inovador e importante para o segmento militar, apontamos as seguintes limitações do estudo: tempo exíguo para pesquisa de campo e elaboração do texto final, trabalho feito em apenas um BPM do estado do Rio de Janeiro, dificuldade natural de pesquisa com questionário autoaplicável sobre DST, sexualidade e comportamento de risco para DST em uma unidade militar e o fato de não termos trabalhado com diagnóstico clínico ou laboratorial de DST ou aids.

Avaliamos ser necessário estender estudo como este para outros BPM do estado do Rio de Janeiro, pois assim teríamos dados mais abrangentes.

## CONCLUSÃO

É alto o conhecimento de DST por parte de PM do 10º BPM-RJ. Existe considerável risco para aquisição de DST por PM do 10º BPM-RJ, pois muitos não usam preservativos, possuem parceria sexual múltipla, têm relação sexual extraconjugal, fazem sexo em grupo e praticam relação sexual com profissionais do sexo.

## Conflito de interesses

Não há conflito de interesses a declarar.

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# STD KNOWLEDGE AMONGST THE 10<sup>TH</sup> MILITARY UNIT POLICE OFFICERS OF THE STATE OF RIO DE JANEIRO

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## ABSTRACT

**Introduction:** STD are a serious public health problem, causing various complications, such as infertility, cervical cancer, penile cancer, and various psychosocial problems. **Objective:** evaluate the knowledge of STD and risk factors of the acquisition of STD among the 10<sup>th</sup> Military Unit police officers of Rio de Janeiro State. **Methods:** cross-sectional epidemiological study through the distribution of individual and anonymous questionnaires. Target population: Military police officers from the 10<sup>th</sup> MU, located in Barra do Pirai, Rio de Janeiro State. The questionnaire consisted of 24 questions addressing social-demographic data (age, sex, marital status, military rank) and sexual behavior/risk practices (partnership type, sexual practices, condom use, number of partners, frequency of intercourse, alcohol use, illicit drugs). **Results:** 600 questionnaires distributed for a total of 771 military officers on active duty, 313 were answered, and 291 included for analysis. The average age was 36.9 years, 76.64% married, 89.7% aware of STD, 94.5% know how to prevent from STD, 90.37% had lessons about STD, 13.05% already had STD, 95.88% use contraceptives, 22.68% had more than 41 sexual partners during their lifetime, 40% had more than two sexual partners last year, 14.42% had six sexual partners in the last 12 months, 23% have an affair, about 13% reported intercourse with sex professionals, 9.27% reported group intercourse, 6.19% use alcohol during intercourse, 4% reported homosexual activity, 45.36% make sex twice to three times a week, 71.14% make oral sex, and 34.02% reported anal sex. **Conclusion:** the 10<sup>th</sup> MU police officers have high knowledge about STD and there is a considerable risk of acquiring STD by these individuals, since many of them do not use condoms, have multiple sexual partners and extramarital sex as well, make group intercourse and also with sex professionals.

**Keywords:** STD, education, police officers, 10<sup>th</sup> MU-RJ

## INTRODUCTION

Sexually transmitted diseases (STD) are a public health problem, especially in developing countries<sup>(1)</sup>. In the study of sexuality, it is necessary to examine the risk practices and prevalence of sexually transmitted infections. Such a relationship is assigned to the morbidity and mortality caused by this type of infection, especially HIV/AIDS<sup>(2)</sup>.

Many factors contribute for the present worldwide situation concerning STD, such as lack of information/sexual education, early age in sexual activity, low income and low education levels, lack of consistent use of condoms, multiplicity of partners, intercourse with sex professionals, use of alcohol and illicit drugs during sexual practices, among others. In a country like Brazil, where financial resources for health and education are still limited and often underused, the solution is not always in the implementation of advanced techniques, but in preventive medicine.

STD are considered high morbidity illnesses, causing serious consequences, such as infertility, neonatal diseases, ectopic pregnancy, genital mutilations, cancers and even death, in addition to a strong predisponent factor for the infection with HIV/AIDS<sup>(3)</sup>. Costa & Germano<sup>(4)</sup> quoting Carrara, author of an important publication on the syphilis history in Brasil, reports the following: "In 1873, the War Minister of the Empire, the physician João José de Oliveira Junqueira, considered syphilis the most common disease

amongst soldiers. In 1883, he guaranteed there was not a single soldier who had not been hospitalised more than once due to a venereal disease".

In 1918, in the 1<sup>st</sup> South-American Congress of Dermatology and Syphilography, the medic officer Júlio Porto Carreto noticed the venereal diseases incidence growth among the police officers. The same authors, Costa & Germano<sup>(4)</sup>, asserted that "the social status given to the police officers put them in a prominent position symbolized by their uniform. For women, this would be an example of masculinity and strength, therefore, of the ideal man". Of course this statement does not apply to all women of all social status.

It is important to identify STD knowledge and their risks among police officers of the State of Rio de Janeiro, in order to create strategies to improve these officers and their families' health. Therefore, after analysing data concerning the knowledge about health education on STD among police officers, it will be possible to propose activities to increase this knowledge and also show safe sex practices to this population. It is then expected that the police officers extend this knowledge to their families. Through this action we hope to contribute to improve police officers health involved in this research, as well as their families.

## OBJECTIVE

Verify STD knowledge as well as risk factors for the acquisition of these diseases among police officers located at the 10<sup>th</sup> Military Unit of the State of Rio de Janeiro (10<sup>th</sup> MU-RJ).

## METHODS

A meeting was held with the commander of the 10<sup>th</sup> MU-RJ for the presentation of the project and the subsequent distribution of questionnaires and sealed boxes for each company. The 10<sup>th</sup> MU-RJ is located in the city of Barra do Pirai, Rio de Janeiro State, and it is composed of five companies (Barra do Pirai, Vassouras, Paty

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This article was submitted and approved by the evaluation committee as a requirement for completion of Improvement Officer Course of the Military Police of Rio de Janeiro.

do Alferes, Valença, and Pirai) and a Command and Service Squad (Pelotão de Comando e Serviço – PCSV).

Each company commander received information on this research, whose participation was voluntary and completely anonymous. Questionnaires and sealed boxes were available for each military unit office. The questionnaire is composed of 24 questions about social-demographic data (age, sex, marital status, military rank) and sexual behavior/risk practices (partnership type, sexual practices, condom use, number of partners, frequency of intercourse, alcohol use, illicit drugs).

The Free and Clarified Consent Term (FCCT) was not used in order not to identify individuals in a research group, especially senior officers, as these officers belong to a smaller contingent. In this manner, our purpose was to have a greater adherence, as the study gives no chance of identification.

Type of study: cross-sectional epidemiological study with application of individual and anonymous questionnaires.

Target population: male and female police privates (corporal, 3<sup>rd</sup> Sergeant, 2<sup>nd</sup> Sergeant, 1<sup>st</sup> Sergeant, Warrant officer) and officers (Cadet, Aspirant, 2<sup>nd</sup> Lieutenant, 1<sup>st</sup> Lieutenant, Captain, Major, Lieutenant Colonel and Colonel) of the 10<sup>th</sup> MU located in Barra do Pirai.

The unit is composed of 771 police officers, and 600 questionnaires were available for the whole contingent, as we considered that several police officers are presently away from their activities due to various reasons (sick leave, vacation).

Place of study: 10<sup>th</sup> MU-RJ located in Barra do Pirai, Rio de Janeiro State, and its companies.

Inclusion criteria: correct questionnaire filling in and insertion in sealed and unidentified box.

Exclusion criteria: blank questionnaires or less than 50% completed.

Period of study: questionnaires were distributed and collected in September and October, 2012.

Statistics analysis: simple frequency.

## RESULTS

Of a total of 600 questionnaires, 313 were collected, however, 291 completed questionnaires were included (92.97%) for analysis.

Regarding gender of the researched individuals, 21 (7.21%) were women, and 269 (92.44%) were men. Only in one questionnaire (0.35%) this question was not answered.

The average age of police officers was 36.9 years, 21 years the youngest and 58 years the oldest. Marital status is shown on **Table 1**.

**Table 1.** Marital Status - PO - 10<sup>th</sup> MU-RJ, 2012.

Marital Status	N (%)
Married	50 (17,19%)
Single	223 (76,64%)
Divorced	12 (4,13%)
Widow	3 (1,03%)
Not answered	3 (1,03%)

Concerning ranks, it was observed that 10 (3.5%) were senior officers, and 273 (93.81%) were corporals. Sixty (20.62%) cor-

porals informed college degree. Considering that the number of women and senior officers is significantly smaller than men and corporals, the remaining results will be shown together.

**Tables 2 to 9** present the main results of our questionnaires.

The 38 police officers who answered having had STD, mentioned the following diseases: syphilis (4/10.52%), gonorrhea (19/50%), genital wart/HPV (8/21.05%), and genital herpes (8/21.05%).

## DISCUSSION

Although there are studies in the medical literature about sexuality, knowledge, and risk factors for the infection with STD, very few of them are about POs<sup>(5-7)</sup>.

In our sample of 600 questionnaires made available, 291 were completed, which means 48.5%. The return was highly satisfactory, considering a research addressing sexuality, behaviour, and vulnerabilities among police officers.

However, of 313 questionnaires answered, 22 (7.02%) were not completed and a few contained comments not appropriate to be

**Table 2.** Knows STD, Knows how to prevent STD, Affraid to be infected with STD, Had lessons about STD, Had STD, Use condom, Use contraceptive, PO - 10<sup>th</sup> MU-RJ, 2012.

Question	Yes N (%)	No N (%)
Know STD?	261 (89.7%)	30 (10.3%)
Know how to prevent STD?	275 (94.5%)	16 (5.5%)
Affraid to be infected with STD?	210 (72.16%)	81 (27.84%)
Had lessons about STD?	263 (90.37%)	28 (9.63%)
Had STD?	38 (13.05%)	253 (86.95%)
Use condom?	117 (40.20%)	174 (59.79%)
Use contraceptive?	279 (95.88%)	12 (4.12%)

**Table 3.** Number of sexual partners during life, PO - 10<sup>th</sup> MU-RJ, 2012.

Number of Sexual Partners During Life	N (%)
1-5	64 (21.99%)
6-10	35 (12.02%)
11-20	59 (20.28%)
21-40	57 (19.59%)
41 or more	66 (22.68%)
Not informed	10 (3.44%)

**Table 4.** Number of sexual partners last year, PO - 10<sup>th</sup> MU-RJ, 2012.

Number of Sexual Partners Last Year	N (%)
None	7 (2.41%)
1	163 (56.01%)
2-5	75 (25,77%)
6-10	19 (6,52%)
11 or more	23 (7,90%)
Not informed	4 (1,37%)

**Tabela 5.** Frequência de relações sexuais por semana, PM – 10<sup>o</sup> BPM-RJ, 2012

Number of Intercourses per Week	N (%)
None	8 (2.75%)
1	18 (6.19%)
2-3	132 (45.36%)
4-5	97 (33.33%)
6 or more	34 (11.69%)
Not informed	2 (0.69%)

**Table 6.** Type of sex, number of sexual partners, PO - 10<sup>th</sup> MU-RJ, 2012.

Sexual Partnership Type	N (%)
Unique	211 (72.50%)
Multiple	72 (24.75%)
No sexual partner at the moment	8 (2.75%)

**Table 7.** Type of intercourse, anatomical location, PO - 10<sup>th</sup> MU-RJ, 2012.

Anatomical Location of Intercourse	N (%)
<b>Vaginal</b>	
Yes	218 (74.92%)
No	65 (22.34%)
Made in the past	8 (2.7%)
<b>Oral</b>	
Yes	207 (71.14%)
No	77 (26.46%)
Made in the past	7 (2.41%)
<b>Anal</b>	
Yes	99 (34.02%)
No	192 (65.98%)
Made in the past	6 (1.03%)

**Table 8.** Extramarital, group and homosexual intercourse, PO - 10<sup>th</sup> MU-RJ, 2012.

Extramarital, Group, and Homosexual Intercourse	N (%)
<b>Extramarital</b>	
Yes	68 (23.37%)
No	223 (76.63%)
In the past	29 (9.97%)
<b>Im group</b>	
Yes	19 (6.52%)
No	272 (93.47%)
In the past	8 (2.75%)
<b>Homosexual</b>	
Yes	9 (3.09%)
No	282 (96.91%)
In the past	3 (1.03%)

analysed. In our evaluation, a small group of police officers from the 10<sup>th</sup> MU-RJ still need to be informed of the seriousness of studies like the present research.

**Tabela 9.** Use of alcohol and illicit drugs, PO - 10<sup>th</sup> MU-RJ, 2012.

Alcohol and illicit drugs	N (%)
<b>Alcohol</b>	
Yes	18 (6.19%)
No	273 (93.81%)
In the past	23 (7.90%)
<b>Illicit drugs</b>	
Yes*	5 (1.72%)
No	286 (98.28%)
In the past**	1 (0.35%)

\*One case of LSD, one case of marijuana, one case of cocaine and ecstasy, one case of marijuana and cocaine.

\*\*One case of cocaine and LSD.

In a study also using questionnaires and STD risk, Pinheiro *et al.*<sup>(5)</sup> worked with 450 police officers from Santa Catarina State and obtained 193 (42.89%) completed questionnaires.

As already mentioned, our analysis was not by gender. However, we would like to emphasize that the percentage of women in the 10<sup>th</sup> MU-RJ is of 7.21%, and according to data found in publication of D’Araujo<sup>(8)</sup>, this rate is greater than the ones found in the military of the following countries in the beginning of 2001: Germany (2.8%), Denmark (5.0%), Spain (5.8%), Greece (3.8%), Italy (0.1%) and Norway (3.2%).

The female police officers participation in Brasil, in 2003, was as follows: Rio de Janeiro (4%), São Paulo (9.7%), Minas Gerais (6.6%), Bahia (12.1%), Espírito Santo (7.5%), Rio Grande do Sul (5.7%), Amazonas (8.6%), Pará (13.4%), Pernambuco (3.3%), Ceará (1.5%), Tocantins (7.4%), Federal District (4.7%)<sup>(9)</sup>.

The average age of officers was 36.9 years, the youngest was 21 years, and the oldest, 58 years. In a Pinheiro *et al.*<sup>(5)</sup> study, the average age was almost the same, 36.7 years. However, the youngest informed 17 years, and the oldest, 65 years. Out of the 291 individuals of the research, 223 (76.64%) reported to be married/living with a partner. The authors observed a percentage of 62.7%.

The PO of our study showed a high rate of knowledge about STD, as 90% of them reported awareness of some STD. However, we emphasize that the author of the present study has already given several lectures on this subject during the last five years in the 10<sup>th</sup> MU-RJ, which we believe could have positively modified the knowledge about STD. In addition, 10% of the individuals reported not knowing about STD, which shows the need for more approach to the subject.

Unfortunately, no similar literature was found for comparison.

In our study, 13.05% (38/291) of police officers mentioned that already had STD in the past. Fifty percent of them reported gonorrhea, 21.05% herpes, 21.05% condyloma acuminata/HPV, and 10.52% syphilis.

Pizzol<sup>(10)</sup> worked with 1,745 patients in the dermatology ambulatory of the PO Hospital in the city of Vitória, Espírito Santo State, and reported 178 (10.2%) cases of STD, 34.83% of them with non-gonococcal urethritis.

Pinheiro *et al.*<sup>(5)</sup>, in 2011, after collecting questionnaires of police officers in the city of Ponta Grossa, State of Paraná, identified 34 individuals (17.61%) with a previous history of STD. As oc-



curred in our study, most individuals reported gonorrhea, followed by HPV, herpes, and syphilis. We emphasize that no PO reported infection with HIV.

In our research, 59.79% (174/291) informed no use of condoms during intercourse. Pinheiro *et al.*<sup>(5)</sup> showed 146/193 (75.64%). In our material, 12/291 (4.12%) reported no use of contraceptives. Regarding this same subject, Pinheiro *et al.*<sup>(5)</sup> mentioned a very different result from ours, which is, 29.5%. In the item “number of partners per year” our results are similar to Pinheiro *et al.*<sup>(5)</sup> study. Nevertheless, when compared to our results, the items “number of partners last year”, “number of intercourses per week”, “vaginal, oral, anal sex practices”, “extramarital intercourse”, “homosexual intercourse”, and “intercourse with sex professionals”, were very similar.

About 10% of POs of our study informed practice of group intercourse. Unfortunately, no publication was found for comparison. However, it is worth saying that this is traditionally considered a high-risk practice for infection with STD.

Our study observed that 5/291 = 1.72% police officers of the 10<sup>th</sup> MU-RJ use illicit drugs (marijuana, LSD, cocaine, ecstasy) two hours before or during intercourse. Pinheiro *et al.*<sup>(5)</sup> showed drug consumption by 27.46% (53/193) of police officers in the State of Paraná. However, this was a general question and not explicitly vinculated to an intercourse. Silveira<sup>(11)</sup> studied firemen of the city of Florianópolis, Santa Catarina State, and observed low alcohol consumption, around 12%. In Pinheiro *et al.*<sup>(5)</sup> investigation, the question about alcohol consumption was not directly related to intercourse. The rate found by the author of the present study was of 67.87% (131/193).

We cannot assure that the 10<sup>th</sup> MU-RJ POs use less drugs and alcohol than the ones from Ponta Grossa, Paraná State, since the questions were elaborated in different ways. Even considering our numbers small, the ideal is that military professionals have zero consumption of illicit drugs.

Although we have worked with an innovative and important subject to the military segment, we point out the following limitations of the study: exiguous time for field research and elaboration of the final text, work done in only one military unit of the State of Rio de Janeiro, natural research difficulty with questionnaires about STD, sexuality and risk behaviour concerning STD in a military unit, and the lack of STD or AIDS laboratory or clinical diagnosis.

We consider necessary to extend this type of study to other MUs in the State of Rio de Janeiro in order to obtain a wider range of data.

## CONCLUSION

The 10<sup>th</sup> MU-RJ POs have a high knowledge about STD. There is a considerable risk of infection with STD by these police officers, as many do not use condoms, have multiple sexual partners, have extramarital intercourse and group intercourse as well, and have intercourse with sex professionals.

## Conflict of interest

There is no conflict of interest to be declared.

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# ABUSO SEXUAL CRÔNICO: ESTUDO DE UMA SÉRIE DE CASOS OCORRIDOS NA INFÂNCIA E NA ADOLESCÊNCIA

*CHRONIC ABUSE: STUDY OF A SERIES OF CASES OCCURRING IN CHILDHOOD AND ADOLESCENCE*

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## RESUMO

**Introdução:** a Organização Mundial de Saúde considera o abuso sexual um dos maiores problemas de saúde pública. Tal agravo atinge crianças e adolescentes muitas vezes silenciosamente e são praticados, usualmente, por pessoas ligadas diretamente às vítimas. **Objetivo:** descrever as características do abuso crônico em crianças e adolescentes, identificar os fatores de vulnerabilidade associados e avaliar o desfecho dos casos. **Métodos:** trata-se de uma série de 264 casos em 260 pacientes de 0 a 18 anos, vítimas de violência sexual, sendo 104 casos de abuso crônico, acompanhados no ambulatório de Atendimento a Crianças e Adolescentes Vítimas de Violência (ACAVV), do Hospital Universitário Antônio Pedro, da Universidade Federal Fluminense. Modelos de regressão logística, simples e múltiplos foram utilizados na análise estatística, considerando abuso crônico a variável dependente. **Resultados:** variáveis relacionadas com os 104 casos de abuso sexual crônico foram crianças (46), residência das vítimas (68) e ambiente intrafamiliar (75). Apesar do sexo feminino prevalente (91/104 casos), meninos tiveram três vezes mais chance de sofrer abuso crônico, tendo as vítimas de outros tipos de maus-tratos duas vezes mais chance de sofrer esse tipo de abuso, e manipulação de genitália, quatro vezes mais chance de acontecer quando comparado com o abuso sexual agudo. **Conclusão:** características das vítimas de abuso crônico foram crianças entre 6 e 10 anos e as adolescentes, abusadas dentro do ambiente familiar, ocorrendo a maioria absoluta na residência das vítimas; metade das vítimas teve sexo vaginal com seus agressores. Observou-se que a violência foi cometida por pais e padrastos, sendo associada a outros maus-tratos.

**Palavras-chave:** estupro, crianças e adolescentes, abuso sexual, DST

## ABSTRACT

**Introduction:** world Health Organization considers sexual abuse one of the greatest health problems publishes. Such grievance reaches children and adolescents many times silently, and are practiced, usually by people linked directly to victims. **Objective:** to describe the characteristics of chronic abuse in children and adolescents, identify vulnerability factors associated with the same and evaluate the outcome of cases attended. **Methods** it is studying a series of 264 cases in 260 patients from zero to 18 years, victims of sexual violence, including 104 cases of chronic abuse, as outpatients Care for Children and Adolescents Victims of Violence (ACAVV), of Antonio Pedro University Hospital, at Universidade Federal Fluminense. Logistic regression models, single and multiple, were used in the statistical analysis, considering chronic abuse, the dependent variable. **Results:** variables related to 104 cases of sexual abuse chronic were kids (46), residence of the victims (68) and family environment (75 cases). Although the prevalent female sex (91/104 cases), boys were three times more likely to suffer chronic abuse, and victims of other types of maltreatment twice as likely to suffer this kind of abuse, and manipulation of genitals four times more likely to happen compared to acute sexual abuse. **Conclusion:** characteristics of victims of chronic abuse were children, aged between six and 10 years and adolescents. The victims were abused within the family environment, where the majority occurred in the victim's residence committed by fathers and stepfathers, associated with other types of maltreatment. Importantly, half of the victims had vaginal sex with their aggressors.

**Keywords:** assault, children and adolescents, sexual violence, STD

## INTRODUÇÃO

A Organização Mundial de Saúde considera o abuso sexual como um dos maiores problemas de saúde pública, trazendo um

enorme desafio para a sociedade e para os profissionais que lidam com essa situação<sup>(1-4)</sup>.

Abuso sexual é qualquer atividade sexual que uma criança não pode compreender ou consentir. Ele inclui atos como carícias, contato oral-genital e relação sexual genital e anal, bem como exibicionismo, voyeurismo e exposição à pornografia<sup>(5)</sup>.

Abuso sexual pode ser dividido em agudo e crônico. O abuso sexual agudo acomete geralmente os adolescentes e as mulheres adultas; ocorre frequentemente no espaço público, usualmente uma única vez, sendo o agressor na maioria das vezes desconhecido. A hipótese diagnóstica é feita com base em denúncia pela vítima ou através de achados no exame físico. O atendimento deve ser realizado em serviço de urgência, o mais precocemente possível, para tratamento das eventuais lesões físicas e pelos prazos para profilaxia das doenças sexualmente transmissíveis e da gravidez<sup>(6)</sup>.

O abuso crônico atinge principalmente crianças cotidianamente, muitas vezes de forma silenciosa, repetidos por um período de tempo, geralmente no espaço privado e nem sempre associado à violência física. O agressor é usualmente conhecido, na maioria dos casos sendo pessoas ligadas às vítimas, sobre as quais exercem poder ou dependência. Trata-se de uma dinâmica complexa que geralmente envolve crises familiares e associação com outros tipos de maus-tratos<sup>(7,8)</sup>.

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De forma direta ou indireta, o abuso crônico inclui todos os membros da família, seja pelo “muro do silêncio” compactuado, seja pela participação ativa no abuso. Este tipo de abuso tende a exigir, além do atendimento inicial, intervenção mais aprofundada por parte de uma equipe multidisciplinar, em caráter ambulatorial, envolvendo médicos, enfermeiros, assistentes sociais, psicólogos, entre outros profissionais da saúde<sup>(2,7,9,10)</sup>.

Geralmente, o “muro do silêncio” costuma erguer-se em torno desse tipo de abuso, o que resulta em graves prejuízos psicológicos, emocionais e sociais para as vítimas. O encobrimento do mesmo pode ocorrer por inúmeras razões, desde a omissão da família até o receio da própria criança em relatar o ocorrido, temendo futuras punições; passando pela dificuldade diagnóstica e de notificação até a falta de dispositivos padronizados e efetivos para a adequada condução desses casos pelo sistema de saúde brasileiro<sup>(11)</sup>.

O abuso crônico propicia um efeito negativo na autoestima e no desenvolvimento psicológico das vítimas, com graves repercussões na vida adulta e, quanto mais nova a criança e estreita a relação da vítima com o abusador, maior poderá ser o dano emocional<sup>(12)</sup>.

## OBJETIVO

Descrever características do abuso crônico em crianças e adolescentes, identificar os fatores de vulnerabilidade associados a esse tipo de abuso e avaliar o desfecho dos casos.

## MÉTODOS

Trata-se de um estudo retrospectivo de uma série de 264 casos ocorridos em 260 pacientes de 0 a 18 anos, notificados como vítimas de violência sexual (agudos e crônicos), sendo 104 casos de abuso crônico, acompanhados no ambulatório de Atendimento a Crianças e Adolescentes Vítimas de Violência (ACAVV), do Hospital Universitário Antônio Pedro, da Universidade Federal Fluminense (HUAP-UFF), no período de março de 2004 a dezembro de 2010.

Foram analisadas variáveis relacionadas com as características da agressão, das vítimas e de seus agressores. Modelos de regressão logística, simples e múltiplo, foram utilizados na análise estatística, considerando como variável dependente o abuso crônico. O modelo de regressão logística múltiplo foi estimado utilizando um procedimento iterativo de inclusão de variáveis, o método *stepwise forward* não automático. A inclusão de cada variável no modelo foi verificada utilizando o teste da razão de verossimilhança e o critério de Akaike (AIC). Foram apresentadas as razões de chances (OR) brutas e ajustadas e os respectivos intervalos de confiança de 95%.

Em todas as análises foi adotado um nível de significância de 5%. As análises foram realizadas no SPSS (*Statistical Package for the Social Sciences*) versão 17.0 e no R versão 2.12.2.

O presente estudo foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da Universidade Federal Fluminense em maio de 2011 (CAAE: 0091.0.258.000-11).

## RESULTADOS

Na **Tabela 1**, avaliamos as características do abuso sexual em crianças e adolescentes, e segundo a classificação do abuso, podemos observar as variáveis que estiveram relacionadas com o abuso crônico.

Observamos que as crianças foram vítimas de abuso crônico em maior número, quando comparadas com o abuso agudo, e ainda que apesar de a maioria envolver o sexo feminino, os meninos estiveram mais relacionados com esse tipo de abuso.

Foi verificado que o abuso crônico aconteceu predominantemente na residência das vítimas, dentro do ambiente familiar, por pais e padrastos, e associado a outros tipos de maus-tratos.

Como se tratou de um estudo retrospectivo, os profissionais envolvidos não tiveram como interferir na condução dos casos, porém, ressalta-se que, dentre os dados recuperados, a manipulação da genitália ocorreu em maior proporção.

As variáveis envolvendo sexo da vítima, contexto do abuso, local da agressão e associação com outros tipos de maus-tratos foram significativas no modelo múltiplo e são apresentadas na **Tabela 2**.

Os meninos tiveram três vezes mais chance de sofrer abuso sexual crônico, e as vítimas de outros tipos de maus-tratos duas vezes mais, mostrando que sofrer maus-tratos está relacionado com esse tipo de abuso.

E, ainda, duas vezes mais chance de ocorrer na residência das vítimas, sendo a maioria desta violência perpetrada por agressores conhecidos das crianças e dos adolescentes, nos quais elas convivem e geralmente confiam.

Por fim, a mediana em dias entre a primeira violência sexual e a sua descoberta foi de 365 dias, sendo o intervalo interquartil (73-726), ou seja, 1 ano, porém entre a descoberta até a procura pelo primeiro atendimento foi somente de 7 dias, intervalo interquartil (2-40), ou seja, de 1 semana.

## DISCUSSÃO

O principal local da agressão no abuso crônico é a residência das vítimas, sendo o domicílio considerado na literatura um local privilegiado para a ocorrência da violência. Uma possível explicação para o fato é que a maioria dos agressores convive com essas crianças e adolescentes, mantendo uma relação de confiança, poder e dependência. Nessas situações, é comum que o abuso sexual seja mantido em sigilo, pois, na maioria das vezes, existem relações de afinidade entre eles<sup>(13,14)</sup>.

Assim, em cerca de 90% dos casos, o autor do abuso sexual crônico é alguém com quem a vítima convive, como o pai biológico, o padrasto, os tios, os irmãos ou vizinhos, em várias situações que impedem o crime de ser descoberto. Observamos que a soma desses agressores foi de 70,2% dos casos, ou seja, aparentados das vítimas, em que padrasto, pais e outros parentes estiveram nessa ordem relacionados com esse tipo de abuso<sup>(14,15)</sup>.

Nossos dados demonstraram ainda que as crianças estão mais relacionadas com o abuso crônico que os adolescentes; uma explicação para tal fato é que as mesmas são mais vulneráveis, pois permanecem por um tempo prolongado dentro do ambiente familiar com os agressores conhecidos<sup>(7)</sup>.

Os meninos, em nosso estudo, estiveram relacionados com o abuso sexual crônico. A violência e o trauma ocasionados por essa violência são intensos para os dois sexos, porém, pode ser mais difícil para os meninos se recuperarem, pois sofrem com a vergonha, calam-se e lidam com os estereótipos sobre a sua masculinidade<sup>(16)</sup>.

Sofrer outros tipos de maus-tratos é considerado um fator de vulnerabilidade para o abuso sexual crônico e encontramos em nosso estudo 97 casos associados a esse tipo de abuso; podemos

**Tabela 1** – Características das ocorrências segundo a classificação do abuso sexual em crianças e adolescentes acompanhadas no ambulatório de Atendimento a Crianças e Adolescentes Vítimas de Violência do Hospital Universitário Antônio Pedro, da Universidade Federal Fluminense, no período de 2004 a 2010

Variáveis	Classificação do Abuso				OR <sub>bruto</sub> (Abuso Crônico)	IC 95%
	Agudo (N = 160)		Crônico (N = 104)			
	n	%	N	%		
<b>Sexo da vítima</b>						
Meninas	146	91,3	91	87,5	1,00	
Meninos	14	8,8	13	12,5	1,49	(0,67-3,31)
<b>Faixa etária da vítima*</b>						
Adolescente	127	79,4	58	55,8	1,00	
Crianças	33	20,6	46	44,2	3,30	(1,90-5,73)
<b>Tipo do abuso – sexo vaginal*</b>						
Sim	102	77,9	42	51,2	0,30	(0,16-0,54)
Não	29	22,1	40	48,8	1,00	
<b>Tipo do abuso – manipulação de genitália*</b>						
Sim	11	8,4	22	26,8	4,00	(1,82-8,79)
Não	120	91,6	60	73,2	1,00	
<b>Contexto do abuso*</b>						
Intrafamiliar	23	14,6	75	72,1	1,00	
Extrafamiliar – conhecido	60	38,0	27	26,0	0,14	(0,07-0,26)
Extrafamiliar – desconhecido	75	47,5	2	1,9	0,01	(0,002-0,04)
<b>Local da agressão*</b>						
Residência do agressor	28	17,6	27	26,0	1,00	
Residência da vítima	33	20,8	68	65,4	2,14	(1,09-4,19)
Rua	72	45,3	3	2,9	0,04	(0,01-0,15)
Outros	26	16,4	6	5,8	0,24	(0,09-0,67)
<b>Relação do agressor com a vítima*</b>						
Pai	3	1,9	26	25,0	1,00	
Padrasto	2	1,3	27	26,0	1,56	(0,24-10,09)
Outros parentes	16	10,0	20	19,2	0,14	(0,04-0,56)
Vizinhos	26	16,3	13	12,5	0,06	(0,01-0,22)
Desconhecidos	74	46,3	2	1,9	0,003	(0,00-0,02)
Outras pessoas não aparentadas	39	24,4	16	15,4	0,05	(0,01-0,18)
<b>Faixa etária do agressor*</b>						
Escolar e adolescente	37	25,5	4	3,9	1,00	
Adulto e idoso	108	74,5	98	96,1	8,39	(2,89-24,40)
<b>Associação com outros casos de maus-tratos*</b>						
Sim	37	23,7	60	58,8	4,59	(2,67-7,88)
Não	119	76,3	42	41,2	1,00	

\*p – valor &lt; 0,05.

destacar a negligência como a forma predominante. Assim, mecanismos protetores para a prevenção da violência sexual como o fortalecimento familiar no cuidado com as crianças e adolescentes devem ser instituídos<sup>(17)</sup>.

Dentre os dados recuperados, encontramos 31 casos de doença sexualmente transmissível, sendo 23 relacionados com DST não viral, e a gonorreia é a mais prevalente. Já na DST viral encontramos oito pacientes, sendo três casos de condiloma acuminado e três de herpes genital; em dois não obtivemos informação quanto ao diagnóstico etiológico. Encontramos, ainda, um caso de soroconversão para hepatite C e quatro casos de gestação relacionados com abu-

so crônico. É importante ressaltar que observamos uma alta taxa de abandono de tratamento, com 76,9% dos casos; portanto, esses desfechos podem ter sido maiores que o encontrado. Assim, a limitação do nosso estudo esteve relacionada com a impossibilidade da recuperação dos dados obtidos e a falta de seguimento desses pacientes no nosso ambulatório. Como o estudo foi retrospectivo, a equipe não teve como interferir na captação dos mesmos.

Estar atento aos sinais diretos, indiretos e fatores de vulnerabilidade relacionados com os episódios de violência, tais como estrutura e dinâmica familiar às quais essa criança ou adolescente estão inseridos, sob a responsabilidade de quem são confiados,

**Tabela 2** – Modelo de regressão múltipla para o abuso crônico em crianças e adolescentes acompanhados no Atendimento a Crianças e Adolescentes Vítimas de Violência do Hospital Universitário Antônio Pedro, da UFF, no período de 2004 a 2010

Variáveis	Abuso Crônico (n = 104)	
	OR <sub>ajustado</sub>	IC 95%
<b>Sexo da vítima</b>		
Meninas	1,00	
Meninos	3,16	(1,13-8,84)
<b>Contexto do abuso</b>		
Intrafamiliar	1,00	
Extrafamiliar	0,11	(0,06-0,24)
<b>Local da agressão</b>		
Residência do agressor e outros (rua, motel etc.)	1,00	
Residência da vítima	1,94	(0,92-4,12)
<b>Associação com outros casos de maus-tratos</b>		
Sim	2,24	(1,13-4,42)
Não	1,00	

sinais sugestivos de outros maus-tratos, e a presença de doenças sexualmente transmissíveis (DST), é de suma importância, a fim de que as intervenções como acolhimento, acompanhamento e tratamento dessas vítimas sejam aplicadas nos casos suspeitos e/ou diagnosticados.

## CONCLUSÃO

As características das vítimas de abuso crônico foram crianças, do sexo feminino, na faixa etária entre 6 e 10 anos de idade e as adolescentes. As vítimas sofreram abuso dentro do ambiente familiar, onde a maioria absoluta ocorreu na residência da vítima e cometido por pais e padrastos, associado a outros tipos de maus-tratos. É importante ressaltar que a metade das vítimas teve sexo vaginal com seus agressores, porém a manipulação da genitália esteve mais relacionada a esse tipo de abuso.

## Conflito de interesse

Não há conflito de interesse declarar.

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# VULNERABILIDADE DOS IDOSOS FRENTE AO HIV/AIDS: TENDÊNCIAS DA PRODUÇÃO CIENTÍFICA ATUAL NO BRASIL

*FRONT OF THE VULNERABILITY OF ELDERLY HIV/AIDS: CURRENT TRENDS OF SCIENTIFIC PRODUCTION IN BRAZIL*

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## RESUMO

**Introdução:** a senilidade é considerada uma fase de grande vulnerabilidade à infecção pelo HIV; isso se deve ao contexto biopsicossocial de inserção do idoso, no qual há, normalmente, associação de sua figura a perdas, limitações, incapacidade de procriação e inatividade sexual. **Objetivo:** identificar as tendências da produção científica a respeito dos fatores que aumentam a vulnerabilidade dos idosos à síndrome da imunodeficiência adquirida (aids). **Métodos:** trata-se de um estudo de revisão integrativa, realizado por meio de consulta à Biblioteca Virtual em Saúde (BVS), sendo utilizadas as bases de dados: *Scientific Electronic Library Online* (SciELO) e *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS). Foram consultados artigos abrangendo o período de 2008 a 2012, e os mesmos foram organizados em um quadro específico e analisados para a descrição dos dados. **Resultados:** vários elementos determinantes da vulnerabilidade ao HIV/aids em idosos foram identificados nos estudos, e quase todos eles constituíram o insumo do nosso trabalho. Dentre os mais encontrados nas leituras realizadas, estão: existência de tabus sobre a sexualidade na velhice e conhecimento escasso dos idosos sobre a infecção pelo HIV. **Conclusão:** o método utilizado mostrou-se eficaz para a efetivação dos nossos objetivos. Os resultados apresentados ao longo da revisão revelam que ainda existem muitos tabus referentes à sexualidade dos idosos, e, conseqüentemente, poucos esclarecimentos sobre prevenção, transmissão e demais questões envolvendo a aids.

**Palavras-chave:** idoso, vulnerabilidade, síndrome de imunodeficiência adquirida

## ABSTRACT

**Introduction:** senility is considered a phase of great vulnerability to HIV infection; this is due to the insertion of the biopsychosocial context of the elderly, in which there is usually a combination of figure losses, limitations, inability to procreation and sexual inactivity. **Objective:** to identify trends in scientific production about the factors that increase the vulnerability of the elderly to Acquired Immunodeficiency Syndrome (AIDS). **Methods:** this is a study of integrative review, conducted by consulting the Virtual Health Library (VHL), and used the databases: *Scientific Electronic Library Online* (SciELO) and *Latin American and Caribbean Health Sciences* (LILACS). Were consulted articles covering the period from 2008 to 2012, and they were organized in a specific table and analyzed for data description. **Results:** several determinants of vulnerability to HIV/AIDS in the elderly were identified in the studies, and almost all of them were the input of our work, among the most commonly found in the readings taken are: existence of taboos about sexuality in old age and little knowledge the elderly about HIV infection. **Conclusion:** the method used was effective for realization of our goals. The results presented throughout the review shows that there are still many taboos concerning sexuality of the elderly, and consequently few clarifications on prevention, transmission and other issues surrounding AIDS.

**Keywords:** aged, vulnerability, acquired immunodeficiency syndrome

## INTRODUÇÃO

O envelhecimento diz respeito a um conjunto de efeitos que ocorrem com o passar dos anos. Biologicamente, corresponde a uma involução que afeta todos os sistemas fisiológicos do corpo, mas que não interfere, necessariamente, no bem-estar do indivíduo; psiquicamente, é uma fase que denota maturidade, sabedoria e compreensão da vida, advindas com as experiências vivenciadas pelo indivíduo<sup>(1)</sup>.

Destarte, o envelhecimento populacional tem sido considerado um evento progressivo em todo o mundo; dados do Instituto Brasileiro de Geografia e Estatística (IBGE) mostram que, em 2009,

havia mais de 22 milhões de idosos no Brasil, o que corresponde a 11,3% da população existente. A expectativa de vida também cresceu, atingindo mais de 73 anos em 2009 (contrapondo aquela encontrada no início do século XX, que não ultrapassava os 33,5 anos)<sup>(2)</sup>.

Entretanto, mesmo com as garantias previstas na Lei 10.741/2003, que dispõe sobre o Estatuto do Idoso, o preconceito e a negação da sociedade com relação à velhice ainda existem, o que dificulta a elaboração de políticas públicas direcionadas e efetivadas com base na atenção adequada, individualizada e holística<sup>(3)</sup>. Esta questão é fortalecida quando se observam as estatísticas nacionais referentes à incidência da síndrome de imunodeficiência adquirida nesta população: dados do Ministério da Saúde apontaram um total de 32.167 casos de aids em maiores de 50 anos no Brasil, e destes, 9.918 indivíduos estão com 60 anos ou mais<sup>(3)</sup>.

As construções sociais habituais consideram o idoso um ser predisposto a perdas (como, por exemplo, a morte do cônjuge), limitações, incapacidade de procriação e inatividade sexual. Isto compromete a percepção sobre as novas trajetórias que estes indivíduos podem traçar, fazendo com que a velhice se torne um processo passivo à vulnerabilidade e à fragilização frente às doenças. É neste contexto que surge a questão da aids na terceira idade<sup>(4)</sup>.

O número crescente de idosos contaminados com HIV e os fatores que contribuem para que isto aconteça despertaram o interesse em conhecer o que está sendo publicado sobre o tema.

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## OBJETIVO

Identificar as tendências da produção científica a respeito dos fatores que aumentam a vulnerabilidade dos idosos à síndrome da imunodeficiência adquirida (aids).

## MÉTODOS

O estudo consiste em uma revisão integrativa da literatura, que trata de um método baseado em pesquisas da prática clínica, ou seja, consiste na busca de evidências na área da saúde a partir de um delimitado tema ou questão, objetivando, de uma forma sistemática e organizada, aperfeiçoar o conhecimento do tema pesquisado, reunido e sintetizado. A revisão integrativa é composta por seis etapas: identificação do tema e formulação da questão norteadora; busca e coleta de dados (escolha das bases, ano de publicação, critérios de inclusão e exclusão); avaliação (definição das informações a serem extraídas, a partir das informações-chave); análise (procura de elucidação para os resultados diferentes ou conflitantes dos estudos incluídos na revisão integrativa); interpretação dos resultados (discussão e avaliação crítica dos estudos); apresentação dos resultados (descrição das etapas percorridas e exposição dos principais resultados da pesquisa)<sup>(5)</sup>.

A presente revisão tem como norteadora a seguinte questão: Quais são os fatores que tornam os idosos vulneráveis à infecção por HIV/aids?

A coleta de dados foi realizada entre março e setembro de 2012. A captura das produções foi processada pela internet, por meio da Biblioteca Virtual em Saúde (BVS), sendo utilizadas as bases de dados: *Scientific Electronic Library Online* (SciELO); Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS). A busca foi realizada utilizando-se as seguintes palavras-chave, encontradas nos DeCS (Descritores em Ciências da Saúde) na Biblioteca Virtual em Saúde: idoso, vulnerabilidade e síndrome de imunodeficiência adquirida. Os critérios de inclusão dos textos foram: textos completos disponibilizados *online*; e artigos publicados na língua portuguesa no período de 2008 a 2012, para que fosse possível aproximar o objetivo da pesquisa ao contexto atual.

Os textos foram identificados e selecionados por meio de três etapas: inicialmente se combinou o descritor “idoso e síndrome da imunodeficiência adquirida”, no qual foram encontrados 219 títulos; em seguida, “vulnerabilidade e síndrome de imunodeficiência adquirida”, onde foram encontrados 127 títulos, havendo, entre estes, alguns já identificados na combinação anterior; por fim, utilizou-se a combinação “idoso, vulnerabilidade e síndrome de imunodeficiência adquirida”, na qual foram encontrados 18 títulos, com alguns deles já encontrados nas buscas anteriores, totalizando, portanto, 365 textos.

Após a leitura dos 365 textos encontrados na busca baseada na questão norteadora, foram selecionados apenas 20 artigos, pois os demais não se adequavam aos critérios de inclusão estabelecidos e não se enquadravam na temática. É importante destacar que, destes 20 artigos selecionados, quatro repetiram-se nas buscas realizadas nas bases supracitadas.

Para a análise dos dados, os artigos foram organizados em uma Tabela específica (**Tabela 1**). As variáveis identificadas após a leitura do texto completo foram: autor(es); periódico; critério de

avaliação de periódico – QUALIS/CAPES; ano de publicação; metodologia; objetivos; e fatores determinantes para o aumento da vulnerabilidade do idoso ao HIV/aids (explanados no tópico “Resultados e Discussão”).

Em seguida, os artigos foram lidos de forma mais criteriosa para a realização da análise descritiva dos dados.

## RESULTADOS E DISCUSSÃO

Após a análise dos 20 artigos, evidenciamos que os mesmos foram publicados em 13 revistas científicas da área da saúde, que possuem artigos relacionados com o idoso frente ao HIV/aids. A Revista Gaúcha de Enfermagem, do Rio Grande do Sul, que contribui fortemente para a divulgação de pesquisas na área da saúde, foi a que apresentou o maior número de publicações referentes ao tema, representando um total de 20% das publicações. Logo em seguida, evidenciamos que o Jornal Brasileiro de Doenças Sexualmente Transmissíveis apresentou o percentual de 15% das publicações analisadas.

Os artigos foram publicados em periódicos da área da saúde em geral (Saúde Pública, Saúde do Idoso, Enfermagem, Atenção Básica), por meio de revistas, jornais e cadernos. No que se refere ao coeficiente de avaliação dos periódicos pela Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (*Qualis* CAPES), a maioria das publicações concentrou-se em revistas de circulação nacional B (18 publicações, ou seja, 90%), seguindo com duas (10%) em revistas de circulação nacional A.

Quanto ao número de publicações por ano da amostra estudada, observa-se que em 2010 houve uma quantidade considerável destas nas revistas que circulam no País. Tal fato pode estar associado ao Pacto pela Saúde, publicado em 22 de fevereiro de 2006 por meio da Portaria/GM nº 399, que inclui o Pacto pela Vida. Nele, a Saúde do Idoso é tratada como prioridade pela primeira vez na história das políticas públicas, oportunizando a apresentação e a discussão, junto aos gestores, profissionais da saúde e população, da nova dinâmica epidemiológica e demográfica que se impõe no Brasil. Outra associação feita é com relação aos desdobramentos da Política Nacional de Saúde da Pessoa Idosa - PNSPI (Portaria nº 2.528, de 19 de outubro de 2006), que se preocupa com a situação da saúde da população idosa ao direcionar sua atenção a recuperação, manutenção e promoção da autonomia e da independência da mesma, priorizando a qualidade da assistência e impondo mudanças profundas nos modos de visualizar a velhice no mundo atual<sup>(3)</sup>.

Ao analisarmos as metodologias dos estudos presentes na amostra estudada, constata-se a predominância de artigos do tipo descritivo (dez artigos, ou seja, 50%). Além disso, quatro artigos (20%) configuraram-se em abordagem quantitativa.

Quanto aos objetivos propostos das pesquisas identificadas em periódicos científicos, verifica-se que em 14 artigos (70%) os autores direcionam sua pesquisa para o conhecimento do idoso com relação ao HIV/aids (o que é aids, medidas preventivas, modos de transmissão, vulnerabilidade, entre outros); em cinco deles (25%) os autores abordam o perfil epidemiológico de pacientes idosos notificados com aids; e, em um deles (5%) o autor faz ambas as abordagens. Estes dados revelam a preocupação dos profissionais da área da saúde com o crescente aumento do número de casos de infecção pelo HIV.



**Tabela 1** – Variáveis dos estudos incluídos na amostra

Autor	Periódico	QUALIS/ CAPES	Ano	Metodologia	Objetivo
Silva; Lope; Vargens	Revista Gaúcha de Enfermagem	B1	2010	Revisão sistemática da literatura	Debater a vulnerabilidade de DST e aids em idosas
Andrade; Silva; Santos	Escola Anna Nery	B1	2010	Estudo de caso, com abordagem qualitativa	Compreender a vivência dos idosos com aids em uma unidade de referência do SUS da região metropolitana de Belém-PA
Silva et al.	Epidemiologia e Serviços de Saúde	B2	2011	Estudo descritivo	Investigar as características epidemiológicas de pacientes idosos com aids notificados em hospital de referência no município de Teresina-PI
Toledo et al.	Revista da Sociedade Brasileira de Medicina Tropical	B2	2010	Estudo de série temporal	Analisar o perfil epidemiológico, socioeconômico e demográfico e a tendência da aids em indivíduos do Espírito Santo-ES
Batista et al.	Cadernos de Saúde Coletiva	B3	2008	Estudo transversal	Investigar o nível de conhecimento dos idosos sobre a aids
Pereira; Borges	Escola Anna Nery	B1	2010	Estudo descritivo, de seguimento seccional	Identificar o conhecimento sobre HIV/aids dos participantes do Centro de Convivência do Idoso em Anápolis-GO
Batista et al.	Revista Brasileira de Geriatria e Gerontologia	B3	2011	Estudo epidemiológico, quantitativo e transversal	Verificar a associação entre conhecimento da aids, atividade sexual e condições sociodemográficas entre idosos participantes do programa de educação permanente em Universidade do Nordeste Brasileiro
Praça; Souza; Rodrigues	Revista Texto & Contexto Enfermagem	A2	2010	Estudo descritivo e exploratório	Analisar a percepção sobre HIV/aids de mulheres com idade igual ou superior a 50 anos frequentadoras de uma UBS do município de São Paulo
Rodrigues; Praça	Revista Gaúcha de Enfermagem	B1	2010	Estudo qualitativo	Verificar a adoção de ações preventivas da transmissão do HIV por mulheres com idade igual ou superior a 50 anos atendidas pelo PSF de um município de São Paulo
Souza et al.	Avances em Enfermeria	B1	2009	Pesquisa quantitativo-exploratória	Verificar o nível de conhecimento de um grupo de idosos em relação ao HIV/aids
Lazzarotto et al.	Ciência & Saúde Coletiva	B1	2008	Estudo transversal	Avaliar o conhecimento sobre HIV/aids dos participantes de grupos de convivência do Vale do Sinos-RS
Melo et al.	Ciência & Saúde Coletiva	B1	2012	Estudo epidemiológico, descritivo e transversal	Comparar conhecimento de homens idosos ao de adultos jovens sobre aids
Godó; et al.	JBDST. Jornal Brasileiro de Doenças Sexualmente Transmissíveis	B3	2008	Estudo epidemiológico descritivo	Identificar a epidemiologia dos casos diagnosticados de aids no Brasil, em indivíduos com idade maior ou igual a 60 anos
Oliveira; et al.	Revista Enfermagem UERJ	B1	2011	Pesquisa descritiva, com abordagem qualitativa	Identificar e descrever os conteúdos das representações sociais do HIV/aids entre idosos e analisar as formas de enfrentamento usadas no cotidiano
Sousa; Suassuna; Costa	JBDST. Jornal Brasileiro de Doenças Sexualmente Transmissíveis	B3	2009	Estudo epidemiológico com abordagem qualitativa do tipo descritiva	Analisar o perfil epidemiológico de idosos com aids no município de João Pessoa-PB
Girondi; et al.	Acta Paulista de Enfermagem	A2	2012	Estudo quantitativo, do tipo ecológico descritivo	Identificar o perfil epidemiológico de idosos no Sistema de Informação de Mortalidade acometidos por aids no Brasil entre 1996 e 2007

Continua

**Tabela 1** – Variáveis dos estudos incluídos na amostra. *Continuação*

Autor	Periódico	QUALIS/ CAPES	Ano	Metodologia	Objetivo
Laroque; et al.	Revista Gaúcha de Enfermagem	B1	2011	Estudo qualitativo, exploratório e descritivo	Identificar o comportamento de idosos na prevenção das DST/aids
Maschio; et al.	Revista Gaúcha de Enfermagem	B1	2011	Pesquisa de caráter prospectivo, quantitativo e descritivo, com abordagem intencional	Identificar as medidas preventivas utilizadas pelos idosos para a prevenção das DST e aids
Sousa	JBDST. Jornal Brasileiro de Doenças Sexualmente Transmissíveis	B3	2008	Revisão de literatura	Abordar os temas da sexualidade na terceira idade, medicamentos para disfunção erétil e a tendência crescente de aids entre idosos
Santos; Assis	Revista Brasileira de Geriatria e Gerontologia	B3	2011	Revisão sistemática da literatura	Abordar os motivos para o aumento de HIV/aids na população acima dos 50 anos, no período de 1999 a 2009

Vários elementos determinantes da vulnerabilidade ao HIV/aids em idosos foram identificados nos estudos, e quase todos eles constituíram o insumo deste trabalho. Dentre os mais encontrados nas leituras realizadas, estão: existência de tabus sobre a sexualidade na velhice e conhecimento escasso dos idosos sobre a infecção pelo HIV.

Os idosos, por muito tempo, não se enquadraram no grupo de risco para acometimento da aids. De modo geral, nota-se que esta doença era restrita a grupos especiais, tais como: homossexuais, hemofílicos/transfundidos e usuários de drogas injetáveis<sup>(6)</sup>. Por este motivo, percebeu-se que muitos deles, ao descobrirem que estavam infectados, vivenciaram uma forma complexa de aceitação e enfrentamento<sup>(7)</sup>, pois não se viam como vulneráveis à infecção.

O mito de que o idoso é um ser assexuado também se fez presente nas leituras realizadas; a sociedade e os próprios profissionais de saúde raramente acreditam que os idosos possam ser atingidos por alguma doença sexualmente transmissível, pois os consideram como sexualmente inativos. Com isso, deixam de detectar precocemente a aids, ao negligenciarem a abordagem da sexualidade dessas pessoas e o exame imediato (sorologia para o HIV) após a observação e o relato dos primeiros sinais e sintomas<sup>(8-12)</sup>.

Além disso, observa-se que não há fornecimento de quaisquer informações aos idosos por parte dos profissionais concernentes às DST<sup>(12)</sup>, e muitos deles descrevem os meios de comunicação, tais como televisão, rádio e jornais, como suas principais referências<sup>(13)</sup>. Relatos de desconhecimento quanto ao simples modo de uso dos preservativos<sup>(14)</sup> fortalecem a ideia de escassez de orientações específicas.

É importante que os serviços de saúde acolham a terceira idade e desenvolvam ações voltadas para o HIV/aids, pois é sabido que muitos idosos deixam de buscar apoio nesses serviços por vergonha de serem vistos recebendo orientações sexuais ou preservativos, ou, quando já infectados, de serem descobertos por conhecidos e, conseqüentemente, estigmatizados e discriminados<sup>(15,16)</sup>.

Em vários estudos, observou-se que a predominância de infecção pelo HIV nesta faixa etária se dá pela transmissão heterossexual. Essa realidade pode ser atribuída à dificuldade de nego-

ciação entre os parceiros para a adoção de medidas preventivas (a mulher, com medo de perder o homem provedor ou despertar dúvidas sobre sua fidelidade, cede à imposição masculina de fazer sexo sem preservativo); dúvidas quanto a eficácia e utilização da camisinha; falta de conhecimento sobre as vias de transmissão; confiança plena no parceiro (visão romântica e eternizada do casamento); e tabu sobre imunidade<sup>(6,17,18)</sup>.

A camisinha é apontada como a forma mais conhecida de prevenção pelos idosos, embora seja seis vezes menos utilizada do que entre jovens<sup>(19)</sup>; seu uso limita-se às relações sexuais com desconhecidos ou desconfiança quanto à fidelidade do parceiro<sup>(20)</sup>.

É importante destacar que os principais fatores que levam o homem a infectar sua parceira monogâmica são: compartilhamento de seringas no uso de drogas e relações extraconjugais com outras mulheres ou outros homens; com isso, percebe-se que a bissexualidade se encontra presente em diversos casos<sup>(18)</sup>, desmistificando a crença de que todo idoso é assexuado, possui apenas relações monogâmicas e heterossexuais ou não pode ser usuário de drogas<sup>(21)</sup>.

O período pós-menopáusico da mulher idosa também foi fortemente incutido nas publicações; por não apresentarem o risco de engravidar, muitas idosas não veem a necessidade de se proteger, embora ainda possuam vida sexual ativa. Entretanto é importante ressaltar que sexo desprotegido é arriscado após a menopausa, pois o ressecamento das paredes vaginais aumenta as queixas e a probabilidade de surgimento de feridas, que funcionam como portas de entrada para o HIV<sup>(13,22)</sup>.

Até mesmo a ciência e a tecnologia se mostraram meios que podem tornar os idosos vulneráveis à aids; com os investimentos feitos visando a melhoria da qualidade de vida dos idosos ocorreu o advento de drogas que aperfeiçoam o desempenho sexual, a fabricação de próteses para homens com disfunção erétil e a reposição hormonal para as mulheres; isso fez com que os idosos se tornassem mais ativos sexualmente e, por conseguinte, propensos às doenças sexualmente transmissíveis<sup>(23,24)</sup>.

Por fim, é oportuno destacar que o grau de escolaridade é um ótimo indicador do nível socioeconômico dos indivíduos e do seu impacto sobre a saúde. Dessa forma, pode-se concluir que, quan-

to menor for o nível de escolaridade do idoso, menor será o seu acesso às informações, e, conseqüentemente, mais vulnerável ele estará ao HIV/aids<sup>(25)</sup>.

## CONCLUSÃO

Com este estudo foi possível evidenciar, na literatura científica nacional, os elementos da vulnerabilidade de idosos ao HIV/aids, os quais foram extraídos das investigações dos artigos produzidos nos últimos 4 anos.

A metodologia empregada propiciou as evidências desses elementos e o aprofundamento teórico sobre as questões referentes à temática. Desta forma, considera-se que este método se mostrou eficaz para a efetivação do objetivo.

Devido ao contexto biopsicossocial no qual o idoso está inserido, percebe-se que a velhice corresponde a uma fase de grande vulnerabilidade à infecção pelo HIV, e que os resultados apresentados ao longo da revisão mostraram que ainda existem muitos tabus referentes à sexualidade dos idosos, e, conseqüentemente, poucos esclarecimentos sobre prevenção, transmissão e demais questões envolvendo a aids.

É de extrema importância que se adote uma visão coletiva sobre os variados contextos socioculturais em que os idosos estão inseridos e vivenciam sua sexualidade. Só assim poderemos compreender como ocorre o processo de fragilização do idoso frente à prevenção da aids e trabalhar para que este conhecimento crie bases e solidifique a promoção da saúde aos indivíduos da terceira idade.

## Conflito de interesses

Não há conflito de interesses a declarar.

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# QUAL O PAPEL DO *TOLL-LIKE RECEPTOR* (TLR) NA INDUÇÃO DE LESÃO DE TUBA UTERINA NAS INFECÇÕES POR *CHLAMYDIA TRACHOMATIS*?

## WHAT IS THE ROLE OF *TOLL-LIKE RECEPTOR* (TLR) IN THE INDUCTION OF TUBAL DAMAGES CAUSED BY *CHLAMYDIA TRACHOMATIS* INFECTION?

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### RESUMO

**Introdução:** a suscetibilidade à infecção por *C. trachomatis*, curso, complicações e resolução da doença depende do tipo da bactéria, de fatores ambientais e da genética do paciente. Entre as mulheres uma forma frequente da infecção é a endocervicite, que pode se complicar com salpingite com consequente lesão tubária. Acredita-se que as complicações a longo prazo desta infecção ocorrem via *heat shock protein* HSP 60 e *toll-like receptors* (TLR). **Objetivo:** realizar uma revisão sistemática de artigos publicados que estudaram as alterações tubárias geradas pela infecção por *Chlamydia trachomatis* e o papel dos TLR durante esse processo. **Métodos:** para realização dessa revisão, três revisores realizaram uma ampla pesquisa nas principais bases de dados científicas: Pubmed, Lilacs, Embase, Cochrane library, Highwire e Google Scholar. As palavras-chave utilizadas foram: *Chlamydia* ou *Chlamydia infections* ou *Chlamydia trachomatis* e *toll like receptors* ou *toll-like receptor* ou *receptor*, *toll-like*, e *fallopian tube diseases* ou *tubal obstruction* ou *tubal occlusion*. Trabalhos em português, inglês e espanhol foram incluídos e excluídos: trabalho de revisão de literatura, estudos publicados em outras línguas e estudos sem desenho experimental definido. A avaliação foi realizada conforme recomendação da Associação Médica Brasileira. **Resultados:** entre janeiro de 2000 e junho de 2012 foram encontrados 536 artigos, dos quais 11 preencheram critérios de inclusão. Após avaliação qualitativa, foram selecionados seis estudos. Entre os resultados encontrados temos que em ratos *knockout* a deficiência de TLR2 esteve associada a menor risco de lesão tubária. Um outro modelo experimental em ratos demonstrou que a ativação do IFN-beta e do IP-10 durante a infecção por *C. trachomatis* é independente de TLR2 e de TLR4, mas dependente de MyD88. Ao se utilizar uma integração entre modelo experimental e clínico, evidenciou-se que TLR4 está associado à severidade, mas não à suscetibilidade a infecção. Já pesquisando em mulheres foram observadas expressões aumentadas de TLR2 e NFκB no epitélio da tuba uterina, indicando o possível envolvimento no aumento de PROKR2, predispondo à gravidez tubária. Outro estudo mostrou que a presença de múltiplos SNPs em múltiplos genes dobrou o risco para patologia tubária em mulheres com anticorpo para *C. trachomatis*. Nesse mesmo contexto é considerado que variações genéticas no sistema imune podem ser impactantes na suscetibilidade e severidade da infecção genital por *C. trachomatis*. **Conclusão:** os estudos demonstram que há uma menor participação de TLR4 na fisiopatogênese da lesão tubária induzida pela *C. trachomatis*, ao passo que TLR2 teria um papel mais importante neste processo e dependente de variação genética no sistema imune.

**Palavras-chave:** *toll-like receptor*, *Chlamydia trachomatis*, doenças tubárias e obstrução tubária, DST

### ABSTRACT

**Introduction:** the susceptibility, course, complications and outcome of *Chlamydia trachomatis* infection depends on the type of bacteria, environmental factors and host genetic factors. Among women, the most common infection is cervicitis that can be complicated by salpingitis leading to tubal damage. It is believed that long-term complications occur via HSP 60 and toll-like receptors. **Objective:** to conduct a systematic review of published articles that studied tubal alterations caused by *Chlamydia trachomatis* infection and the role of toll like receptors during this process. **Methods:** to perform this review, three reviewers conducted extensive research in major scientific databases: PubMed, Lilacs, Embase, Cochrane library, Google Scholar and Highwire. The keywords used were: *Chlamydia* or *Chlamydia trachomatis* and *Chlamydia infections* or *toll like receptors* and *toll-like receptor* or *receptor*, *toll-like* diseases *fallopian tube occlusion* or *tubal obstruction* or *tubal*. Studies in English, Portuguese and Spanish were included. Studies excluded: literature review, studies published in other languages and studies without experimental design set. The evaluation was performed as recommended by the Brazilian Medical Association (from 2000 to 2012). **Results:** we found 536 articles, of which 11 were included in this study. After a qualitative assessment, we selected six articles. In our research we found that TLR2 knockout mice were associated with tubal pathology protection. Another experimental model using mice, demonstrate that IFN-beta and IP-10 activation during *C. trachomatis* infection are not TLR2 and TLR4 dependent, but MyD88 dependent. An integration between a clinical and an experimental model showed that TLR4 is associated to severity but not to susceptibility to *C. trachomatis* infection. In women it was observed increased expressions in TLR4 and NFκB in the tubal epithelium, indicating a possible involvement in the increased PROKR-2, which predisposes to ectopic pregnancy. Another study showed that the presence of SNPs in multiple genes doubled the risk of tubal pathology in *C. trachomatis* infected women. Finally, it is believed that genetic variations in the immune system might have an impact in the susceptibility and severity to the genital infection by *C. trachomatis*. **Conclusion:** these studies showed a minor involvement of TLR4 in the pathogenesis of tubal damage induced by *C. trachomatis*, while TLR2 have a major role in this process and it is dependent of the immune system genetic variations.

**Keywords:** *toll-like receptor*, *Chlamydia trachomatis*, fallopian tube diseases and tubal obstruction, STD

## INTRODUÇÃO

*Chlamydia trachomatis* (CT) é uma bactéria Gram-negativa intracelular obrigatória que infecta principalmente células epiteliais colunares, causando doenças genitais, oculares e respiratórias.

Pode ser dos tipos A, B, C, D, E, F, G, H, I, J, K, sendo os sorotipos A ao C responsáveis pela doença tracoma e os D ao K responsáveis por doenças do trato genital<sup>(1,2)</sup>.

A infecção do trato genital por este patógeno é a doença bacteriana sexualmente transmissível mais prevalente no mundo<sup>(3)</sup>, sendo muito comum em países desenvolvidos como EUA, Inglaterra, Japão, Alemanha e França<sup>(4)</sup>.

A Organização Mundial de Saúde (OMS) estima que a ocorrência de infecções por clamídia, na população sexualmente ativa, é de 1.967.200 casos por ano<sup>(5)</sup>. No Brasil, há poucos dados sobre a prevalência dessa infecção.

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A suscetibilidade à infecção por *C. trachomatis*, o curso, as complicações e resolução da doença dependem do tipo da bactéria, de fatores ambientais e da genética do paciente<sup>(6)</sup>.

A CT é capaz de produzir potenciais ligantes que ativam os componentes da imunidade inata, em especial os *toll-like receptors* (TLR)<sup>(2)</sup>, que são atores muito importantes na resposta imune natural a diversos microrganismos. São encontrados na superfície celular e em membranas intracelulares de diversas células, como macrófagos, células dendríticas, neutrófilos, células epiteliais mucosas e células endoteliais<sup>(7)</sup>.

Quando o ligante se acopla a esses receptores, eles se dimerizam e mudam sua conformação, gerando uma cascata de sinalização que culminará na produção de citocinas inflamatórias.

São relatados dez tipos de TLR em humanos. Estes apresentam codificação genética, formas de ativação e cascatas de sinalização diferentes, gerando distintas respostas frente aos estímulos recebidos<sup>(8)</sup>.

Acredita-se que o TLR tipo 4 (TLR4) e o TLR tipo 2 (TLR2) participam do reconhecimento do ataque de bactérias Gram-negativas, já que o TLR4 parece reconhecer o lipopolissacarídeo (LPS), componente de membrana externa de bactérias Gram-negativas, e o TLR2 participa do reconhecimento de lipoproteínas e glicolipídios presentes em bactérias Gram-negativas, Gram-positivas e micoplasmas<sup>(8)</sup>.

As regiões mais afetadas pela *Chlamydia*, em mulheres, são o colo do útero e a uretra, podendo gerar endocervicite e disúria. Se não tratada rapidamente, a infecção endocervical pode atingir as trompas, culminando na doença inflamatória pélvica (DIP) e em aderências<sup>(9)</sup>. A DIP, em longo prazo, pode gerar complicações como: dor pélvica crônica, gravidez ectópica e infertilidade<sup>(10)</sup>. Acredita-se que 15 a 35% dos casos de infertilidade são devidos à lesão tubária, a qual está muito ligada à infecção por *Chlamydia trachomatis*<sup>(11-13)</sup>.

## OBJETIVO

O objetivo dessa revisão foi avaliar artigos publicados que estudaram as alterações tubárias geradas pela infecção por *Chlamydia trachomatis* e o papel dos TLR, durante esse processo.

## MÉTODOS

Para realizar essa revisão sistemática foi feita uma ampla pesquisa na literatura científica utilizando bases de dados como: Pubmed, Lilacs, Embase, Cochrane library, Highwire e Google Scholar. Na pesquisa na mídia digital, foram utilizados termos como: *Chlamydia* ou *chlamydia infections* ou *Chlamydia trachomatis* e *toll-like receptors* ou *toll-like receptor* ou *receptor*; *toll-like e fallopian tube diseases* ou *tubal obstruction* ou *tubal occlusion*. Após avaliação criteriosa feita por três revisores, realizada conforme recomendação da Associação Médica Brasileira, foram incluídos trabalhos realizados entre os anos 2000 a 2012, em português, inglês e espanhol, sendo excluídos trabalhos de revisão de literatura, estudos publicados em outras línguas e estudos sem desenho experimental definido. Os artigos selecionados foram então avaliados por três revisores quanto à qualidade metodológica. Os artigos aprovados foram incluídos na pesquisa. Os artigos que apresentaram discordância foram avaliados por um quarto revisor para definição de sua inclusão ou exclusão.

## RESULTADOS

Entre 2000 e 2012 foram encontrados 536 artigos, dos quais 11 preencheram os critérios de inclusão do estudo. Após avaliação qualitativa, foram selecionados seis estudos com grau de recomendação e força de evidência B, mas não foi possível realizar avaliação quantitativa dos mesmos devido à heterogeneidade dos dados (Figura 1).

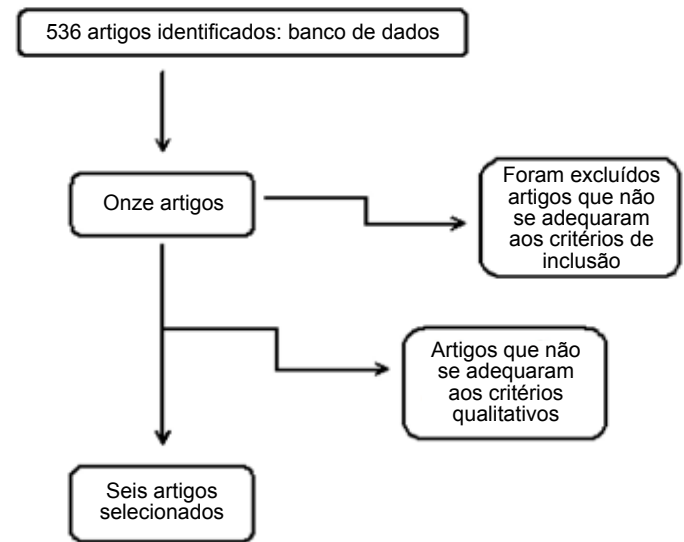


Figura 1 – Processo de seleção dos artigos.

Darville *et al.*, em experimentação com animais, avaliaram a função dos TLR2 e TLR4 na ativação de citocinas inflamatórias durante infecção por *C. trachomatis*. As ratas com deficiência no TLR2 tiveram diminuição na produção de *tumor necrosis factor-alfa* (TNF- $\alpha$ ), *macrophage inflammatory protein-2* (MIP-2), *interleucina-6* (IL-6) e *interferon-gama* (IFN-gama), os dois primeiros com redução estatisticamente significativa. Em contrapartida, ratas deficientes para TLR4 tiveram um aumento inesperado nos níveis dessas citocinas quando analisadas *in vitro*, mas não *in vivo*. Assim, a deficiência de TLR4 parece estimular vias alternativas de outros TLRs para produção dessas citocinas. A produção mais significativa de citocinas só foi observada quando a infecção pela CT era ativa. Em todos os grupos, o curso da infecção foi o mesmo, mas, nos grupos com deficiência para o TLR2, a patologia de oviduto crônica foi marcadamente menor, aparecendo menos dilatação de oviduto, menos células de inflamação aguda, menor inflamação mesossalpingeal e menos fibrose que o controle. As ratas deficientes para o TLR4 não demonstraram diferenças em relação ao grupo-controle<sup>(14)</sup>.

Shaw *et al.*, estudando 38 pacientes com patologia ginecológica benigna submetidas a histerectomia, em que nenhuma paciente estava infectada por CT, 14 mulheres tiveram resultado positivo para infecção antiga por CT e 24 nunca tiveram infecção. Comparando os grupos, foi encontrada uma expressão maior de PROKR2 (receptor do PROK 2, que predispõe a gravidez ectópica) em pacientes com infecção prévia. O mecanismo pelo qual isso ocorre também foi proposto, visto que foram encontradas expressões aumentadas de TLR2 e NF $\kappa$ B (*nuclear factor kappa-light-chain-enhancer of activated B cells*) no epitélio da tuba uterina, indicando o possível envolvimento dessas substâncias no aumento de PROKR2 e, conseqüentemente, predispondo à gravidez tubária<sup>(15)</sup>.



No estudo de Hartog *et al.* foi feita uma pesquisa com 227 pacientes com subfertilidade, em busca de possível patologia tubária causada por *C. trachomatis*. Um risco aumentado para desenvolvimento dessa patologia foi mostrado nos genótipos do TLR9, TLR4, CARD15/NOD2 (gene envolvido no processo de reconhecimento bacteriano pelos monócitos). A presença de múltiplos SNPs (*single nucleotide polymorphisms*) em múltiplos genes dobrou o risco para patologia tubária em mulheres com anticorpo para CT em comparação ao grupo IgG negativo (73% e 33%, respectivamente), o que mostra uma tendência, apesar de não ser estatisticamente significativa, devido à amostra ser pequena<sup>(3)</sup>.

Karimi *et al.* estudaram 468 mulheres holandesas, das quais 147 apresentaram sorologia positiva ou teste de DNA positivo pra *C. trachomatis*. Este estudo mostrou que não existe diferença estatística em relação à distribuição genotípica do TLR2 entre os grupos estudados quando relacionamos com suscetibilidade e severidade da infecção pela CT. Entretanto, quando os polimorfismos foram combinados em haplótipos foi demonstrada a ação protetora dos polimorfismos do TLR2 contra o desenvolvimento de complicações após infecção bacteriana<sup>(16)</sup>.

Por sua vez, Hartog *et al.*, em outro estudo, fizeram uma integração entre modelo clínico e experimental, em um estudo com 614 mulheres para analisar a suscetibilidade da infecção por *C. trachomatis* e 259 pacientes participaram do estudo para avaliar a subfertilidade em mulheres com patologia tubária decorrente da infecção. Para o modelo experimental foram utilizadas ratas *knockout* para TLR4 e ratas normais, em que ambos os grupos foram infectados e reinfectados. Ambos os modelos demonstraram que o TLR4 está associado à severidade da infecção, mas não à suscetibilidade, desempenhando um papel modesto no reconhecimento da *C. trachomatis*<sup>(6)</sup>.

No estudo de Nagarajan *et al.* foi usado um modelo experimental em ratos, no qual mostrou a ativação do IFN-beta (interferon-beta) e do IP-10 (*inducible protein 10*) durante a infecção por *C. trachomatis* independentemente de TLR2 e de TLR4, mas altamente dependente de MyD88 (*myeloid differentiation primary response protein*). Ainda nos ratos deficientes para MyD88 foi demonstrado que a taxa para eliminação do patógeno se encontrava reduzida, quando comparada com o controle ou com ratos com deficiência de TLR2 e TLR4. Segundo esse estudo a expressão de IP-10 é regulada por IFN tipos 1 e 2<sup>(17)</sup>.

## CONCLUSÃO

Podemos inferir com esse estudo que entre os diversos TLRs encontrados no organismo, os que mais podem ser implicados nas complicações pela infecção por CT são os TLR2 e TLR4.

O TLR2 está mais relacionado a complicações devido à estimulação exagerada, levando a uma produção maior de citocinas inflamatórias. Já o TLR4 aparentemente exerce um papel modesto na estimulação da imunidade inata durante a infecção por CT.

Entender as consequências imunológicas de uma infecção genital por CT serve como base para estímulo de mais pesquisas que comprovem o papel de cada receptor neste processo.

A heterogeneidade dos estudos que abordam este assunto é fator limitante para melhores conclusões, sugerindo a necessidade de um mais amplo estudo.

## Conflito de interesses

Não há conflito de interesses a declarar.

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# SÍFILIS CUTÂNEA E VISCERAL: APRESENTAÇÃO INUSITADA

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## RESUMO

A sífilis é a doença sexualmente transmissível mais comum no mundo e apresenta alto índice de incidência em nosso País. Sua evolução clínica é bem estabelecida e aceita universalmente, porém há casos em que a diversidade de sinais e sintomas da doença pode fazer do diagnóstico um desafio. Por este motivo é conhecida como doença de “mil faces” ou a “grande simuladora”. Os autores apresentam um relato de caso de sífilis em que há acometimento hepático, raro nesta doença.

**Palavras-chave:** sífilis, doenças sexualmente transmissíveis, treponematose, DST

## INTRODUÇÃO

A sífilis é uma doença com uma diversidade clínica bastante inusitada, compromete pele e órgãos internos e é uma das infecções do trato sexual (ITS) mais frequentes tanto no mundo quanto em nosso País. No Brasil, em 2003, a estimativa na população de 15 a 49 anos foi de 843.300 casos de sífilis<sup>(1)</sup>. Entre 2005 e junho de 2012 foram notificados no Sinan 57.700 casos de sífilis em gestantes, dos quais a maioria ocorreu nas Regiões Sudeste e Nordeste, com 21.941 (38,0%) e 14.828 (25,7%) casos, respectivamente<sup>(2)</sup>. Sua apresentação clínica, apesar de já estar estabelecida dentro da academia médica, algumas vezes traz quadros bastante exuberantes e imprevisíveis, que levam a uma dificuldade para seu diagnóstico, retardando o tratamento e, muitas das vezes, favorecendo a evolução para quadros graves<sup>(1,3,4)</sup>.

A sífilis secundária, fase altamente contagiosa, é a sequência lógica da sífilis primária não tratada e caracteriza-se por uma erupção cutânea que aparece de 1 a 6 meses (geralmente 6 a 8 semanas) após a lesão primária ter desaparecido<sup>(1,4)</sup>. Trata-se de uma erupção frequentemente eritematosa que surge simetricamente no tronco e nos membros, podendo atingir a região palmo-plantar. Apesar de esta descrição já estar estabelecida, outras formas de apresentação podem ser observadas<sup>(3,5)</sup>.

Os sintomas gerais da sífilis secundária mais relatados são mal-estar (23-46%), cefaleia (9-46%), febre (5-39%), prurido (42%) e hiporexia (25%). Outros, menos comuns, são dor nos olhos, dor óssea, artralgia, meningismo, irite e rouquidão. Sinais mais específicos ocorrem nas seguintes frequências: exantema (88-100%), linfadenopatia (85-89%), cancro primário residual (25-43%), condiloma plano (9-44%), hepatoesplenomegalia (23%),

placas mucosas (7-12%) e alopecia (3-11%). Manifestações raras incluem meningite aguda, que acontece em aproximadamente 2% dos pacientes, hepatite, doença renal, doença cardíaca, gastrite, proctite, colite ulcerativa, artrite, periostite, neurite do nervo óptico, irite e uveíte<sup>(3,4,6-8)</sup>.

Demonstramos aspectos cutâneo e hepático correlatos, de etiologia treponematosa, em uma paciente HIV-soronegativa.

## RELATO DE CASO

Paciente feminino, adulta, procurou vários profissionais de saúde por apresentar surgimento de lesões disseminadas pela face. Fez uso de vários tratamentos tópicos (sic) sem melhora. Com piora do quadro, foi encaminhada à nossa instituição para avaliação. Em nossa primeira consulta, além das lesões cutâneas, queixava-se de dor abdominal localizada em quadrante superior direito; recebeu atendimento clínico e foram solicitados exames laboratoriais. Ao exame físico, apresentava dor à palpação de hipocôndrio direito e fígado palpável a 2 cm do rebordo costal direito; ao exame dermatológico, observamos pápulas eritemato-violáceas disseminadas na região centrofacial e na fronte (**Figura 1**). Algumas lesões, principalmente as localizadas nas regiões periorifical e nasal, apresentavam aspecto vegetante. Notamos na região retroauricular uma lesão que apresentava colarete de Bielt em sua superfície.

Na palpação dos gânglios foi observada micropoliadenomegalia generalizada. Também notamos conjuntiva e tegumento ictericos. Nossas impressões diagnósticas foram as seguintes: histoplasmose, paracoccidiodomicose, criptococose, hepatite e lues. Os exames solicitados para elucidação foram: biópsia cutânea, com envio de material para histopatologia e cultura, VDRL, FTA-Abs e sorologias para fungos e bactérias, para HIV e hepatites A, B e C. Os resultados foram os seguintes: VDRL: 1/256; TPH: positivo; gama-glutamiltransferase: 275; fosfatase alcalina: 162; alanina transaminase: 168; aspartato aminotransferase: 82; cultura: não evidenciou crescimento de fungo ou bactéria; anti-HIV: negativo; demais sorologias: negativas; biópsia cutânea com infiltrado linfo-histioplasmocitário em torno de vasos congestos, circundando, sem invadir o filete nervoso (**Figura 2**).

Foi estabelecido o diagnóstico de sífilis secundária e instituído tratamento específico baseado no manual de controle do Programa Nacional de DST/Aids do Brasil. Houve evolução favorável do quadro, com resolução da dor abdominal, normalização das enzimas hepáticas e resolução da icterícia (**Figura 3**). Os resultados dos exames laboratoriais, 30 dias após a terceira dose da penicilina benzatina, foram: gama-glutamiltransferase: 38; fosfatase alcalina: 82; alanina

Trabalho realizado no Laboratório de Hanseníase, Instituto Oswaldo Cruz (IOC) – FIOCRUZ – Rio de Janeiro (RJ), Brasil.

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transaminase: 22; aspartato aminotransferase: 18.

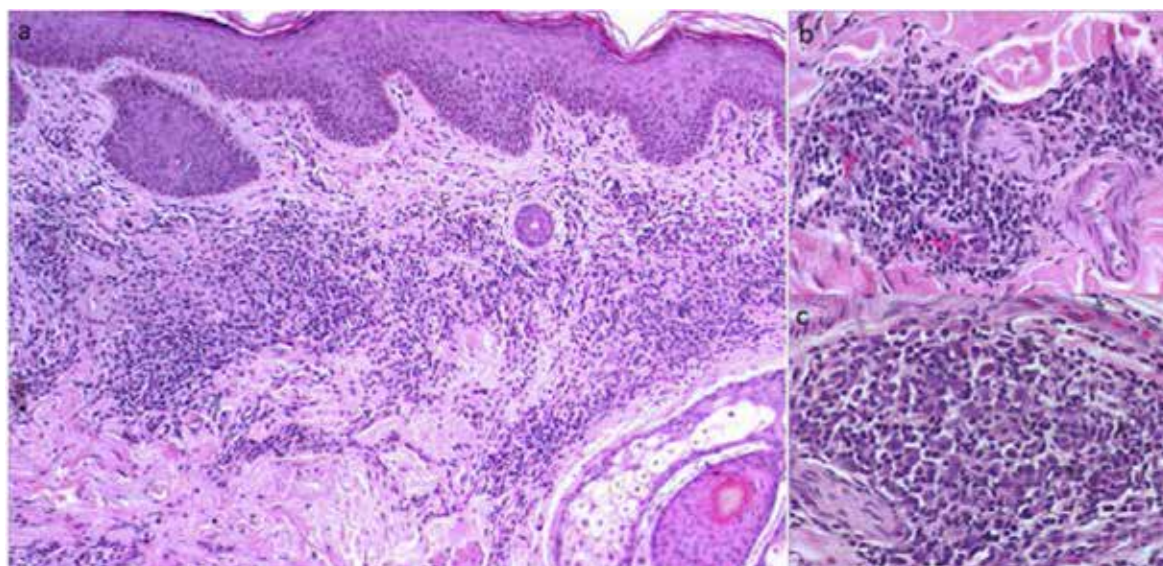
## DISCUSSÃO

É interessante ressaltar haver clareza das manifestações dermatológicas da sífilis, porém o comprometimento sistêmico ainda não está tão bem estabelecido. É possível que o acometimento

de outros órgãos, além da pele, em estágios mais precoces, seja mais frequente do que se possa imaginar. Em serviços especializados, tem sido observada superposição de fases cutâneas mesmo em pacientes HIV-soronegativos, além de aparecimento precoce de sintomas sistêmicos neste mesmo grupo. A divisão da sífilis em estágios é apenas didática, e por tratar-se de uma infecção, se não



**Figura 1** – Pápulas eritemato-violáceas disseminadas na região centrofacial e na frente.



**Figura 2** – (a): Menor aumento (10x): epiderme espessada, com exocitose moderada e derme com infiltrado mononuclear denso, formando faixa na porção superficial; (b): aumento médio (20x): infiltrado linfo-histioplasmocitário em torno de vasos congestionados, circundando, sem invadir o filete nervoso; (c): maior aumento (40x): detalhe do infiltrado inflamatório, com numerosos plasmócitos, macrófagos e linfócitos, com filete sem alterações no canto inferior esquerdo.



**Figura 3** – Notar diminuição das lesões 7 dias após a primeira dose de penicilina benzatina 2.400.000 UI intramuscular.

reconhecida e tratada de maneira correta pode evoluir em até um 1/3 dos casos com danos graves.

A lesão hepática na sífilis foi reconhecida há mais de 400 anos, embora se considere rara. É uma entidade nosológica bem caracterizada, estimando-se que ocorra em cerca de 0,2% dos casos de sífilis. Apesar de o mecanismo patogênico subjacente à doença hepática sífilítica ser desconhecido, várias hipóteses foram propostas para explicá-lo, desde a inoculação direta do agente etiológico no sistema venoso portal (associada a um período de bacteremia que ocorre na fase secundária da doença) à lesão do hepatócito mediada por imunocomplexos, a qual é, na maioria das vezes, assintomática<sup>(9,10)</sup>.

Na hepatite desencadeada pela sífilis clinicamente podem ser observadas dor abdominal, hepatomegalia e icterícia. Laboratorialmente é marcada por um padrão colestático, caracterizado por discreto aumento de transaminases e bilirrubina, e maior aumento de fosfatase alcalina e gama-GT<sup>(11,12)</sup>. Apesar de haver relato na literatura de hepatite fulminante, a maioria dos casos apresenta cura clínica e normalização das enzimas hepáticas com o tratamento correto da sífilis<sup>(12,13)</sup>.

Consideram-se como critérios de diagnóstico de uma hepatite sífilítica os seguintes: elevação das atividades séricas das enzimas marcadoras de lesão hepática e evidência sorológica de sífilis, associados a manifestações clínicas sugestivas de sífilis secundária; exclusão de outras causas passíveis de causar dano hepático; rápida recuperação da função hepática após instituição da medicação antibiótica. O prognóstico da hepatite sífilítica é geralmente bom, apesar dos raros casos de falência hepática fulminante que se encontram descritos na literatura<sup>(9,13,14)</sup>.

## CONCLUSÃO

A paciente em questão apresentou quadro cutâneo e hepatite como comprometimento sistêmico. Acreditamos que a condição seja decorrente da treponematose, já que foram afastadas outras causas possíveis de hepatite para a paciente (hepatites virais, alcoolismo e uso de medicamentos) e por ter apresentado melhora clínica e laboratorial com o tratamento da sífilis.

Com a apresentação do caso em tela, chamamos a atenção de que órgãos internos possam ser afetados de forma concomitante à expressão cutânea da sífilis, devendo ser considerada desde o início como doença sistêmica.

## Conflito de interesses

Nenhum.

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# CUTANEOUS AND VISCERAL SYPHILIS: UNUSUAL PRESENTATION

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## ABSTRACT

Syphilis is the most common sexually transmitted disease in the world, showing a high incidence rate in our country. Its clinical course is well established and universally accepted, although there are cases in which the diversity of its signs and symptoms can make diagnosis a challenge. This is the reason why it is known as a “thousand faces” or a “great imitator” disease. Authors present a case report with hepatic involvement, which is rare when syphilis is concerned.

**Keywords:** syphilis, sexually transmitted diseases, treponematosi, STD.

## INTRODUCTION

Syphilis is a disease with a very unusual clinical diversity, compromising skin and internal organs, and it is one of the most frequent sexually tract infections (STI) both around the world and in our country. In Brazil, in 2003, the estimate of the population between 15 and 49 years was of 843,300 syphilis cases<sup>(1)</sup>. From 2005 to June, 2012, 57,700 cases of syphilis in pregnant women were notified to SINAN (a notification system held by Brazilian Health Ministry), most of which occurred in the Southeast and Northeast regions, with 21,941 (38.0%) and 14,828 (25.7%) cases, respectively<sup>(2)</sup>. Syphilis clinical symptoms, although already determined by the Medical Academy, sometimes brings exuberant and unpredictable symptoms, leading to a difficulty of the diagnosis as well as to a delay in treatment, and often, favouring the evolution to severe conditions<sup>(1,3,4)</sup>.

Secondary syphilis, a highly contagious stage, is the logical sequence of untreated primary syphilis, and it is characterised by an ulceration that appears from 1 to 6 months (usually 6 to 8 weeks) after the primary lesion has disappeared<sup>(1,4)</sup>. It is an often erythematous ulceration that appears symmetrically on the trunk and limbs, and may reach the palmoplantar region. Although this description has already been established, other forms of manifestation can also be observed<sup>(3,5)</sup>.

The most reported secondary syphilis general symptoms are the following: uneasiness (23-46%), headache (9-46%), fever (5-39%), pruritus (42%), hyporexia (25%). Other symptoms, less common, are: eye pain, bone pain, arthralgia, meningism, iritis and hoarseness. More specific signs occur in the following frequencies: skin rash (88-100%), lymphadenopathy (85-89%), primary cancer (25-43%), flat

condyloma (9-44%), hepatosplenomegaly (23%), mucous plaques (7-12%) and alopecia (3-11%). Rare manifestations include: acute meningitis, that occurs in approximately 2% of patients, hepatitis, renal disease, cardiac disease, gastritis, proctitis, ulcerative colitis, arthritis, periostitis, optic neuritis, iritis and uveitis<sup>(3,4,6-8)</sup>.

This work demonstrates cutaneous and liver co-related aspects, of treponematosi etiology, in a HIV-seronegative patient.

## CASE REPORT

An adult female patient sought several health professionals due to the eruption of disseminated lesions through her face. Patient made use of various topical treatments (*sic*) with no improvement. As conditions became worse, patient was sent to our Institution for evaluation. During our first consultation, apart from the cutaneous lesions, she complained about abdominal pain in the right upper quadrant. Patient received clinical care, and laboratory tests were requested. On physical examination, patient presented pain on palpation of the right hypochondrium and palpable liver 2 cm from the costal right edge; dermatological examination showed erythematous-violaceous papules, scattered over the centrofacial region and forehead (**Figure 1**). Some lesions, especially those located in the periorificial and nasal regions presented vegetant aspect. A lesion in the retroauricular region presented Biett's collarete in its surface.

On palpation of ganglions a difuse *micropolyadenomegaly* was noted. It was also observed conjunctive and icteric teguments. Our diagnosis impressions were as follows: histoplasmosis, paracoccidioidomycosis, cryptococcosis, hepatitis, and syphilis. Tests required for diagnosis elucidation were the following: cutaneous biopsy, with material sent for histopathology and culture, VDRL, FTA-Abs and serology for fungi and bacteria, HIV and hepatitis types A, B and C. The results were as follows: VDRL: 1/256; TPH: positive; gamma-glutamyltransferase: 275; alkaline phosphatase: 162; alanine transaminase: 168; aspartate aminotransferase: 82; culture: showed no growth of fungus or bacteria; anti-HIV: negative; other serologies: negative; cutaneous biopsy with infiltrated limph-histio-plasmocitary around congestion vessels, surrounding but not invading the nervous filament (**Figure 2**).

Diagnosis of secondary syphilis was established, and the specific treatment based on the control manual of the Brazilian National Program of STD/Aids was indicated. There was a favourable evolution of the symptoms, with the resolution of abdominal pain, normalisation of liver enzymes and resolution of icterus as well (**Figure 3**). The results of laboratory tests 30 days after the third dose of benzathine penicillin were the following: gamma-gluta-

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myltransferase: 38; alkaline phosphatase: 82; alanine transaminase: 22; aspartate aminotransferase: 18.

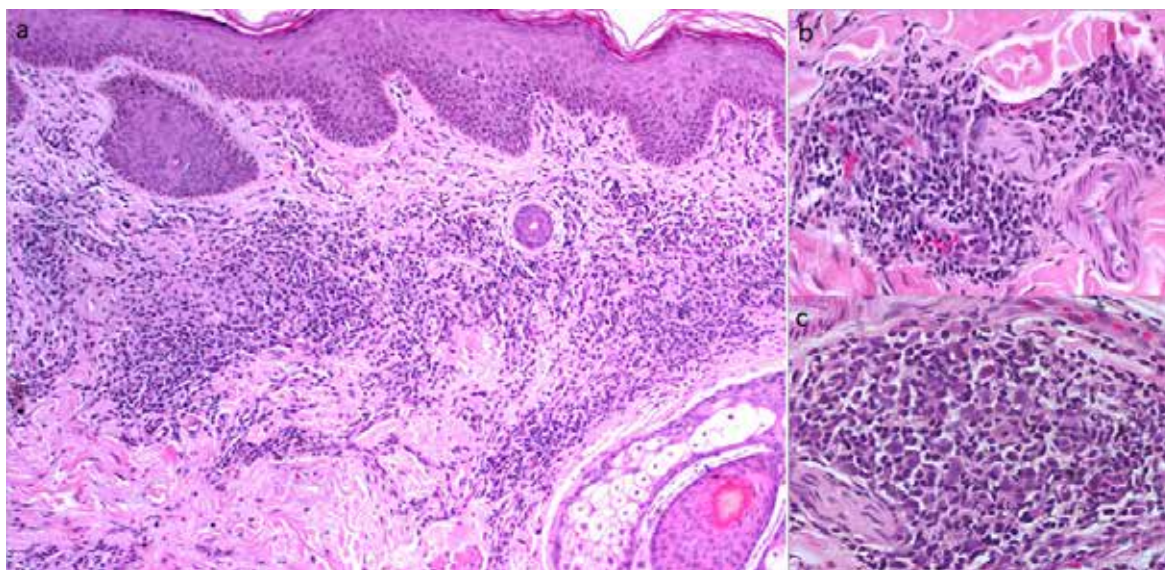
## DISCUSSION

It should be noted that syphilis dermatological manifestations are very clear, but the systemic involvement is still not so

well established. It is possible that the association with other organs in earlier stages, besides skin, is more frequent than one can imagine. Specialized services have observed cutaneous stages overlay even in HIV-seronegative patients, apart from early onset of systemic symptoms in this same group. Syphilis classification in stages is only didactic, and as it is an infection,



**Figure 1** – Erythematous-violaceous papules scattered over the centropalpebral region and forehead.



**Figure 2** - (a): Smallest increase (10x): thickened epidermis, with moderate exocytosis and dermis with dense mononuclear infiltrate forming a stripe in the superficial portion; (b): average increase (20x): infiltrated lymphohistioplasmocytic around congestion vessels, without invading the nervous filament; (c): largest increase (40x): detail of the inflammatory infiltrate with numerous plasmacytes, macrophages and lymphocytes with filaments without changes in the lower left corner.



**Figure 3** - Lesions' reduction after 7 days of the first dose of benzathine penicillin 2.400.000.

when not recognized and correctly treated, the disease can evolve into serious damage to 1/3 of cases.

The liver damage in syphilis, although rare, has been recognized for more than 400 years. It is a nosological entity well characterized, and it is estimated to occur in about 0.2% of syphilis cases. Although the pathogenic mechanism underlying liver syphilitic disease is unknown, various hypotheses have been proposed to explain it, from the direct inoculation of the etiological agent in the portal venous system (associated with a period of bacteremia that occurs on the secondary phase of the disease) to the hepatocyte injury mediated by immune complexes, which is most often asymptomatic<sup>(9,10)</sup>.

Abdominal pain, hepatomegaly and icterus are clinically observed in hepatitis triggered by syphilis. Laboratory marks it as a cholestatic pattern, characterized by a discreet increase of transaminasemia and bilirubin, and a largest increase of alkaline phosphatase and gamma-GT<sup>(11,12)</sup>. Although there are case reports in literature of fulminant hepatitis, most cases present clinical healing and normalization of liver enzymes with the correct treatment of syphilis<sup>(12,13)</sup>.

A diagnosis criterion of syphilitic hepatitis should take into consideration the following: elevation of serum marker enzymes activities of liver damage and serological evidence of syphilis, associated with clinical manifestations suggestive of secondary syphilis; exclusion of other causes which may induce to liver damage; rapid recovery of hepatic function after introduction of antibiotic medication. The prognosis of syphilitic hepatitis is generally favourable, although there are rare cases of acute liver failure described in literature<sup>(9,13,14)</sup>.

## CONCLUSION

Patient presented cutaneous lesions and hepatitis as a systemic involvement. We believe this condition was caused by treponematoses, since all other possible causes for the patient's hepatitis (viral hepatitis, alcoholism and drug use) were rejected, and patient also showed clinical and laboratory improvements due to syphilis treatment.

By presenting this case, we call the attention to the fact that internal organs may be concomitantly affected by syphilis cutaneous manifestation, and it shall be considered as a systemic disease from its beginning.

## Conflict of interest

There was no conflict of interest.

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# 28<sup>th</sup> INTERNATIONAL PAPILLOMAVIRUS CONFERENCE & CLINICAL AND PUBLIC HEALTH WORKSHOPS

## NOV 30 - DEC 6, 2012 • SAN JUAN, PUERTO RICO

*Abstracts of research presented at the conference selected by Edison Natal Fedrizzi (Universidade Federal de Santa Catarina) e Mauro Romero Leal Passos (Universidade Federal Fluminense)  
We believe that this activity is a way to socialize and spread the knowledge to those who have not participated in important international scientific event.*

Resumos de pesquisas apresentadas no congresso selecionadas por Edison Natal Fedrizzi (Universidade Federal de Santa Catarina) e Mauro Romero Leal Passos (Universidade Federal Fluminense)

Consideramos que esta atividade é uma forma de disseminar e socializar o conhecimento para aqueles que não participaram de importante evento científico internacional.

### Basic Science Basics of prophylactic vaccines

#### Cross-Reactivity to VLP HPV 31, 45 and 58 in a Group of Women Vaccinated with the Quadrivalent Vaccine in Bogotá, Colombia

Presenter: Alba Lucia Combata, PhD

Investigators/Collaborators: Combata AL, Molano M, Duarte D, Rodríguez J, Martínez L, Trujillo L, Gonzales M, Luna J, Ortiz N, Touzé A, Corsaget P

Country: Colombia

**Objectives:** To characterize the humoral immune response (HIR) to HPV16, 18, 31, 45 and 58 HPV capsids in women who has been vaccinated with the quadrivalent vaccine. **Method:** 82 women aged 18-28 years old attending HPV clinic at the Instituto Nacional Cancerología were enrolled and vaccinated according to the vaccination scheme. Follow-up visits were scheduled at 1, 6, 18 months after last vaccination dose. Before and after vaccination, samples for Papanicolaou tests, HPV DNA typing, and immunological assays were collected. IgG Ab were measured by ELISA using HPV16, 18, 31, 45 and 58 VLPs. HPV-DNA detection was done by GP5+/GP6+PCR-ELISA and typing of 37 types was performed using a reverse line-blot assay. **Results:** Before vaccination, anti-VLP HPV16, 18, 31, 45 and 58 prevalence was 39%, 31.7%, 15.9%, 31.7% and 23.2% respectively. This prevalence increased to 98.8%, 97.5% and 98.7% for types 16, 18 and 58 respectively one month after vaccination. For HPV31 and 45 the prevalence was 88.8% and 86.4% respectively. Six months after vaccination, prevalence of anti-VLP HPV16, 18 and 58 remained high 98.6%, 87.7% and 89.0% respectively. a decrease was observed for HPV31 and 45 types: 65.7% and 56.2%, respectively. after 18 months, prevalence of anti-VLP HPV16 was 95.8%, while for HPV18 was 76%. For HPV31, 45 and 58 the prevalence was reduced to 46.5%, 38% and 53.5% for respectively. the HPV DNA prevalence before vaccination was 39%, which slightly increased after one month of vaccination (46.9%), but decreased to 26% and 23% after six and 18 months. HPV16 and 18 prevalence was 6.1% for both types before vaccination and remained similar one month after (7.4%). Six months after vaccination this prevalence decreased to 2.7% for HPV16, while HPV18 not infections were detected (0%). 18 months post vaccination no HPV16 and 18 infections were observed. Before and one month after vaccination the prevalence of types related to HPV16 was 13.4%, and decreased six months after vaccination (5.5%). However, it increased to 9.8% after 18 months of vaccination. For types related to HPV18, the prevalence was low before and after vaccination (2.4%). For other HR-HPV types unrelated, we observed an increase in prevalence after vaccination (15.5%) compared to before vaccination (9.8%). **Implications and Impact:** It was observed an increase in HIR to VLP16 and 18 after vaccination. For VLP16 this response was maintained during all follow up, while to VLP18 this response decrease slightly. For other HPV VLPs types like HPV31, 45 and 58 also was observed an increase in the HIR. This response decrease about 50% after 18 months of follow up. These results could suggest a possible cross-reactivity to VLP HPV 31, 45 and 58.

### Basic Science Basics of prophylactic vaccines

#### HPV16 L1 Virus-Like Particle Expressed in *Lactobacillus casei* Induces Mucosal and Systemic Immune Responses in Vivo

Presenter: Ji-Na Won, Student

Investigators/Collaborators: Won JN<sup>1,2</sup>, Sung MH<sup>3,4</sup>, Lee IH<sup>4</sup>, Poo H<sup>1,2</sup>



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Country: Republic of Korea

**Objectives:** Human papillomaviruses (HPVs) are non-enveloped DNA viruses causing warts on skin or genital track, and malignant cancer as well. among more than 100 different strains or types, HPV type 16 (HPV16) has been regarded as one of the most causative agents for cervical cancer. L1, the major capsid protein of HPV, self-assembles into virus like particles (VLPs), and is currently used as a HPV vaccine component because of its strong immunogenicity in vivo. **Method:** We have constructed a lactose-inducible system using lactose operon promoter of *Lactobacillus casei*, lacT, (LacT), and have expressed the L1 major capsid proteins of HPV16. For immunization, BALB/c mice were administrated with equal amount of the *L. casei*-HPV16L1 by the oral routes. Anti-VLP immunoglobulin a (IgA) and IgG were also detected in serum, vagina. **Results:** We generated the HPV16 L1 VLPs in *Lactobacillus casei* (*L. casei*), which is a potential vaccine vector for the induction of both mucosal and systemic immune responses. Oral administration of *L. casei*/HPV16 L1 induced strong systemic IgG and mucosal IgA antibody responses in Balb/c mice, which is comparable to the immune responses of conventional HPV16 L1 VLP-injected group. Also, oral immunization of *L. casei*/HPV16 L1 resulted in higher neutralizing activity against HPV16 pseudovirus infection to 293TT cells in vitro. More importantly, *L. casei*/HPV16 L1 conferred significant protection against pseudovirus challenge through the genital tract, a major infection route of HPV. **Implications and Impact:** Our results show that *L. casei*/HPV16 L1 could be an efficacious prophylactic vaccine which induces strong neutralizing immune responses in mucosa with the safety and ease of administration.

### Basic Science Basics of prophylactic vaccines

#### Multivalent HPV L1 DNA Vaccination Utilizing Electroporation

Presenter: Kihyuck Kwak, Ph.D. candidate

Investigators/Collaborators: Kwak K<sup>1</sup>, Jiang R<sup>1</sup>, Jagu S<sup>1</sup>, Wang J<sup>1</sup>, Christensen ND<sup>2</sup>, Roden R<sup>1</sup>

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Country: United States

**Objectives:** The two licensed HPV vaccines require a cold chain and remain expensive to produce. Naked DNA vaccines can be manufactured at low cost and are stable at ambient temperature, but require a novel delivery technology. in vivo electroporation is an emerging approach to deliver naked DNA, and here we explore its potential for multivalent HPV L1 and L2 DNA vaccination. **Method:** Balb/c mice were vaccinated three times at two week intervals with L2 N-termini multimer protein or its DNA expression vector, DNA constructs expressing L1 only or L1+L2 of a single HPV type, or as a mixture of several high-risk HPV types utilizing electroporation, i.m. injection or gene gun. Serum was collected two weeks and 3 months after the last vaccination. Sera from immunized mice were tested for in-vitro neutralization titer, and protective efficacy upon passive transfer to naive mice and vaginal HPV challenge. To explore co-assembly, 293TT cells were transfected with DNA constructs, HPV6, HPV16, and HPV18 L1 together, and HPV18 L1 immunoprecipitated with monoclonal antibody, H18. F8. Chimeric VLP was detected by western blotting of immunoprecipitates with anti-HPV6, 16, 18 L1 antibody. **Results:** Electroporation with L2 multimer DNA did not elicit detectable neutralizing antibody titer, whereas L1 DNA induced robust neutralizing antibody titers, approaching those induced by Gardasil. L1+L2 DNA vaccination induced similar levels of type restricted neutralizing antibodies as L1 only DNA vaccine. Reduced neutralizing antibody titers were observed when vaccinating with a mixture of L1 (or L1+L2) vectors of multiple HPV types, likely resulting from co-assembly of mixed particles observed in coimmunoprecipitation studies. High titers were restored by vaccinating with individual constructs at different sites. **Implications and Impact:** Delivery of HPV L1 DNA via in vivo electroporation produces a stronger antibody response compared to i.m. injection or i.d. ballistic delivery via gene gun, and was not augmented by co-expression of L2. Electroporation with L2 multimer DNA failed to induce a neutralizing response. When L1 DNA vaccines derived from multiple HPV types are mixed prior to administration, this leads to a reduction in neutralizing antibody titer, likely reflecting the formation of mixed type VLPs. This issue could be resolved by spacial separation of individual type L1 DNA vaccines at different sites, but not by co-expressing the cognate L2 proteins.

### Basic Science Basics of therapeutic vaccines & antivirals

#### Effect of Local Tumor Irradiation on Homing of Tumor-Specific CTLs

Presenter: Oana Draghiciu, M.Sc.

Investigators/Collaborators: Walczak M<sup>1</sup>, Hoogeboom BN<sup>1</sup>, Meijerhof T<sup>1</sup>, Nijman HW<sup>2</sup>, Daemen T<sup>1</sup>

1 Department of Medical Microbiology, Molecular Virology Section, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

2 Department of Gynecology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Country: Netherlands

**Objectives:** Current therapeutic approaches of cervical cancer involve aggressive surgery and/or radiotherapy combined with chemotherapy, depending on the stage of disease. Non-invasive therapies, like immunotherapy, might optimize treatment outcome of these patients. Therapeutic immunization protocols aim at inducing antigen-specific cytotoxic T lymphocytes (CTLs), capable of specific recognition and

irradiation of established tumors. To achieve optimal benefit from immunization protocols, strategies need to be developed that support optimal migration and activity of CTLs into the tumor microenvironment. Evidence is accumulating that local irradiation therapy can induce chemokines involved in CTLs recruitment to the tumor site. Therefore, combination of immunization, to induce antigen-specific CTLs, with local irradiation therapy could increase the antitumor effect. **Method:** We developed a method allowing us to assess the trafficking of tumor-induced, adoptively transferred as well as vaccine-induced antigen-specific CTLs into tumors. To obtain antigen-specific CTLs, donor mice were immunized with recombinant Semliki Forest virus (rSFV) encoding human papilloma virus (HPV)-E6,7 tumor antigens. *in vitro* restimulated E6,7-specific CTLs were CFSE labeled and adoptively transferred into TC-1 (HPV-transfected) tumor-bearing recipient mice four days after local tumor irradiation. Homing of both tumor-induced effector T cells and adoptively transferred E6,7-specific CTLs to TC-1 tumors was analyzed one day after transfer. **Results:** Local tumor irradiation induced a significant increase in intratumoral levels of adoptively transferred E6,7-specific CTLs. a similar effect was observed in the infiltration of tumor-induced effector T cells and MDSCs (myeloid derived suppressor cells), when compared with non-irradiated tumors. To assess the effect of irradiation on tumor trafficking of vaccine-induced antigen-specific CTLs, TC-1 tumor bearing mice were locally irradiated and one day later intramuscularly vaccinated. Local tumor irradiation caused a drastic increase in intratumoral levels of both tumor- and vaccine-induced specific CTLs. Intratumoral levels of vaccine-induced specific CTLs were 5-fold higher than intratumoral levels of adoptively transferred E6,7-specific CTLs. **Implications and Impact:** In summary, we demonstrated that vaccine-induced CTLs home into tumors and that local tumor irradiation increases the tumor homing efficacy of antigen-specific CTLs. This study indicates that rSFV-based immunotherapy combined with tumor radiotherapy could improve treatment outcome.

#### Basic Science Basics of therapeutic vaccines & antivirals

### HPV VLPs Can Directly Prevent HPV Tumoral Effect

Presenter: William Bonnez, MD

Investigators/Collaborators: William Bonnez<sup>1</sup> and Carrie DaRin<sup>1</sup>

<sup>1</sup> University of Rochester School of Medicine and Dentistry, Rochester, NY 14642 (USA)

Country: United States

**Objectives:** HPV VLPs and infectious HPV particles share the same general conformation, thus may interact with the same host molecules and compete with one another. This simple assumption creates the possibility of interfering with the viral cycle by the prior exposure of the target tissue to HPV VLPs. We are presenting a proof of this concept. **Method:** Human neonatal foreskin fragments were exposed to different dilutions (1:1, 1:10, 1:100, and diluent alone) of a suspension (8 µg) of HPV VLPs prior to being exposed to a suspension of infectious HPV-6 virions ( $5 \times 10^8$  DNA copies). These grafts were singly implanted subcutaneously on the flank of a SCID mouse. For each replicate experiment 2 foreskin donors were used, one for each side of the mouse. Three mice were used for each HPV VLP dilution, and each experiment was done in quadruplicate, requiring a total of 48 mice. the animals were sacrificed 12 weeks later, and the planned primary endpoint was graft size, measured as the composite geometric mean diameter (cGMD) of the two grafts born by each mouse. the secondary endpoints were graft histology for the presence of HPV and average copy number of HPV-6 cDNA in the mouse grafts. Separate experiments were conducted with L1 VLPs of HPV types 6, 16, and 18 (supplied by Merck USA). **Results:** HPV VLPs regardless of the dilutions tested or genotype strongly inhibited HPV-6-induced graft proliferation. the mouse graft sizes (mean±SD cGMD in mm) for the HPV-6 VLP dilutions of 1:1, 1:10, 1:100, and control (diluent), were respectively  $2.0 \pm 0.5$ ,  $2.0 \pm 0.5$ ,  $2.0 \pm 0.5$ , and  $3.1 \pm 0.6$  ( $p = 10^{-7}$ ). with HPV-16 VLPs they were  $1.5 \pm 0.5$ ,  $1.7 \pm 0.4$ ,  $1.8 \pm 0.3$ , and  $2.6 \pm 0.3$  ( $p = 10^{-6}$ ), and with HPV-18 VLPs,  $2.1 \pm 0.3$ ,  $2.0 \pm 0.2$ ,  $2.0 \pm 0.2$ , and  $2.8 \pm 0.4$  ( $p = 5 \times 10^{-7}$ ). in contrast, HPV VLPs did not prevent HPV-6 infection of the graft as measured by histology or HPV-6 cDNA copy numbers (data not shown). **Implication and Impact:** HPV VLPs, regardless of genotype, can directly prevent HPV-6 induced tumor proliferation when applied prior to virus challenge. Our inability to reach a limiting dilution of the HPV VLPs and the use of a highly supra-physiologic virus challenge dose is very encouraging for a potential clinical use of this effect, as it is likely to persist under less extreme conditions of challenge. Although we anticipated a mechanism of action by specific blockade of virus entry, the occurrence of this effect in the presence of active viral expression suggests at least a different, but undefined antiviral mechanism of action. From a practical and clinical standpoint, the inhibition of the pathogenesis of any HPV genotype irrespective of the genotype of the blocking VLPs is an attractive feature.

#### Basic Science, Basics of therapeutic vaccines & antivirals

### The Development of a Novel Curcumin-Based Vaginal Cream Vacurin Which Selectively Eliminates Cervical Cancer Cells

Presenter: Mario Castellanos, MD

Investigators/Collaborators: Priya Ranjan Debata, Ph.D., Mario Castellanos, M.D., Jimmie Fata, Ph.D., Sara Baggett, Sriitha Rajupet, M.D., Anita Szerszen, D.O., Sultana Begum, Anita Mata, Lynne M.Opitz, M.D., Probal Banerjee, Ph.D.

Country: United States

**Objective:** Globally, human papillomavirus (HPV) infections remain a leading cause of morbidity and mortality. Despite significant progress, an effective antiviral treatment remains elusive. Curcumin, a component of the culinary spice turmeric, has potent anticancer and antiviral properties. However, its use is limited by low plasma solubility, rapid clearance and overall poor oral bioavailability. To overcome these limitations, we develop and test a curcumin-based vaginal cream as new approach to treat cervical lesions associated with HPV. **Method:**

First, we show that curcumin eliminates HPV (+) cervical cancer cell lines. HeLa, ME-180, SiHa, SW756 and normal fibroblast cells were treated with different doses of curcumin (96 hours). WST-1 assays performed and IC50 values obtained. Cells were also treated with curcumin (50  $\mu$ M) for 8 h. Western blotting of cell lysates done, HPV E6 and E7, EGFR, Rb and p53 levels measured. Next, intravaginal formulation containing 2%, 5%, 10% and 20% (w/w) curcumin were developed, named Vacurin-2, Vacurin-5, Vacurin-10, and Vacurin-20, respectively. Uniformity of these colloid mixtures were examined by measuring curcumin fluorescence on thin spreads. Vacurin was then tested for curcumin release and effectiveness. HeLa cells were cultured in a 12-well cluster plates and different concentrations of Vacurin were placed on a porous membrane in a tissue culture insert suspended 1mm above the cultured cells for 72 hours. Juxtaposed and peripheral cell death measured. Toxicity of Vacurin was determined by examining daily intravaginal infusions of either PBS, vehicle alone or Vacurin-20 for 2-3 weeks in mice. Animals euthanized and histopathology of lower reproductive tract done. **Results:** Curcumin selectively eliminates HeLa, Me180, SiHa, and SW756 cells. It suppresses HPV E6, dramatically inhibits the expression of EGFR and concomitantly induces p53. We show that Vacurin is a uniform colloidal solution of curcumin in a clinically used amphipathic cream. Vacurin eliminates juxtaposed HeLa cells in a culture system. in mice, daily intravaginal Vacurin-20 infusion produced no changes in body weight and when mice were scarified, the vaginal tract epithelium showed no mucosal injury or adverse effects. **Implications and Impact:** There is a worldwide need for an effective treatment against HPV, especially in developing countries with limited resources. Our compound is promising as it is derived from a low cost nutraceutical. Our curcumin-based vaginal cream effectively and preferentially eradicated HPV (+) cancer cells. Our preclinical data demonstrates a safe and novel therapy for the treatment of cervical lesions associated with HPV.

### Basic Science Immunology

#### Anal Condylomata as Potential Risk Factors for HIV-1 Acquisition

Presenter: Zoon Wangu, MD

Investigators/Collaborators: Zoon Wangu, MD<sup>1</sup>, Jeffrey Pudney, PhD<sup>2</sup>, Joseph Politch, PhD<sup>2</sup>, Lori Panther, MD, MPH<sup>3</sup>, Antonio de las Morenas, MD<sup>4</sup>, Deborah Anderson, PhD<sup>5</sup>

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Country: United States

**Objectives:** Anal HPV infections in young homosexual men have been associated with increased risk of HIV acquisition and seroconversion independent of other sexually transmitted diseases; however, the specific mechanism is unclear. We hypothesize that HPV-induced low grade condylomata enhance HIV transmission due to increased vascularity, friability and leukocytic infiltrates containing HIV host cells. Our objective was to compare presence and abundance of HIV target cells in anal condylomata vs. normal anal tissue. **Method:** Coded, archived samples of low-grade (up to AIN1) anal condylomata were obtained from the Boston Medical Center pathology department. Condylomata and normal anal tissue controls were sectioned and reacted with primary antibodies recognizing lymphocyte subsets (CD3+, CD4+, CD8+), antigen presenting & inflammatory cells (CD68+, CD15+, CD1a+) and HIV coreceptors (CCR5+, CXCR4+). Cells expressing these markers were visualized by an alkaline phosphatase detection system. Relative quantity & location of cell types were compared between samples and controls using a semi-quantitative scale. Differences in cell populations between samples and controls, and correlations between cell types within tissues, were assessed using the Spearman Rank Correlation Test. **Results:** Thirty condylomata samples were obtained from 24 patients (46% Caucasian, 46% male, median age 35 years). Forty-three percent of samples contained large numbers of epidermal CD1a+ dendritic cells, some with large focal dermal accumulations; 20% of samples contained large numbers of dermal CD68+ macrophages and CD4+ lymphocytes. in contrast, normal tissue contained few such dermal or epidermal cells. CD3+, CD15+ and CD8+ cells were present in varying numbers in most samples but were more numerous in condylomatous tissue compared to controls. All samples contained CCR5+ cells, whereas few (30%) contained CXCR4+ cells. in the condylomata epidermis, CD8+ lymphocyte infiltrates were associated with increased numbers of CD15+ granulocytes and CD1a+ dendritic cells. **Implications and Impact:** Our results indicate that low-grade condylomatous anal tissue often contains large accumulations of HIV target cells in contrast to normal anal epithelium. These data provide evidence that condylomata may enable HIV entry and infection, especially in the setting of typical lesion vascularity and friability. If so, treatment and/or prevention of anal condylomata may decrease HIV acquisition. This provides additional impetus for HPV vaccination both in populations with high HPV prevalence and in the general population especially before the age of sexual debut.

### Basic Science Novel Diagnostics

#### Bead-Based Detection of Sexual Transmitted Infections and their Association with Cervical Cancer

Presenter: Markus Schmitt, PhD

Investigators/Collaborators: Christophe Depuydt, Michel Stalpaert and Michael Pawlita

Country: Germany

**Objectives:** Data on prevalence of sexual transmitted infections (STIs) and bacteria of the normal genital flora are scarce. in addition, it remains controversially discussed whether STIs may act as co-factors in the development of cervical cancer. **Method:** We report the development and validation of a novel multiplex genital pathogen assay (MGPA) that detects different genital pathogens in cervical swabs using a single multiplex PCR followed by Luminex bead-based target-specific hybridisation. MPGA was used to reanalyse HPV-characterised

samples from a Mongolian populations- and a cancer-based study. **Results:** MGPA specifically detects *Chlamydia trachomatis*, HSV1, HSV2, *Treponema pallidum*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, *M. hominis*, *M. pneumonia*, *Ureaplasma urealyticum* and *U. parvum*, and quantifies BV-associated *Atopobium vaginae* and *Gardnerella vaginalis* as well as the normal genital flora *Lactobacillus iners*, *L. crispaticus* and *L. jensenii*. As little as 10 to 100 target copies per PCR could be detected for all pathogens. Quantification of *A. vaginae* and *G. vaginalis* was possible over 4 to 5 orders of magnitude. Additional validation, prevalence and association data will be presented. **Implications and Impact:** In conclusion, the novel MGPA assay is a powerful high-throughput tool in assessing sexual transmitted infections.

#### Basic Science Transformation and carcinogenesis

### Association of *Chlamydia trachomatis* Infection in HPV Positive Women with Severity of Cervical Neoplasia

Presenter: Luiz Carlos Zeferino, PhD

Investigators/Collaborators: Juçara Maria de Castro-Sobrinho, Silvia Helena Rabelo-Santos, Rosane Ribeiro Figueiredo Alves, Sophie Françoise Mauricette Derchain, Luis Otávio Zanatta Sarian, Denise Rocha Pitta de Moraes, Elisabete Aparecida Campos, Luísa Lina Villa, Luiz Carlos Zeferino

Country: Brazil

**Objectives:** Human Papillomavirus (HPV) is widely accepted as the central cause of cervical cancer. Cofactors might affect the risk of the progression from HPV infection to cervical precursor lesions and invasive cancer. Bacterial co-infection by *Chlamydia trachomatis* (CT) in women with a history of HPV infection has been studied as a potential factor that contributes to the development of cervical intraepithelial neoplasia and cervical cancer. This study was designed to analyze the association of co-infection HPV and CT with the severity of cervical neoplasia. **Method:** This was a cross sectional study that included women who were subjected of LLETZ or conization due to cervical intraepithelial neoplasia (CIN) 2 and CIN 3 by biopsy; suspicious image penetrating the cervical canal and those in whom colposcopy was unsatisfactory and second cervical smear was abnormal. From 290 consecutive women, 251 were infected by high risk HPV (86.6%) and they were included in the study. the average age was 34.2 years and the median age was 32 years, ranging from 17 to 75 years. HPV- DNA was amplified using PGMY09/11 HPV specific primers and HPV-DNA genotyping was performed using a reverse line blot hybridization assay. the detection of CT was done by PCR to amplify a sequence in the cryptic plasmid generating a fragment of about 512 base pairs. **Results:** The prevalence of CT in HPV positive women was 15.1% (38/251). Significant association was observed between women with 30 years or older and CIN 2 or worse diagnosis for those CT negative (OR 2.11; 1.13-3.95), but this association was not observed for those CT positive (OR 2.03; 0.5-8.23). HPV 16 and/or HPV 18 were detected in 50% of the women under 29 years with CIN 2 or worse who were negative CT, and in 19.5% for those women with CIN 1 or cervicitis. in these women the association between HPV 16 and/or 18 and CIN 2 or worse revealed OR of 5.83 (2.19-15.57), but this association also was not observed considering the group CT positive (OR = 0.28; 0.04-1.98). **Implications and Impact:** This study did not show any association between CT infection and CIN2 or worse diagnosis among women with high risk HPV, specifically considering the types HPV 16 and or HPV 18.

#### Basic Science, Transformation and carcinogenesis

### The Implication of HPV Infection in Human Reproduction

Presenter: Franco Borruto, PhD

Investigators/Collaborators: Ciro Comparetto<sup>1</sup>, Valérie Giordanengo<sup>2</sup>, Alain Treisser<sup>3</sup>, Franco Borruto<sup>4</sup>

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Country: Monaco

**Objectives:** Beside other mucosal targets, HPV-16 was reported to infect the placenta and to replicate in trophoblastic cells. Since these cells share invasive properties of tumoral cells, they represent an ideal model to investigate several oncogenic processes. in the present work, we analyzed the impacts of HPV-16 E5, E6, and E7 oncoproteins on the trophoblastic model. We sought to determine if HPV infection of extravillous trophoblast cells reduces cell invasion and if placental infection is associated with adverse reproductive outcomes attributed to placental dysfunction. **Method:** We conducted apoptosis and invasion assays using extravillous trophoblast cells that were transfected with a plasmid containing the entire HPV-16 genome. in order to associate HPV infection with reproductive outcomes, we conducted a case-control study to detect HPV DNA in the extravillous trophoblast region of placentas from cases of spontaneous preterm delivery, severe preeclampsia requiring delivery at < 37 weeks and controls who delivered at term. **Results:** Our results showed that E5 impaired the viability of trophoblastic and cervical cell lines but E6 and E7, favoring cell growth, neutralized the E5 cytotoxic effect. in addition, E5 decreased the adhesiveness of trophoblastic cells to the tissue culture plastic and to endometrial cells similarly as described previously for E6 and E7. E5 and E6 plus E7 increased also their migration and their invasive properties. Cells expressing HPV-16 early proteins under the control of the long control region endogenous promoter displayed growth advantage and were also more motile and invasive compared with control cells. Rates of apoptosis were 2- to 4- fold greater in transfected cells than in non-transfected cells or cells transfected with an empty plasmid. Invasion of transfected cells through extracellular matrices was 35-75% lower than that of the controls. HPV was detected more frequently

in placentas from spontaneous preterm deliveries than in placentas from controls ( $p = 0.05$ ). Identification of HPV in placentas from cases of pre-eclampsia was not significantly different to controls. **Implications and Impact:** HPV-16 early proteins enhance trophoblastic growth and intensify the malignant phenotype by impairing cell adhesion leading to increased cellular motile and invasive properties. HPV infection of extravillous trophoblast induces cell death and may reduce placental invasion into the uterine wall. Thus, HPV infection may cause placental dysfunction and is associated with adverse pregnancy outcomes, including spontaneous preterm delivery.

### Clinical Science Biomarkers: New and improved for cancer prevention/management of disease

#### Overexpression of ANXA1 in Penile Carcinomas Positive for High Risk HPVs

Presenter: Paula Rahal

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**Background:** Penile squamous cell carcinoma (PSCC) is associated with a number of established risk factors and associated diseases including phimosis with chronic inflammation, Human Papillomavirus (HPV) infection, poor hygiene and smoking. In penile carcinomas the most common HPV types are HPV 16 and HPV 18 being that HPV 16 is most prevalent in North America, Europe, South America and India. **Objectives:** The objective of this study was to identify genes related to penile carcinoma. **Methods:** Forty-seven patients diagnosed with PSCC were enrolled in this study. HPV detection was done by PCR with generic primers GP5+/GP6+ and HPV typing was done by INNO-LiPA kit. RaSH methodology was performed in PSCC positive for high-risk HPV and normal penile tissues to identify differential expression in PSCC. The genes selected were validated in fresh tumour samples by qPCR and their proteins expressions were analyzed by immunohistochemistry. **Results:** HPV DNA was detected in 48.9% of PSCC cases. High-risk HPV were present in 42.5% of cases and low-risk HPV were detected in 6.4% of PSCC. The RaSH approach identified differential expression of Annexin A1 (ANXA1), p16, RPL6, PBEF1 and KIAA1033 in high-risk HPV positive penile carcinoma; ANXA1 and p16 were overexpressed in tumoral cells by qPCR. ANXA1 and p16 proteins were significantly more expressed in the cells from HPV-positive penile carcinoma as compared to HPV-negative tumors ( $p < 0.001$ ) by immunohistochemistry. **Conclusion:** Overexpression of ANXA1, which has anti-inflammatory, antipyretic and anti-hyperalgesic activities and is associated with various physiological processes including cellular differentiation, cell proliferation and signal transduction, was demonstrated in penile squamous cell carcinoma samples and its protein expression is strongly associated with high risk HPV infection. We suggested the p16 could be a marker for penile carcinoma, confirming the diagnosis of malignant penile lesions infected with high risk HPVs.

### Clinical Science, Biomarkers: New and improved for cancer prevention/management of disease

#### HPV 6 in One Case of Invasive Cervical Cancer: Analysis of Biomarkers

Presenter: Alcina F Nicol, PhD

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Country: Brazil

**Objectives:** The goal of this study is to report an unusual case where a single infection with low-risk HPV (type 6) is observed in an invasive cervical cancer sample and to analyze the expression of p16, Ki-67, MCM-2 and p53 in this rare case. **Method:** One invasive cancer specimen was analyzed by means of immunohistochemistry for p16, Ki-67, MCM-2 and p53. HPV DNA was detected by PCR following the genotyping by sequencing. **Results:** The single HPV 6 infection was confirmed by the three techniques: automatic sequencer, INNO-LiPA and PapilloCheck. The markers related to proliferation, Ki-67 and MCM-2, were overexpressed with a mean of 65% and 35% positive cells per field, respectively. The literature has reported high p16 positivity but low-level expression of p53 in ICC. Curiously, in this case p16 was reported negative, while p53 was overexpressed showing a mean greater than 90% of positive cells per field. **Implications and Impact:** Consideration should be given to alternate pathways leading to virally induced carcinogenesis. Other factors such as polymorphic or epigenetic events may play a role in an association with cervical cancer. **Introduction:** Single low-risk HPV infections in high-grade lesions are rare and p53 has often been associated with low expression in ICC. **Objective:** the goal of this study is to report an unusual case where a single infection with low-risk HPV (type 6) is observed in an invasive cervical cancer sample and to analyze the expression of p16, Ki-67, MCM-2 and p53 in this rare case. **Methodology:** One invasive cancer specimen was analyzed by means of immunohistochemistry for p16,

Ki-67, MCM-2 and p53. HPV DNA was detected by PCR following the genotyping by sequencing. Additionally, INNO-LiPA and Papillo-Check Kit were used in order to confirm the single HPV type infection. **Results and Discussion:** The single HPV 6 infection was confirmed by the three techniques: automatic sequencer, INNO-LiPA and PapilloCheck. the markers related to proliferation, Ki-67 and MCM-2, were overexpressed with a mean of 65% and 35% positive cells per field, respectively. the literature has reported high p16 positivity but low-level expression of p53 in ICC. Curiously, in this case p16 was reported negative, while p53 was overexpressed showing a mean greater than 90% of positive cells per field. **Conclusions:** Consideration should be given to alternate pathways leading to virally induced carcinogenesis. Other factors such as polymorphic or epigenetic events may play a role in an association with cervical cancer.

#### Clinical Science, Biomarkers: New and improved for cancer prevention/management of disease

### Effect of Condom Use after CIN Treatment on HPV Positivity and Other Biomarkers: a Randomised Controlled Trial

Presenter: George Valasoulis, MD

Investigators/Collaborators: George Valasoulis<sup>1</sup>, Maria Kyrgiou<sup>2</sup>, Marc Arbyn<sup>3</sup>, Sofia Melina Stasinou<sup>1</sup>, Pierre Martin-Hirsch<sup>4</sup>, Aristotelis Loufopoulos<sup>5</sup>, George Koliopoulos<sup>1</sup>, Petros Karakitsos<sup>6</sup>, Evangelos Paraskevaidis<sup>1</sup>

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Country: Greece

**Objectives:** To investigate whether consistent condom use after treatment of CIN reduces HPV positivity post-operatively and possibly as a result, the risk of treatment failure. **Method:** Design: Single-blinded randomised controlled trial. Period: From May 2009 to February 2012 Setting: University Hospital of Ioannina Inclusion criteria: Women planned to undergo conservative treatment for CIN. Intervention: Women randomly allocated to Group a were given recommendation for condom use, whilst women in Group B received routine post-treatment information. An LBC sample was tested for HPV DNA and typing, E6 & E7 mRNA (NASBA technique), E6 & E7 mRNA by flow cytometry, p16INK4a and microspectroscopy at 0 (pre-treatment), 6 and 12 months. a questionnaire to assess compliance was also completed. Outcomes: HPV and other biomarkers status at 6, 12, 18, 24 months, treatment failures at 24 months and compliance rates. Analysis: the relative risk (RR) and absolute RR (ARR) were calculated in an intention-to-treat analysis. the number needed to treat (NNT) and compliance to condom use recommendation, were also assessed. **Results:** A total of 204 women were recruited. All of them have completed the 6 and 176 the-12 month follow-up. the positivity for all the tested markers at follow-up was significantly reduced in Group A. in particular, 29.8% of women tested positive for HPV in Group a in comparison to 69.2% in Group B [RR:0.569(95%CI:0.376-0.702), ARR:0.394(95%CI:0.244-0.518) at the 6month visit. the NNT was 2. So far, we had 12 treatment failure cases with significantly higher proportion in control arm. Analysis of HPV positivity in relation to the excision margins, treatment failures and compliance rates as well as histological data for both groups will be presented. **Implications and Impact:** Post-treatment condom use significantly reduces HPV positivity. It remains to be confirmed whether this will also result in decreased number of treatment failures.

#### Clinical Science Biomarkers: New and improved for cancer prevention/management of disease

### Susceptibility To Human Papillomavirus Infection and Association with Other Microbial Pathogens

Presenter: Maria Clara Bicho, MD PhD

Investigators/Collaborators: Andreia Matos<sup>1</sup>; M. Carreira<sup>3</sup>; Carina Farinha<sup>2</sup>; Marcia Veiga<sup>2</sup>; Herminia Pereira<sup>3</sup>; Carlos Cardoso<sup>3</sup>

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Country: Portugal

**Objectives:** To analyze the possible relation with microbial gynecology and increase risk for severe dysplasia. **Method:** We studied 193 patients mean age 36, 96 ± 11, 36 (range: 17 – 66 years old) from the Gynecology/Oncology ambulatory of Santiago Hospital. the cervical samples were obtained for cytology, HPV, *Ureaplasma parvum*, *Chlamydia trachomatis* and *Mycoplasma hominis* detection. the method used for HPV detection and genotyping determination was Polymerase Chain Reaction followed by hybridization. Chlamydia trachomatis was detected by using a Real-Time Polimerase Chain Reaction (qPCR). the statistical methods used were Chi-square (Primer version 5) and ANOVA (SPSS version 20). the statistical significance level was established for p < 0.005. **Results:** Among 193 patients, there were 53 (32.3 %) patients with positive HPV DNA among women with normal and abnormal cytology. HPV DNA positive exhibited 16 (30.2 %) with normal and 37 (69.8 %) with negative results cytology. in 55 patients with HPV the incidence was highest in women aged 20 – 40 years old (58, 2 %). We identified 18 HPV types, which HPV 16 was the most predominated (10 (14.49 %) followed by HPV types 31, 52 and 53 (7 (10, 14 %)), type 58 (6 (8.70 %)) and types 66 and 33 (5 (7, 25%)). According to HPV results, we aggregated it in low (4 (2.4 %)), high (34 (20.7 %)), 2 or more high risk types (15 (9.1 %) and unknown (3 (1.8%)). Molecular diagnostic tests and among HPV positive women, we found that 16 (33.33 %) with normal cytology, 6 (12.5 %) with High - grade squamous intraepithelial lesions (HSIL), 11 (22.92 %) with

Low-grade squamous intraepithelial lesions (LSIL) and 15 (31.25 %) with atypical squamous cells of undetermined significance (ASCUS). When we associated HPV results between inflammation and ASCUS, we found a significant prevalence of ASCUS with HPV positive (15 (56 %), ( $\chi^2 = 4.297$ ,  $p = 0.038$ ). We found a trend to association with molecular diagnostic tests for genital microorganisms and HPV DNA positive (39%,  $p = 0.079$ ). When considered the HPV stratification, 2 or more high risks, was significantly associated with a positive molecular diagnostic tests (Positive: 66.7% versus negative: 33.3%,  $p = 0.040$ ). *Ureaplasma parvum* was more prevalent particularly in high risk (22.2%) and 2 or more high risks (33.3%) of detected HPV ( $p = 0.038$ ). **Implications and Impact:** Although the study population was small, we found a significant association between the presence of *Ureaplasma parvum* and HPV positive women, particularly in high risk and 2 or more high-risks HPV. We propose that the screen for the presence of different microorganisms could be important in prevention of severe dysplasias.

#### Clinical Science Biomarkers: New and improved for cancer prevention/management of disease

### Detection of Anal Neoplasia Using Anal Cytology (PAP Smear) - Can We Do Better?

Presenter: John Thornhill, MD

Investigators/Collaborators: Dr Naveena Singh, Ms Damilola Awosika, Dr Michael Sheaff, Dr Mayura Nathan

Country: United Kingdom

**Objectives:** To assess the performance of anal cytology against High Resolution Anoscopy (HRA) guided biopsy for the detection of high grade anal intraepithelial neoplasia. **Method:** We retrospectively compared anal cytology results with histological diagnosis of anal HPV disease/neoplasia. We included all patients referred to our tertiary referral service in London, UK. Episodes with concurrent anal cytology and histopathology results (from HRA directed biopsy) were included. Liquid based anal cytology and HRA was performed (any area suspicious of disease was biopsied). Data pertaining to cytology, histopathology, number of affected disease quadrants (by area), and HIV status were recorded. of 3,520 episodes, 522 had concurrent anal cytology and histology and therefore included. Anal cytology was deemed “positive” if any grade of abnormality was detected. Disease was considered “high grade” if the histopathology was AIN 2/3. Sensitivity and specificity analyses of anal cytology were performed with respect to “high grade” disease and for “any disease”. **Results:** 522 matched samples were included. 58.6% were HIV+ and 35.1% were HIV-. the sensitivity of anal cytology for detecting high grade disease was 77.5% (95% CI 67-82) while the specificity was 39.7% (95% CI 34-44). the sensitivity and specificity for high grade disease in HIV- individuals was 75% and 49.3%, while in the HIV+ group it was 75.2% and 29.9%. the no. of patients who were HIV+ with 2+ quadrants involved was 110. the sensitivity and specificity for high grade disease in this group was 87.9% and 15.6%. in the HIV- group with 2+ quadrant disease it was 92.9% and 41.7%. of those with negative smears and high grade disease ( $n = 36$ ), the majority (80.5%) had zero to 1 quadrant disease (29/36) on HRA, 5/36 had two or more quadrants of disease. 10 of those with negative smears had AIN 3, the remainder had AIN 2. **Implications and Impact:** The sensitivity of anal cytology for detection of high grade AIN disease was 77.5%. This was comparable in HIV+ and HIV- groups (75% and 75.2% respectively). the sensitivity of anal cytology improved when 2+ quadrant disease was present on HRA; this was true in both the HIV+ and HIV- groups (87.2% and 92.9%, respectively) Anal cytology detects the majority of “large” lesions in HIV+ and HIV- individuals, however there may be scope for it’s use with other biomarkers to improve performance.

#### Clinical Science, Biomarkers: New and improved for cancer prevention/management of disease

### Comparison of Carcinogenic HPV Detection by Urine, Vulvar, and Cervical Sampling among Women Attending a Colposcopy Clinic

Presenter: Vikrant Sahasrabudhe, MBBS, MPH, DrPH

Investigators/Collaborators: Vikrant V. Sahasrabudhe, Patti E. Gravitt, S. Terence Dunn, David Brown, Richard A. Allen, Katie Smith, Rosemary E. Zuna, Michael A. Gold, Mark Schiffman, Philip E. Castle, Joan L. Walker, Nicolas Wentzensen

Country: United States

**Objectives:** Non-invasive, urine-based sampling for carcinogenic HPV testing offers the potential for improving anogenital cancer screening in hard-to-reach populations. We sought to compare HPV detection through urine-based sampling versus cellular sampling of the cervix and vulva, and correlate results with cervical disease status in a controlled clinical setting. **Method:** In a cross-sectional study at a colposcopy clinic, 72 participants provided a urine sample prior to a clinician collecting a vulvar (external genital) sample using a Dacron swab and cervical sample using a cytobrush. Cervical disease status was defined by combining colposcopy/histology and cervical cytology results. HPV genotyping of urine (after centrifugation), vulvar, and cervical samples was conducted using the Linear Array HPV Genotyping Test. **Results:** Carcinogenic HPV genotypes (HPV16/18/31/33/35/39/45/51/52/56/58/59/68) were present in 42/72 (58.3%) urine samples, 49/68 (72.1%) vulvar samples, and 53/72 (73.6%) cervical samples. Carcinogenic HPV detection in urine samples showed a ‘moderate’ agreement with HPV detection in cervical samples (Kappa: 0.55) and a ‘substantial’ agreement with vulvar samples (Kappa: 0.62). the agreement between carcinogenic HPV detection in cervical and vulvar samples was also ‘substantial’ (Kappa: 0.70). Highgrade cervical lesions (CIN2+ histology or HSIL cytology) were present in 25/66 (37.9%) women. Urine-based detection of carcinogenic HPV had a clinical sensitivity of 76.0% and a clinical specificity of 56.1% for diagnosing high-grade cervical lesions. the corresponding sensitivity and specificity values for vulvar sampling were 88.0% and 39.5%, and those for cervical sampling, 92.0% and 39.0% respectively. HPV16 was the most common carcinogenic genotype, detectable in 25.0% of urine, 33.8% of vulvar, and 31.9% cervical samples. **Implications and Impact:** HPV detection based on sampling from non-cervical sites may offer a simple approach for anogenital cancer screening in medically underserved areas. Population-based research studies are needed to evaluate the operational challenges in implementation of such sampling approaches.

It will be important to evaluate the acceptable levels of the decrement in sensitivity (as compared to cervical HPV) that may be offset by the benefits of non-invasive/non-obtrusive or home-based sampling.

### Clinical Science, Clinical immunology

## Immunogenicity of Quadrivalent HPV Vaccine among Girls Aged 11-13 Years Vaccinated Using Alternative Dosing Schedules: Results 32 Months after Third Dose

Presenter: D. Scott LaMontagne, PhD MPH, FRSPH

Investigators/Collaborators: LaMontagne DS<sup>1</sup>; VD Thiem<sup>2</sup>; VM Huong<sup>1</sup>; Y Tang<sup>1</sup>; Neuzil KM<sup>1</sup>

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Country: United States

**Objectives:** To demonstrate that anti-HPV 16 and anti-HPV 18 immune responses more than 24 months post-dose 3 among 11-13 year old girls are non-inferior using three different alternative dosing schedules (0, 3, 9 months; 0, 6, 12 months; or 0, 12, 24 months) to those obtained when the vaccine is administered on the standard 3-dose schedule of 0, 2, 6 months. **Method:** We collected a single blood sample of 7 milliliters from girls enrolled in an original open-label, cluster-randomized trial of alternative dosing schedules that demonstrated non-inferior immunogenicity one-month post-dose 3 for two of three alternative dosing schedules compared to the standard schedule (Neuzil KM, et al. JAMA April 2011). Girls on the standard schedule were followed for 29 months and those on the alternative schedules for 32 months. An interim measure of 20 months post-dose 3 was performed for girls on the 0, 12, 24 month alternative schedule. The same type-specific competitive Luminex immunoassay was performed by Merck & Co. (USA) to quantify levels of neutralizing antibodies. Non-inferiority was defined as in the original trial: the lower bound of the 97.5% confidence interval for both the anti-HPV 16 and anti-HPV 18 GMT ratios between the alternative and standard schedule was  $> 0.50$ . Both parents and enrolled girls provided written informed consent to participate in this follow-up study. **Results:** Of the 809 girls aged 11-13 years who completed the original study, 741 were eligible for this follow-up study, and 518 had a valid blood sample at 29 or 32 months after dose three (which was 64% of the population who completed the original trial). Preliminary analyses indicate that the immunogenicity of HPV vaccine when delivered on either the 0, 3, 9 month or 0, 6, 12 month alternative dosing schedule was non-inferior for types 16 and 18 at 32 months post-dose 3 compared to girls at 29 months post-dose 3 who were vaccinated on the 0, 2, 6 month standard schedule. Results for girls vaccinated on an annual schedule (0, 12, 24 months) will be available at the time of the conference; however, an interim blood draw for this group showed that GMTs for types 16 and 18 remained high at 20 months post-dose 3. **Implications and Impact:** Young adolescent girls may have similar antibody responses for HPV 16 and 18 when vaccinated on a variety of dosing schedules. Provision of dosing flexibility without reduction in immunogenicity could facilitate more feasible delivery strategies in low resource settings and provide evidence for administration of missed doses up to two years after initiating the three-dose series.

### Clinical Science, HPV testing: Prevention and management trials (RTC)

## Overtreatment in See-and-Treat Management of Cervical Intraepithelial Lesions: Thirty Years of Experience in a Single Institution in the Netherlands

Presenter: Remko Bosgraaf, MD

Investigators/Collaborators: Remko P. Bosgraaf, MD, Peter-Paul Mast, BSc, Petronella H.T.H. Struik-van der Zanden, Johan Bulten, MD, PhD, Leon F.A.G. Massuger, MD, PhD, Ruud L.M. Bekkers, MD, PhD.

Country: Netherlands

**Objectives:** The major cause of cervical intraepithelial neoplasia (CIN) is persistent infection of the cervix with high-risk types of human papillomavirus (hr-HPV). HPV appears to cause cervical dysplasia and may lead to the development of cervical cancer. Much controversy still exists on how to assess a patient referred for colposcopy after an abnormal cervical smear. A see-and-treat management is appealing because of low-costs, decreased patient anxiety and increased compliance. A major downside is the rate of overtreatment, with increased premature birthrate as major complication. The aim of this study is to determine the rate of overtreatment in see-and-treat management at colposcopy in relation to the cervical smear result, age, and colposcopic impression. **Method:** Out of a total of 4808 patients referred for an initial colposcopy to the Radboud University Nijmegen Medical Center over the last 30 years, 3192 (66%) patients underwent a see-and-treat protocol, and were analyzed in the current study. Overtreatment, defined as CIN 1 or less at final histopathological analysis, was investigated in relation to the age of the women, referred cervical smear result, colposcopic impression, and histopathology result. **Results:** The overall rate of overtreatment in see-and-treat management was 18.1%. The lowest overtreatment rate (4.5%) was seen in women with both a high-grade cervical smear, and a high-grade impression on colposcopy. The rate of overtreatment also showed a relation with age; women under forty were less likely to be overtreated than women above this age. **Implications and Impact:** This is the first time that age influences on the rate of overtreatment are studied in what is – as far as we know – the largest single institute case series. The overtreatment rate for patients in all age groups referred with a high-grade smear, and with a high-grade impression on colposcopy is low, and a see-and-treat approach in these patients is the preferred management strategy. In women with either a high-grade smear, or high-grade impression on colposcopy, see-and-treat may still be preferred but has higher overtreatment rates. Given the side effects of cervical surgery on pregnancy outcome, especially young women may benefit from a two-step approach if they have either a low-grade smear, or low-grade impression on colposcopy, while older women may prefer a see-and-treat policy.



**Clinical Science New vaccine trials (Phase I-III; preventive and therapeutic trials)****Immunogenicity and Safety of the Bivalent HPV Vaccine in Female Juvenile Idiopathic Arthritis Patients versus Healthy Female Adolescents: a Prospective Controlled Observational Cohort Study**

Presenter: Mirte Scherpenisse, PhD student

Investigators/Collaborators: Mirte Scherpenisse\*<sup>1,2</sup>, Marloes W. Heijstek\*<sup>3</sup>, Noortje de Groot<sup>3</sup>, Carline Tacke<sup>3</sup>, Anne-Marie Buisman, Guy A.M. Berbers<sup>1</sup>, Nico M. Wulffraat\*<sup>3</sup>, Fiona R.M. van der Klis\*<sup>1</sup>

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Country: Netherlands

**Objectives:** In healthy young women the bivalent HPV vaccine is safe and immunogenic, and it induces a high degree of protection against HPV16/18 infection and their associated pre-cancer lesions. Children with chronic rheumatic diseases as juvenile idiopathic arthritis (JIA) are at increased risk of persistent HPV infections that may progress into HPV-associated malignancies. We conducted a prospective controlled clinical trial in order to assess the immunogenicity and safety of the HPV vaccine in female patients with JIA compared to healthy female adolescents. **Method:** Female patients (n = 68) and healthy female adolescents (n = 55) aged 12 to 18 years were recruited and vaccinated with Cervarix in a 2+1 vaccination schedule. Study visits with blood sampling occurred pre-vaccination and at 3, 7, and 12 months postvaccination. Serum samples were tested for HPV16/18-specific antibodies and antibody avidity using a multiplex immunoassay in which VLP16 and 18 were coupled to fluorescent microspheres. Memory B-cell responses were assessed by HPV16/18-specific ELISpot assays. Adverse events and the effect of vaccination on JIA disease were registered during the trial (ClinicalTrials.gov, registration number NCT00815282). **Results:** All participants were seropositive for HPV16 and 18 at 7 months. One patient turned seronegative at 12 months for both HPV16 and 18. No significant differences in HPV16/18-specific antibody concentrations were found between patients and controls but antibody concentrations were consistently lower in patients. No effect of anti-rheumatic drugs on HPV16/18 antibodies was detected (methotrexate, HPV16 p = 0.790, HPV18 p = 0.372). Patients using anti-TNF $\alpha$  were all seropositive after vaccination. Avidity Index of HPV16/18-specific antibodies at 12 months was similar in patients and controls for HPV16 and HPV18. The kinetics of HPV16/18 memory B-cell responses was comparable between patients and controls. However, the magnitude of memory B-cell responses at 7 and 12 months appeared lower in patients. No relevant differences in adverse events were found between both groups. No detrimental effect of the HPV vaccine on JIA disease activity was detected. **Implications and Impact:** The bivalent HPV16/18 vaccine is immunogenic, well tolerated and safe in JIA patients. However, HPV-specific antibody concentrations and the magnitude of B-cell responses were consistently lower in JIA patients compared to healthy controls during follow-up. It is possible that long-term protection against HPV infection is not guaranteed. Therefore, immunosurveillance in JIA patients seems warranted.

**Clinical Science New vaccine trials (Phase I-III; preventive and therapeutic trials)****Cross-Protective Efficacy of HPV 16/18 AS04-Adjuvanted Vaccine: 4-Year End-Of-Study Analysis of Patricia Trial Utilising the Type Assignment Algorithm**

Presenter: Barbara Romanowski, MD

Investigators/Collaborators: PATRICIA Study group

Country: Canada

**Background:** The human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine (Cervarix®, GlaxoSmithKline Vaccines) has shown high and sustained vaccine efficacy (VE) against infections and cervical intraepithelial neoplasia (CIN)<sup>2+</sup> associated with HPV-16/18, and may provide a broader protection as shown by evidence of VE against some non-vaccine oncogenic types. **Objectives:** To present end-of-study results (Month 48) from the Phase III PATRICIA study with respect to cross-protective VE against infection and CIN<sup>2+</sup>, using HPV Type Assignment Algorithm (TAA). This is an alternative case definition assigning likely causality of CIN<sup>2+</sup> lesions infected with multiple HPV types based on type-specific detection of HPV DNA in the lesion as well as in the preceding cytology samples. **Methods:** In this study (NCT00122681), women aged 15–25 years were randomised (1:1) to receive HPV-16/18 vaccine (N = 9319) or control (N = 9325) at Months 0, 1 and 6. Cervical samples were collected every 6 months for HPV DNA typing; gynaecological and cytopathological examinations were performed every 12 months. VE results are reported for the total vaccinated cohort (TVC)- naïve (women who received  $\geq 1$  vaccine dose, seronegative for HPV-16/18 and HPV DNA negative for 14 oncogenic HPV types, with normal cytology at baseline). **Results:** During the study period (overall mean follow-up for TVC-naïve was 44.3 months), VE (95% CI) against CIN<sup>2+</sup> was 92.1% (68.1, 99.1) for HPV-31, 79.3% (44.6, 93.8) for HPV-33 and 100.0% (41.7, 100.0) for HPV-45. VE against CIN<sup>2+</sup> associated with any non-vaccine oncogenic HPV type (HPV-31/33/35/39/45/51/52/56/58/59/66/68) was 55.3% (35.9, 69.3), and 69.8% (57.8, 78.8) against any oncogenic HPV type including vaccine types (HPV 16/18/31/33/35/39/45/51/52/56/58/59/66/68). VE against CIN<sup>3+</sup> was 100% (15.5, 100) for HPV-31, 71.6% (-49.3, 97.1) for HPV-33, 100.0% (-429.7, 100.0) for HPV-45, 94.8% (79.8, 99.4) against any oncogenic HPV type including HPV 16/18, and 91.0% (63.2, 99.0) against any non-vaccine oncogenic HPV type. **Implications and Impact:** End-of-study (4-year follow-up) cross-protective VE results using TAA were similar to those using the primary case definition based on detection of HPV DNA in the lesion only (Wheeler CM, et al. Lancet Oncology 2012;13:100–10). These results strengthen the causal link between CIN<sup>2/3+</sup> lesions and associated non-vaccine HPV types in the evaluation of cross-protective VE. Cervarix® is a registered trademark of the GlaxoSmithKline group of companies.

### Clinical Science, New vaccine trials (Phase I-III; preventive and therapeutic trials)

#### Interchangeable Use of Gardasil and Cervarix: Preliminary Safety Data

Presenter: Vladimir Gilca, MD PhD

Investigators/Collaborators: Chantal Sauvageau MD, MSc; Geneviève Deceuninck MD, MSc; Nicole Boulianne RN, MSc; Gaston De Serres MD, MSc; Marc Dionne MD, MSc

Country: Canada

**Background:** Disruption in delivery of vaccines used in public immunization programs were previously reported in different countries. the availability of the same vaccine for the full course of vaccination should not be taken for granted. No data on interchangeable use of two HPV vaccines in humans are available. Evidence based data on the interchangeable use of two HPV vaccines is needed. **Objectives:** the main objective of this study was to assess the comparative immunogenicity and safety of Gardasil and Cervarix when administered to girls who previously received 2 doses of Gardasil. Here we present safety data. **Methods:** 416 12-14 year-old girls previously vaccinated with 2 doses of Gardasil at the age of 9-10 years according to a 0-6 months schedule were invited to participate in this blinded randomised (1:1) clinical trial. All reported adverse events were included in this analysis. **Results:** 366 girls accepted to participate and were randomised to receive Gardasil or Cervarix. after the administration of Gardasil or Cervarix, 81% and 91% reported a local ( $p = 0.004$ ), and 58% and 59% a general adverse event ( $p = 0.83$ ), respectively. after each of two vaccines similar proportions of vaccinees reported fatigue (34-35%), headache (26-29%), gastrointestinal symptoms (9-12%), rash (2-3%), myalgia (25-30%), arthralgia (13-14%), urticaria (1-2%) and fever  $\geq 37.5^{\circ}\text{C}$  (0-1%) (all  $p > 0.05$ ). Slightly higher proportion of vaccinees who received Cervarix reported redness (28% vs. 22%;  $p = 0.15$ ) and swelling (26% vs. 18%;  $p = 0.04$ ) than those who received Gardasil. Overall pain, and grade 3 pain at the injection site was more often reported after Cervarix when compared to Gardasil: 89% vs. 72% ( $P < 0.001$ ) and 9% vs. 2% ( $P = 0.003$ ), respectively. No vaccine related serious adverse event was reported. in the group who received 3 doses of Gardasil, a higher proportion of participants reported local (81% vs. 62%) and general adverse events (58% vs. 42%) after the third dose when compared to first two doses of vaccine (all  $p < 0.05$ ). **Implications and Impact:** The results of this study show that Cervarix has an acceptable tolerability profile when given to girls who previously received two doses of Gardasil. the higher proportion of vaccinees reporting adverse events after the third dose of Gardasil when compared to first 2 doses of the same vaccine is most probably related to the age when the vaccine was administered. the results from the ongoing immunogenicity tests will allow concluding on the possibility of interchangeable use of two HPV vaccines.

### Clinical Science New vaccine trials (Phase I-III; preventive and therapeutic trials)

#### Efficacy and Safety of RO5217790 Treatment in Patients with High Grade Cervical Intraepithelial Neoplasia(CIN2/3)

Presenter: Pekka Nieminen, MD

Investigators/Collaborators: Pekka Nieminen<sup>1</sup>, Diane Harper<sup>2</sup>, Mark H. Einstein<sup>3</sup>, Francisco Garcia<sup>4</sup>, Gilbert Donders<sup>5</sup>, Warner Huh<sup>6</sup>, Thomas C. Wright<sup>7</sup>, Mark Stoler<sup>8</sup>, Alex Ferenczy<sup>9</sup>, Olga Rutman<sup>10</sup>, Anna Shikhman<sup>10</sup>, Mimi Leung<sup>10</sup>, Barry Clinch<sup>11</sup>, Elizabeth Calleja<sup>10</sup>

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8 University of Virginia Health System, Charlottesville, VA, USA

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10 Hoffmann La Roche, Inc, USA

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Country: Finland

**Objectives:** NV25025 is a randomized Phase 2 study to determine the safety and efficacy of RO5217790 compared to placebo in CIN2/3 patients. RO5217790 is a targeted HPV immunotherapeutic comprised of Modified Vaccinia Ankara (MVA) with modified HPV16 E6 and E7 as well as the gene for human IL2. **Methods:** Patients with CIN2/3 were randomized 2:1 to receive subcutaneous injections of RO5217790 or placebo weekly 3 times within 60 days of initial biopsy diagnosis followed by conization at Month 6. Randomization was stratified by the presence of HPV16 mono-infection or other genotypes. Histology of biopsies obtained at baseline and from conization at Month 6 was centrally reviewed. HPV response was determined using the Roche linear array and defined as clearance of baseline HPV genotypes. Efficacy was assessed in the modified intent to treat population (mITT) defined as patients who received at least one study injection and had a CIN2/3 at entry by central pathology. **Results:** Overall, 206 patients were enrolled and dosed. the mITT population included 192 patients: 129 received RO5217790 and 63 received placebo. There were 85 patients with HPV16 mono-infection: 56 in the active arm and 29 in the placebo arm. the number of HPV16 mono-infected patients who achieved histologic resolution (no CIN) was 5 times greater in the active arm compared to the placebo (20% vs. 4%). a histologic response ( $< \text{CIN}2$ ) was observed in this same group in 31% in the active arm vs. 22% in the placebo arm. the rates of histologic resolution and response in the mITT patients (all genotypes) were 15% higher in the RO5217790 arm than in the placebo arm (25% vs. 10% for resolution and 36% vs. 21% for response). At Month 6, patients treated with RO5217790 had a higher clearance of baseline HPV genotypes than those who received placebo: 38% vs. 9% in the HPV16 mono-infected group and 37%

vs. 14% in the mITT population. Treatment with RO5217790 was safe and well tolerated, with injection site reactions (ISRs) reported as the most frequent drug-related adverse events. The majority of the ISRs were mild to moderate in intensity. There were only 2 related serious adverse events: lymphadenopathy in the active arm and breast cancer in the placebo arm. There was one unrelated death in the placebo arm. **Implications and Impact:** RO5217790 showed higher activity when compared with placebo in both histologic resolution and response as well as viral clearance at 6 months in patients with CIN2/3. This targeted immunotherapy was safe and well tolerated.

#### Clinical Science New vaccine trials (Phase I-III; preventive and therapeutic trials)

### Efficacy of an HPV16/18 Vaccine against Oral HPV Infections: a Randomized Clinical Trial

Presenter: Rolando Herrero, MD

Investigators/Collaborators: Rolando, Herrero, Wim Quint, Allan Hildesheim, Paula Gonzalez, Linda Struijk, Hormuzd a Katki, Carolina Porras, Mark Schiffman, Ana Cecilia Rodriguez, Diane Solomon, Silvia Jimenez, John T. Schiller, Douglas R. Lowy, Leen-Jan van Doorn, Sholom Wacholder, and Aimée R. Kreimer, for the CVT Vaccine Group.

Country: France

**Objectives:** Human papillomavirus (HPV) infection, particularly with type 16, causes a growing fraction of cancers of the oropharynx, whose incidence has significantly increased in recent decades, mainly in developed countries. We evaluated vaccine efficacy (VE) of an ASO4-adjuvanted HPV16/18 vaccine against oral HPV infections. **Method:** In a double-blind controlled trial, 7,466 women 18-25 years of age were randomized (1:1) to receive the HPV16/18 vaccine or hepatitis a vaccine as control. At the final blinded study visit, approximately four years after vaccination, 5 840 participants provided oral specimens (91.9% of eligible women) to evaluate VE against oral infections. Our primary analysis evaluated prevalent oral HPV infection at the four-year study visit in the cohort of all vaccinated women with oral and cervical HPV results. Corresponding VE against prevalent cervical HPV 16/18 infection was calculated for comparison. **Results:** Oral prevalence of identifiable mucosal HPV was low (1.9%) but comparable to previous reports. Approximately four years after vaccination, there were 15 prevalent HPV16/18 infections in the control group and one in the vaccine group, for a VE of 93.3% (95% CI = 63-100). Corresponding efficacy against prevalent cervical HPV16/18 infection for the same cohort at the same visit was 72.0% (95% CI = 63-79) (p versus oral VE = 0.04). There was no statistically significant evidence of protection against other oral HPV infections, though power was limited for these analyses. **Implications and Impact:** HPV prevalence four years after vaccination with the ASO4-adjuvanted HPV16/18 vaccine was much lower among women in the vaccine arm compared to those in the control arm, suggesting that the vaccine affords strong protection against oral HPV16/18 infection, with potentially important implications for prevention of increasingly common HPV-associated oropharyngeal cancer.

#### Clinical Science, New vaccine trials (Phase I-III; preventive and therapeutic trials)

### Prevention of Anal Condyloma with Quadrivalent Human Papillomavirus Vaccination of Older Men who Have Sex with Men: a Nonconcurrent Cohort Study

Presenter: Stephen Goldstone, MD

Investigators/Collaborators: Kristin a Swedish, MD, MPH Stephen E. Goldstone, MD

Country: United States

**Objectives:** The quadrivalent human papillomavirus vaccine (qHPV) is FDA-approved for use in males 9 to 26 years old to prevent anogenital condyloma. QHPV has been shown to decrease anal and cervical high-grade dysplasia recurrence post treatment. The objective of this study is to determine if qHPV is effective at preventing anal condyloma among MSM 26 years of age and older. **Method:** This non-concurrent cohort study evaluated HIV-negative MSM aged  $\geq 26$  years seen at a single site during 2007-2010. Patients either had no history of anal condyloma or had previously-treated anal condyloma recurrence-free for at least 12 months. We determined the recurrence rate of anal condyloma in vaccinated versus unvaccinated patients. **Results:** Of 308 eligible patients, 114 (37 %) patients had received the full 3-dose qHPV vaccine electively and 110 (35.7%) had history of anal condyloma. Vaccinated patients were significantly younger (vaccinated mean age 38.5 years with standard deviation [SD] 7.4, unvaccinated mean age 44.2 years with SD 10.4, p = 0.000) and were more likely to test positive for oncogenic HPV within 8 months prior to study entry (vaccinated 43.9%, unvaccinated 33.5%, p = 0.028). Groups were comparable in respect to race/ethnicity; insurance type; smoking status; history of anal condyloma; history of high-grade anal intraepithelial neoplasia; and history of gonorrhea, chlamydia, and syphilis. During 588.0 person-years follow-up, 8 (7.0%) vaccinated patients and 36 (18.6%) unvaccinated patients developed anal condyloma. Multivariable hazards ratio (HR) analysis at one year showed qHPV and testing negative for oncogenic HPV genotypes were significantly associated with decreased risk of anal condyloma (qHPV HR 0.34, 95% confidence interval [CI] 0.11-1.00, p = 0.049; negative HPV HR 0.17, 95% CI 0.04-0.76, p = 0.021). At two years, multivariable HR analysis showed testing negative for oncogenic HPV was associated with decreased risk of anal condyloma (HR 0.31, 95% CI 0.11-0.85, p = 0.024). qHPV approached significance for decreased risk of anal condyloma (HR 0.43, 95% CI 0.19-1.01, p = 0.052) and history of chlamydia approached significance for increased risk (HR 2.29, 95% CI 1.00-5.26, p = 0.051). Multivariable HR analysis at three years showed qHPV and testing negative for oncogenic HPV were significantly associated with decreased risk of anal condyloma (qHPV HR 0.43, 95% CI 0.19-1.00, p = 0.049; negative HPV HR 0.37, 95% CI 0.15-0.91, p = 0.030). **Implications and Impact:** Among MSM 26 years of age and older with and without history of anal condyloma, qHPV reduces the risk of anal condyloma development. A randomized controlled trial is needed to confirm these findings in this age group.

**Clinical Science, Non-vaccine treatment for HPV associated disease****Treatment of Anal Intraepithelial Neoplasia in HIV+ MSM: A Triple Arm Randomized Clinical Trial of Imiquimod, Topical 5-Fluoruracil and Electrocautery**

Presenter: Olivier Richel, MD

Investigators/Collaborators: Richel O, De Vries HJC, Van Noesel CM, Dijkgraaf M, Prins JM

Country: Netherlands

**Objectives:** Anal cancer is an increasing problem among HIV+ men-who-have-sex-with-men (MSM). Screening for its precursor lesion anal intraepithelial neoplasia (AIN) is subject of discussion. Current treatment options are suboptimal and have not been compared in a prospective trial. In this randomised clinical trial we compared efficacy and side effects of imiquimod, topical 5-fluoruracil (5-FU) and electrocautery (ECA) for the treatment of AIN. **Method:** 148 HIV+ MSM with histological confirmed AIN were randomised between 16 weeks of imiquimod (3 times a week), 5-FU (twice a week) or monthly ECA for 4 months. Participants were evaluated by high-resolution anoscopy with biopsies 4 weeks and 6 months after treatment. Response rates were compared by chi-square analysis. **Results:** 57% of patients had high grade (HG) AIN. In an intention to treat analysis imiquimod showed a response rate of 39% (95% CI 27-52), 5-FU of 29% (95% CI 18-43) and ECA of 48% (95% CI 34-62). Complete response was seen in 26% (95% CI 16-39), 17% (95% CI 8-30) and 41% (95% CI 28-56) respectively ( $p = 0.03$ ), of which 25%, 57% and 17% recurred 6 months after treatment. In a multivariate logistic regression, HGAIN, peri-anal AIN and high plasma CD4 cell count were significantly associated with response to treatment, with odds ratios of 3.5 ( $p = 0.003$ ), 31.9 ( $p = 0.003$ ) and 1.003 (per cell/ $\mu$ l;  $p = 0.002$ ) respectively. Severe side effects were seen in 43% (imiquimod), 27% (5-FU) and 18% (ECA) ( $p = 0.02$ ). **Implications and Impact:** This study showed that regarding both efficacy and side effects electrocautery is superior to imiquimod and efudix in treatment of AIN, but recurrence rates are substantial.

**Clinical Science, Non-vaccine treatment for HPV associated disease****Risk of Preterm Delivery after Treatment for Cervical Intraepithelial Neoplasia in England**

Presenter: Alejandra Castanon, MD

Investigators/Collaborators: A Castanon, R Landy, P Brocklehurst, H Evans, N Singh, P Walker, J Patnick, D Peebles, P Sasieni, for the PaCT Study Group

Country: United Kingdom

**Objectives:** To estimate the association between treatment for cervical intraepithelial neoplasia and the risk of preterm birth in England. In particular, whether the amount of material excised modifies the risk. **Method:** We carried out a retrospective prospective cohort study (phase 1) with a nested case-control study (phase 2) using record linkage. We identified women with a histological sample taken at colposcopy from pathology and colposcopy records from 12 English hospitals between 1989 and 2011. These women were linked by HES (Hospital Episode Statistics) to hospital obstetric records between 1998 and 2009 for the whole of England to identify live births. The main outcome measure is the risk ratio of preterm births following excisional treatment (LLETZ/knife cone/laser cone) for cervical intraepithelial neoplasia. Using phase 2 data we also consider the amount of material excised. Analyses were adjusted by age at delivery, parity and the hospital where colposcopy was carried out. **Results:** Phase 1 included 18,441 singleton births: 4,176 before histology and 14,265 after. Among first births subsequent to histology, the adjusted relative risk of a preterm birth associated with previous treatment was 1.19 (95% CI 1.01 to 1.41); among first births prior to histology the relative risk associated with subsequent treatment was 1.47 (95% CI 1.05 to 2.05). Combining these gives the relative risk associated with treatment adjusted for timing relative to histology of 0.91 (95% CI 0.66 to 1.26). Preliminary phase 2 data included 1842 births of which 1356 were after histology: about half of these births were preterm (by design). Of those with a birth after histology 836 had a single treatment and 417 had a punch biopsy only. The height of the cone ranged from 1 to 30 mm with 20% being 14 mm or greater. The median height was 10 mm. About 8.5% of treated women had multiple treatments. We will have sufficient power to explore the risk of preterm delivery by treatment height in women with single and multiple treatments. **Implications and Impact:** The overall risk of preterm delivery in women treated by colposcopy in England was substantially less than that in many other studies, predominantly from Nordic countries. However only a small proportions of treated women had deep excision (only 10% were 15mm or greater) and it is possible that large excisions increase the risk of preterm birth.

**Clinical Science Non-vaccine treatment for HPV associated disease****Effects of REBACIN in Treatment of Cervical Intraepithelial Neoplasia (CIN) Following LEEP Procedure**

Presenter: Chunfa Zhang, PhD

Investigators/Collaborators: Li Cheng<sup>1</sup>, G.Y. Wang<sup>2</sup>, C.F. Zhang<sup>3</sup>1 Dept. of Obstetrics and Gynecology, the 1<sup>st</sup> Hospital, Shanxi Medical University, Taiyuan, China

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**Background:** We have previously reported that REBACIN, a novel antiviral factor, is effective in high risk HPV infection clearance with notable virus negative conversion rate in a clinical study. REBACIN also exerts drastic suppression on the HPV E6/E7 oncogene expression, and largely reduces the growth of tumors induced by HPV16/18 infection in a mouse model. **Objective:** To evaluate the clinical effect of

REBACIN in the treatment of high grade cervical dysplasia following loop electrosurgical excision procedure (LEEP). **Methods:** 102 cases (patients) with CIN 2-3 and high risk HPV positive were LEEP treated and then were randomly divided into two groups. An experimental group of 53 cases received REBACIN treatment via vaginal administration for three months from the date LEEP was completed. a control group of 49 cases received no further treatment after LEEP. a 24-month follow up was conducted post the LEEP procedure, during which HPV-DNA test, colposcopy, and cervical biopsy were performed at 3-, 6-, 12- and 24-month intervals for both groups. the residual and recurrence disease rates were measured accordingly. **Results:** At both 12- and 24-month follow ups, 51 out of the 53 cases in the REBACIN-treated group were both CIN free and HPV negative. This 96% disease-free rate is significant higher than that of the control group, which is 73.5% accounting for 36 out of the 49 cases. 2 cases of the REBACIN group showed persistent HPV positive, and re-developed CIN again during the follow up, thus account for the disease recurrence rate of this group at 3.8%. the recurrence rate of the control group, on the other hand, is 26.5% for which 13 out of the 49 cases had CIN again in the course of the follow ups. **Conclusion:** These data has illustrated that REBACIN treatment in combination with LEEP procedure can effectively enhance the cure rate for high grade cervical intraepithelial neoplasia, and significantly reduce the disease recurrence rate compared with patients who were treated with LEEP only.

### Epidemiology/Public Health, Biomarkers

#### Is HPV-16 Integration a Predictor Marker of Cervical Lesions?

Presenter: Rui Medeiros, PhD

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**Objectives:** The persistent infection with carcinogenic types of human papillomavirus (HPV) has been established as the main etiological factor for the development of squamous intraepithelial lesions of the cervix which may progress to high-grade dysplasia or invasive carcinoma. the integration of HPV genome into the host's genome is considered the hallmark of HPV-associated carcinogenesis. However, the significance of HPV physical status detection remains unclear. the aim of this study was to characterize the physical status of HPV-16 in samples with different histological classifications. **Method:** We have selected 53 cervical specimens from women with different histological classification (7 normal, 15 atypical cells of undetermined significance (ASC-US), 12 low-grade squamous intraepithelial lesion (LSIL), 15 high-grade squamous intraepithelial lesions (HSIL) and 4 invasive cervical carcinoma (ICC)) that have been identified with HPV-16 infection (45 single infection and 8 co-infections). the physical status of HPV16 was analyzed using a multiplex Real-time PCR that allows simultaneous amplification of the E2 and E6 regions. HPV-16 status classification was based on the principle that, when integration occurs, the E2 gene is partially or totally disrupted while the E6 gene remains intact. **Results:** In this study, the prevalence of HPV16 integration was of 26.4% (14/53, 13 mixed forms and 1 integrated only). Results showed no significant association observed comparing HPV-16 integration with single vs co-infections with others HPVs ( $p = 0.647$ ). Prevalence of HPV-16 integration among different cervical lesions was 28.6% (2/7) in samples without cytological lesion, 13.3% (2/15) in ASCUS, 33.3% (4/12) in LSIL, 33.3% (5/15) in HSIL and 25.0% (1/4) in ICC. Additionally, we no found statistical significant differences in HPV-16 integration distribution among the histological specimens ( $p = 0.735$ ). **Implications and Impact:** Our study revealed that HPV 16 integration is not exclusive event of high-grade lesions/ICC. It was not possible to detect integrated forms in all cases of HSIL/ICC. This fact reveals the need to reconsider the role of viral genome integration in HPV associated carcinogenesis and suggests the requirement of further studies, preferably cohort studies, to follow-up normal, ASC-US and LSIL cases which present HPV integration and evaluate their progression.

### Epidemiology/Public Health Epidemiology/Natural history of anogenital HPV in females

#### Microinvasive Adenocarcinoma of the Cervix in Young Woman Vaccinated against HPV: from Studies to Reality

Presenter: Julio Teixeira, PhD

Investigators/Collaborators: Julio Cesar Teixeira<sup>1</sup>, Eliane R. Zambelli Oliveira<sup>1</sup>, Círbia S. Campos Teixeira<sup>1</sup>, Liliana A. L. A. Andrade<sup>1</sup>, Carlos Eduardo Bacchi<sup>2</sup>, Luiz Carlos Zeferino<sup>1</sup>, Sophie Françoise Mauricette Derchain<sup>1</sup>

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Country: Brazil

**Objectives:** Several factors are associated with an increased in the number of adenocarcinoma of the cervix. HPV vaccines and new screening technologies can counter this trend. It is expected a transition period with cases simulating limitations or flaws in the process vaccination-screening-treatment. the objective of this report is to illustrate with a real situation what may occur in the coming years. **Method:** A teenager 16 years old (she had a baby one year before), started in June 2005 the participation in the Phase III study (HPV-008/NCT00122681) to evaluate the efficacy of the HPV 16-18 AS04-adjuvanted vaccine (GSK). Received all three vaccine doses (zero, 30 and 180 days) and completed all procedures according to protocol: cervical sample collection every six months for PCR (SPF10 LiPA25) for identification

of 14 HR-HPV and 11 LR-HPV and yearly for cytology. Only cytology results, five negative exams, were available for clinical follow-up. Upon completion of the study and breakdown of blinding, this patient had received the HPV vaccine and had a HR-HPV test (+) at the final visit (May/2009). Due to HPV test (+), she was invited to continue the annual monitoring through an extension of the initial study, for up to four additional years. **Results:** In JAN/2011, remains the test HR-HPV (+) and cytology (-), with colposcopy (-). in JAN/2012, aged 23 years old, test HR-HPV (+) with an ASC-H cytology. the colposcopic evaluation had a focal area of aceto-white epithelium, slightly evident within a small ectropion, without further images. the biopsy showed an Adenocarcinoma in Situ in this area. We performed a LEEP cone with endocervical reinforce and the result was a Microinvasive adenocarcinoma of the cervix (invasion < 1 mm) with resections margins and canal reinforcement, negatives. She was instructed to keep strict follow-up. Due to HPV vaccination in 2005 and developments presented were obtained further information from the HPV-008 study: 7/8 of HPV testing performed in cervical samples from 2005 to 2009 detected a single infection with HPV-18, including the initial visit before the first dose. PCR and Immunohistochemical Study of material from the LEEP showed the presence of HPV-18 L1, p16 + and Ki-67 reagent. **Implications and Impact:** HPV-18 DNA was present in the cervix prior to vaccination. Persistent infection with HPV-18 can be considered an important factor in the development of lesions of the glandular epithelium. the glandular lesions are more difficult to be detected by cytology and colposcopy. It is evident the importance of vaccination before sexual debut and adequacy of screening in vaccinated.

#### Epidemiology/Public Health Epidemiology/Natural history of anogenital HPV in females

### Molecular Detection of Chlamydia Trachomatis Infections in Screened Women for Cervical Cancer

Presenter: Cecilia Roteli Martins, PhD

Investigators/Collaborators: Renata RLM de Barros<sup>1</sup>, Mariangela F Silveira<sup>2</sup>, Dulce Stauffert<sup>2</sup>, Marco Zonta<sup>3</sup>, Priscila H de Oliveira<sup>4</sup>, Ilana Di Fiore G Palermo<sup>4</sup>, Solana Terrazas Martins<sup>5</sup>, Cecilia M Roteli-Martins<sup>6</sup>, Adhemar Longatto Filho<sup>7</sup>

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Country: Brazil

**Objectives:** To verify the prevalence of CT infections in cervical samples obtained from women undergoing routine cytological screening for cervical cancer **Method:** Women aged 15 to 64 years were invited to routine cytological examination. Pap tests were collected and prepared with BD SurePath liquid-based. after cytological preparation residual samples were tested for CT using BD ProbeTec™ ET, an amplified DNA Assays, that use Strand Displacement Amplification (SDA) technology for the direct, qualitative detection of CT DNA **Results:** Women's mean age were 40.9 ± 11.2. the overall prevalence of CT was 15.7% (CI 95% 13.9%-17.6%). There was no statistical significant difference in CT prevalence within age groups (< 25 years: 16.4% (CI 95%: 9.6%-23.1%); 25 to 44 years: 16.9% (CI 95%: 14.3%-19.5%); 45 to 64 years: 14.0% (CI 95%: 11.2%-16.8%)). 15.0% (CI 95%: 10.5%-19.5%) of CT positive women had an abnormal cytology result (ASCUS or worse), with no statistical significant difference with the CT negative group (p = 0.689) **Implications and Impact:** Chlamydia trachomatis (CT) infection is one possible co-factor that lead to HPV persistence and cervical cancer. Basic epidemiological data about HPV and CT infection in Brazilian territory are still scarce. Our preliminary data indicate that the prevalence of CT infection in São Paulo, Brazil is high, but was not associated with abnormal Pap results. the present work could provide a framework for improving national strategies to control CT infection.

#### Epidemiology/Public Health, Epidemiology/Natural history of anogenital HPV in females

### Human Papillomavirus (HPV) Perinatal Transmission and Risk of HPV Persistence among Children: a Cohort Study

Presenter: Helen Trottier, PhD

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Country: Canada

**Objectives:** The perinatal epidemiology of HPV and its impact on newborns and children is not well understood although it is recognised that subclinical and clinical infections occur following perinatal transmission. **Objective:** To measure the probability of perinatal transmission of type-specific mucosal HPV (in conjunctival, laryngeal, buccal and genital mucosa of newborns) and its determinants; the risk of HPV persistence among children and its determinants; the presence of antibodies against HPV in mothers and children; and the association

between placental HPV infection and pregnancy outcome. **Method:** We are recruiting pregnant women 18-30 years of age during the first trimester of pregnancy in a prospective cohort study at three tertiary care centers in Montreal, Canada. Cervicovaginal swabs are taken at enrolment (1st trimester) and during the 3rd trimester for women positive at enrolment, and tested for 36 HPV genotypes by Linear Array. Children of positive mothers are followed until 2 years of age, at an interval of 3-6 months. At each visit, conjunctival, buccal, laryngeal and genital samples are collected for HPV testing. At each visit, mothers also provide information on sociodemographic, lifestyle, etc. Patient charts are reviewed to document pregnancy and outcome. Placenta specimens (biopsies and swabs) are also collected for HPV PCR testing. Blood samples from mothers and children are collected at different time points for HPV antibodies testing using HPV Virus-Like-Particle(VLP)-Based Enzyme Immunoassay for seroreactivity to HPV types 6/11/16/18 capsids. **Results:** Recruitment of pregnant women was completed at the end of June 2012 (N = 166). Follow-up is ongoing. PCR testing has been done for 160 women at enrolment (1st trimester). the prevalence of HPV was 44% (67% were positive for at least one HR-HPV) and 49% of them have multiple genotypes (range 2 to 11). 68 placentas were tested for HPV; 24% of the women with an HPV positive cervicovaginal sample during the first trimester had a positive placenta (8/33) whereas 3% of the women who were negative for HPV at enrolment had a positive placenta (1/35). 33 babies were born and tested for HPV at birth and all of them were HPV negative (conjunctival, buccal, laryngeal and genital samples). Final results (completed follow-up) will be available in 2015. **Implications and Impact:** We found a significant prevalence of HPV in pregnant women. Although HPV could be detected in the placenta, few newborns had HPV. This study will further our understanding of the perinatal transmission at different body sites in children born from HPV positive mother.

#### Epidemiology/Public Health, Epidemiology/Natural history of anogenital HPV in females

### The Long-Term Study of GARDASIL™ in Previously Vaccinated Women: Absence of HPV Replacement Disease

Presenter: Joakim Dillner, MD

Investigators/Collaborators: Susanne Krüger Kjær, Bo Terning Hansen, Laufey Tryggvadóttir, Christian Munk, Lara Sigurdardóttir, Maria Hortlund, Michael Ritter, Mari Nygård and Alfred Saah

Country: Sweden

**Background:** The GARDASIL™ long-term follow-up (LTFU) study is an ongoing extension of a pivotal randomized, placebo-controlled, doubleblind, 4-year study to investigate the safety, immunogenicity, and effectiveness of quadrivalent Human Papillomavirus vaccine (qHPV) on the incidence of HPV 16/18-related cervical intraepithelial neoplasia (CIN) 2 or worse in 16-to 23-year old women (Protocol 015). **Methods:** Follow-up of subjects is being accomplished in 2 ways: 1) registry-based follow-up for effectiveness data as well as safety data including but not limited to deaths, cancer, and hospitalizations; 2) active follow-up for blood collection for immunogenicity assessments. Effectiveness and safety data represent a mean follow-up of 8 years following the start of Protocol 015. Cohort 1 included approximately 2,700 subjects who received qHPV vaccine at the start of Protocol 015. Cohort 2 consists of approximately 2,100 subjects who received placebo at the start of Protocol 015 and qHPV vaccine prior to entry into the LTFU. Vaccine effectiveness against HPV 16/18-related CIN 2 or worse was estimated by calculating the expected incidence of CIN 2/3 or worse in an unvaccinated (placebo) cohort using historical registry data. the primary analysis approach was Generally HPV Naïve (GHN) for the HPV replacement analysis. **Results:** Previous data indicated no cases of CIN 2+ observed in the GHN population irrespective of HPV type. There were seven (7) cases of CIN 1 observed with follow-up time of 1,088.6 person-years regardless of HPV type in the GHN population. the incidence rate for this endpoint was 0.6 (95% CI: 0.3, 1.3) per 100 person-years at risk. the incidence rates for CIN 1 related to any of the 10 nonvaccine HPV types and not related to any of the 14 assay-identified HPV types were 0.4 (95% CI: 0.1, 0.9) and 0.2 (95% CI: 0.0, 0.7) per 100 person-years at risk, respectively. Data will be presented from 8 years of follow-up (not available at the time of abstract submission). Comparisons will be made to regionally obtained population-based rates of occurrence of certain HPV types prior to the introduction of the vaccine. **Implications and Impact:** HPV-type replacement did not occur at any appreciable level. HPV type replacement will continue to be assessed and further analyses will be performed at two-year intervals.

#### Epidemiology/Public Health, Epidemiology/Natural history of anogenital HPV in males

### The Influence of Male Circumcision on the Incidence and Clearance of Genital Human Papillomavirus Infection in Men: Results from the HIM Study

Presenter: Ginesa Albero, PhD student

Investigators/Collaborators: Ginesa Albero<sup>1,2</sup>, Luisa L Villa<sup>3</sup>, Eduardo Lazcano-Ponce<sup>4</sup>, William Fulp<sup>5</sup>, Mary R Papenfuss<sup>5</sup>, Xavier Castellsague<sup>1,2</sup>, Alan G Nyitray<sup>5</sup>, Beibei Lu<sup>5</sup>, Martha Abrahamson<sup>5</sup>, F. Xavier Bosch<sup>1</sup>, Anna R Giuliano<sup>5</sup>

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Country: Spain

**Objectives:** To determine whether male circumcision (MC) affected the incidence and clearance of type-specific genital HPV infections in a multinational cohort study of men. **Method:** The HIM Study cohort enrolled healthy men, aged 18-70 years, from 2005 to 2009 in a study of genital HPV infections in Brazil, Mexico, and the USA. the current analysis included 4,033 men who were followed every 6 months for a

median of 17.5 months (interquartile range, 6.9 – 31.0 months). Saline-wetted Dacron swabs were used to collect exfoliated cell specimens from the coronal sulcus, glans penis, penile shaft, and scrotum at each study visit. Swabs were combined into one sample and genotyped for 37 HPV types using the Roche Linear Array. Circumcision status was determined by clinician exam. Cox proportional hazards models were used to evaluate the association between MC status and the incidence and clearance of HPV infections. Here we present models adjusted for age, country and sexual behavior variables. **Results:** The overall incidence of new genital HPV infection did not differ by MC status (adjusted hazard ratio (aHR) for circumcised men relative to uncircumcised men: 1.05 [95% confidence interval (CI): 0.98-1.13]). However, the incidence of HPV type 55 was significantly higher among circumcised men. Infection clearance was significantly decreased among circumcised men as compared to uncircumcised men (aHR: 0.86 [95% CI: 0.79-0.93]). Circumcised men were significantly less likely to clear HPV types 16, 51, 52, 58, and 82. In contrast, circumcised men were significantly more likely to clear HPV type 11. **Implications and Impact:** The data from this study show that incidence of new genital HPV infection is not associated with MC status. Clearance of HPV was reduced among circumcised men for certain HPV types but not for others. The use in our study of a combined sample from the coronal sulcus, glans, foreskin (if present), shaft, and scrotum likely limited our ability to identify a true effect at the distal penis. Additional prospective data on the effects of MC by specific anatomical sites are necessary to better assess the role of MC in the natural history of HPV infections in men.

#### Epidemiology/Public Health Epidemiology/Natural history of anogenital HPV in males

### Alcohol Consumption and Inconsistent Condom Use Increase Risk for Acquisition of Oncogenic Genital HPV among Gay Men in South and North America: the HIM Study

Presenter: Alan Nyitray, PhD

Investigators/Collaborators: Authors: AG Nyitray<sup>1</sup>, RJ Carvalho da Silva<sup>2</sup>, ML Baggio<sup>3</sup>, J Salmerón<sup>4,5</sup>, M Quiterio<sup>4</sup>, M Abrahamsen<sup>1</sup>, M Papenfuss<sup>1</sup>, LL Villa<sup>3</sup>, E Lazcano-Ponce<sup>4</sup>, AR Giuliano<sup>1</sup>

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Country: United States

**Objectives:** There are no reports of behavioral factors associated with acquisition of genital HPV among men having sex with men (MSM). Given that penile-anal sex increases risk for HPV infection in the anal canal, knowledge about modifiable risk factors may be particularly important for MSM, most of whom are over age 26 years and not eligible for HPV vaccination and among whom annual incidence of anal cancer in the United States may be up to 35/100,000 persons. The purpose of the current study was to assess modifiable factors that increase risk for genital HPV acquisition among MSM and men having sex with women and men (MSWM) recruited in São Paulo, Brazil, Cuernavaca, Mexico, and Tampa, USA. **Method:** Genotyping using the linear array method was conducted for genital specimens from men, ages 18-70, who attended semiannual visits for a 4-year prospective study. Eligibility included no history of genital warts or HIV. A total of 147 MSM and 259 MSWM provided evaluable specimens at greater than or equal to 2 visits. Specimens from the glans, penile shaft, and scrotum were combined for analysis. Twelve-month cumulative incidence was assessed among men negative for type-specific infection at the pre-enrollment visit. Baseline factors that may affect acquisition of genital HPV were assessed using Cox proportional hazard regression. **Results:** Median age of the MSM and MSWM was 29 and 33 years, respectively. The median follow-up time for MSM and MSWM was 19 and 18 months, respectively. During follow up, 68% of MSM and 59% of MSWM acquired one or more of 13 oncogenic HPV types. The 12-month cumulative incidence for any oncogenic type was 31.8% and 25.4% among MSM and MSWM, respectively, while 12-month cumulative incidence for HPV-16 was 9.9% and 5.0%. After controlling for confounders among MSM, modifiable behaviors that increased risk for oncogenic detection were alcohol consumption (compared to 0-30 drinks/month: Hazard ratio (HR), 2.30 [95% CI 1.10-4.83] for > 60 drinks/month) and inconsistent recent condom use for anal sex (compared to always using condoms, HR, 3.05 [95% CI 1.46-6.36]). Among MSWM, former smokers were at decreased risk for detection of genital oncogenic HPV (compared to current smokers: HR, 0.16 [95% CI 0.05-0.51]). **Implications and Impact:** Acquisition of oncogenic HPV genotypes at the genitals was very common among MSM and MSWM. Decreased alcohol consumption and consistent condom use among MSM, and quitting smoking among MSWM are modifiable risk factors that may slow acquisition of genital HPV. Such knowledge may be important for gay and bisexual men not eligible for HPV vaccination.

#### Epidemiology/Public Health, Measuring the impact of HPV vaccination

### Estimations of Herd Immunity Benefit Under Different Assumptions Regarding Natural Immunity: a Case-Study Based on the Australian National HPV Vaccination Program

Presenter: Igor Korostil, Mr

Investigators/Collaborators: Gareth Peters, School of Mathematics and Statistics, University of New South Wales, Sydney, Australia; Matthew Law, the Kirby Institute, University of New South Wales, Sydney, Australia; David Regan, the Kirby Institute, University of New South Wales, Sydney, Australia;

Country: Australia

**Objectives:** To investigate the differences in estimations of herd immunity benefit (when a vaccination benefits those not vaccinated) in Australian setting, produced by mathematical models differing in assumptions regarding natural immunity to reinfection with the same HPV type. This is relevant in view of recent epidemiological findings suggesting that the assumption of life-long natural immunity, com-



monly accepted in health-economic evaluations of HPV vaccination programs using dynamic mathematical models, may be not plausible. Estimation of herd immunity benefit is an important component of such evaluations: the less significant the benefit is, the less effective is a vaccination program and the more likely is a need for public health decisions aimed at its improvement. **Method:** We develop three mathematical models to describe HPV-6/11/16/18 transmission in an Australian heterosexual population: an SIR type model (commonly used, assumes life-long natural immunity), an SIS model (less popular, no natural immunity) and a model representing a compromise between SIR and SIS (limited natural immunity). This model, which may provide a more accurate characterisation of natural immunity than SIR or SIS, is selected based on the recent literature and calibration of a variable structure general model to observational data. Calibration is performed using a statistically robust Bayesian approach based on an adaptive Markov chain Monte Carlo algorithm. **Results:** In our comparison herd immunity benefits, measured as relative reductions in HPV prevalence in unvaccinated female and male populations, estimated by the non-SIR models, are much more substantial than for the SIR model. In particular, for the unvaccinated female population, they are higher than for the SIR model by at least 27% (HPV-16), 45% (HPV-18) and 75% (HPV-6/11), depending on the assumed vaccine efficacy. Similar differences are observed for the unvaccinated male population. **Implications and Impact:** Studies evaluating vaccination programs which rely only on SIR models may significantly underestimate herd immunity benefits of these programs. As a possible solution, we suggest that several model structures should be considered in such studies, each assigned a “weight” derived from expert opinions or any other current information which can help improve our understanding of natural immunity.

### Epidemiology/Public Health, Measuring the impact of HPV vaccination

## Comparing the Cost-Effectiveness of the Bivalent, Quadrivalent and Nonavalent HPV Vaccines: a Model-Based Analysis

Presenter: Marc Brisson, PhD

Investigators/Collaborators: Marc Brisson, Nicolas Van de Velde, Jean-François Laprise, Mélanie Drolet, Marie-Claude Boily

Country: Canada

**Objectives:** Bivalent (HPV2) and quadrivalent (HPV4) HPV vaccines are now licensed in several countries, and a clinical trial is examining the efficacy of a nonavalent vaccine (HPV9). Our aim was to compare the cost-effectiveness of the HPV2, HPV4 and HPV9 to provide evidence for policy decisions. **Method:** We developed HPV-ADVISE, a multi-type individual-based transmission-dynamic model of HPV infection and disease (genital warts (GW), and cervical, anogenital and oropharyngeal cancers). We calibrated the model to epidemiologic data from Canada, and estimated Quality-Adjusted Life-Years (QALYs) lost and costs (2010\$CAN) from the literature. We assumed vaccine-type efficacy is 95% for all vaccines, and cross-protective efficacy against HPV-31,-33,-45,-52,-58 is 77, 43, 79, 19,0% and 46, 29, 8, 18,6% for HPV2 and HPV4, respectively. In addition, we assumed duration of vaccine-type efficacy and cross-protection is 20 and 10 years, respectively. The analysis was performed from the healthcare provider perspective, and costs and benefits were discounted at 3%. Sensitivity analysis was performed varying vaccine efficacy, duration of protection, and burden of illness (QALY-lost and costs). Uncertainty in model predictions is presented using the median [10th-90th percentiles] of simulations. **Results:** Under base-case assumptions (vaccinating 10-year-old girls, 80% coverage, 95\$/dose), using HPV2, HPV4 and HPV9 was estimated to cost \$20,000[\$16,000-\$25,000], \$14,000[\$11,000-\$19,000] and \$12,000[\$9,000-\$17,000] per QALY-gained, respectively. At equal price, HPV9 remained more cost-effective than HPV2 and HPV4, even when assuming shorter duration of protection (HPV9 = 20 years vs. HPV2/HPV4 = lifelong) and lower vaccine-type efficacy (HPV9 = 85% vs. HPV2/HPV4 = 95%). HPV4 remained more cost-effective than HPV2 under all scenarios investigated, except when simultaneously assuming longer HPV2 duration of protection (HPV2 = lifelong vs. HPV4 = 20 years), high cross-protection, and low burden of GW. Under base-case assumptions, the maximum additional cost/dose for HPV9 to be cost-effective compared to HPV2 and HPV4 was \$67[57-74] and \$12[3-39], respectively (using a \$50,000/QALY-gained threshold). The maximum additional cost/dose of HPV4 for it to be cost-effective compared to HPV2 was \$54[9-64]. Comparative cost-effectiveness results were most sensitive to differential durations of protection and GW burden of illness. **Implications and Impact:** Vaccinating pre-adolescent girls against HPV is predicted to be highly cost-effective. If equally priced, the most cost-effective vaccine is HPV9, followed by HPV4 and HPV2. However, ultimately, the most cost-effective HPV vaccine will be determined by the relative prices of the vaccines and durations of protection.

### Epidemiology/Public Health Measuring the impact of HPV vaccination

## HPV6/11/16/18 Vaccine Efficacy in Women 24 to 45: Follow-up Through 6.3 Years Post-Vaccination

Presenter: Joaquin Luna, MD

Investigators/Collaborators: on behalf of the Protocol 019 investigators

Country: Colombia

**Objectives:** The quadrivalent HPV (types 6, 11, 16 18) (qHPV) vaccine is highly effective in preventing HPV6/11/16/18-related persistent infection, CIN, EGL, and abnormal Pap smears in women aged 24 to 45 naïve to vaccine HPV types. Vaccine efficacy in the prevention of HPV6/11/16/18-related CIN or EGL was 95.7% (95% CI: (73.4, 99.9) through 3.8 years of follow-up. We present the results of an interim analysis of a long-term follow-up study of qHPV in women aged 24-45 designed to determine the long-term immunogenicity, effectiveness, and safety of the qHPV vaccine. This report summarizes data collected as of year 6 post-vaccination (relative to day 1 of the base study). Future analyses are planned at years 8 and 10 (end-of-study analysis). **Method:** This extension study was conducted in Colombia. Subjects who were vaccinated in the base study from Colombia are referred to as the “early vaccination group” (EVG) in this report. Subjects vaccinated after the completion of the base study (catch-up cohort) have not had sufficient follow-up as of this report. **Results:** Enrollment

into the base study was 1,610 in total (804 randomized to qHPV, 806 randomized to with placebo). a total of 1,360 Colombian subjects participated in this extension (84% of the subjects enrolled in base study in that country). No new cases of HPV 6/11/16/18-related genital warts/cervical dysplasia have been reported in the EVG (N = 684). Month 72 antibody titers against HPV 6/11/16/18 are comparable to those observed at Month 48 (end of base study), indicating no further diminution of titers between 4 years and 6 years post-vaccination. No serious adverse experiences have been reported in the EVG between years 4 and 6. **Implications and Impact:** In summary, data through 6.3 years after the start of the 019 base study shows that administration of the qHPV vaccine among women aged 24-45 is generally well tolerated. Anti-HPV 6, 11, 16, and 18 responses have persisted over the long-term, and no additional cases of disease related to vaccine HPV types 6/11/16/18 were observed.

#### Epidemiology/Public Health, Measuring the impact of HPV vaccination

### Long-Term Effectiveness of GARDASIL™ in the Nordic Countries

Presenter: Susanne Krüger Kjær, MD

Investigators/Collaborators: Mari Nygård, Joakim Dillner, Brooke Marshall, Bo Terning Hansen, Lara G. Sigurdardottir, Maria Hortlund, Laufey Tryggvadóttir, Alfred Saah, Christian Munk

Country: Denmark

**Objectives:** The GARDASIL™ long-term follow-up (LTFU) study is an ongoing extension of a pivotal randomized, placebo-controlled, doubleblind, 4-year study to investigate the safety, immunogenicity, and effectiveness of quadrivalent Human Papillomavirus vaccine (qHPV) on the incidence of HPV 16/18-related cervical intraepithelial neoplasia (CIN) 2 or worse in 16-to 23-year old women (Protocol 015). the LTFU study is taking place in 4 Nordic countries (Denmark, Iceland, Norway, and Sweden). **Methods:** Every citizen in the Nordic countries is assigned a unique personal identification number (PIN) at birth, which is registered in the Civil Registration System in each country. Due to the existence of the PINs and the nationwide registers, it is possible to do follow up studies with virtually no loss to follow-up in the Nordic countries. All women in the trial are followed through different national registries for effectiveness data as well as safety data such as deaths, cancer, and hospitalizations. Effectiveness and safety analyses started approximately 2 years following completion of Protocol 015 and will occur approximately every 2 years thereafter for 10 years. Cohort 1 included approximately 2,700 subjects who received qHPV vaccine at the start of Protocol 015. Cohort 2 consists of approximately 2,100 subjects who received placebo at the start of Protocol 015 and qHPV vaccine prior to entry into the LTFU. Vaccine effectiveness against HPV 16/18-related CIN 2 or worse was estimated by calculating the expected incidence of CIN 2/3 or worse in an unvaccinated (placebo) cohort using historical registry data. the primary analysis approach was perprotocol. **Results:** In the initial analysis of effectiveness after the first 7 years, there were 1,080 subjects that contributed to the follow-up period out of a total of 2,195 eligible subjects in the per-protocol population in Cohort 1. in these subjects there were no cases of HPV 16/18-related CIN 2 or worse observed. There were also no cases of HPV 6/11/16/18-related CIN, vulvar cancer, and vaginal cancer observed. However, the follow-up time in person-years is insufficient to make a definitive statement about the effectiveness of the qHPV vaccine for the current time period. **Implications and Impact:** The qHPV vaccine shows a trend of continued protection in women, although there is as yet insufficient data to confirm that protection is maintained. the qHPV vaccine continues to be generally safe and well tolerated up to 7 years following vaccination.

#### Epidemiology/Public Health Measuring the impact of HPV vaccination

### Decrease in Anogenital Warts Incidence after the Introduction of HPV Vaccination in Germany: Model Predictions and Real Data

Presenter: Andreas Kaufmann, PhD

Investigators/Collaborators: Rafael Mikolajczyk<sup>1,2</sup>, Johannes Horn<sup>1</sup>, Oliver Damm<sup>3</sup>, Renate Schulze-Rath<sup>4</sup>, Edeltraut Garbe<sup>5</sup>, Andreas M Kaufmann<sup>6</sup>

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Country: Germany

**Objectives:** Anogenital warts (AGW) are considered the best early indicator of HPV-vaccine effects on the population level, since in contrast to cervical intraepithelial neoplasia (CIN) anogenital warts become clinically apparent within months after the initial infection. in two recent independent projects, we addressed changes in the incidence of AGW. First, we developed a mathematical model to study long term effects of HPV vaccination. Second, we studied changes in the incidence of AGW at the population level using health insurance claims data. in this analysis, we aimed to derive model predictions regarding incidence of AGW and compare them with the empirical data. **Method:** A dynamic transmission model for HPV infection and disease progression was developed on the basis of previous models and calibrated to fit the HPV prevalence and incidence of HPV related lesions in Germany. with respect to AGW, the model utilised a multiplicative approach based on incident infections with HPV types 6 and 11 and was fitted to incidence of AGW derived from health insurance data for the years 2005 and 2006, i.e. before introduction of HPV vaccination in Germany. Assuming vaccination coverage of 50% among 17 years old girls with a market share of 90% for Gardasil and 100% effectiveness against anogenital warts, we used the model to predict the development

of AGW incidence in Germany after the introduction of HPV vaccination in 2007. In an independent analysis, changes in the incidence of AGW following the introduction of HPV vaccination up to the end of 2008 were studied based on the ICD-10 diagnoses A63.0 recorded in claims data from a large health insurance company including about six million insurants (8% of the population in Germany). **Results:** Empirical data demonstrated a decrease in the incidence of AGW among those 15 to 17 years old starting after the introduction of HPV vaccination and matching the vaccination coverage. The decline observed in real data was well reproduced in the modeling approach. Assuming that vaccination will continue at the same level, our model predicts an almost complete eradication of AGW in Germany 35 years after the introduction of the HPV vaccine. **Implications and Impact:** Changes in the incidence of AGW accompanying introduction of HPV vaccination in Germany are an early indicator of vaccine effects at the population level. Agreement between observed changes and model prediction verify the modelling approach. Eradication of AGW in Germany is possible, even at a relatively low vaccination coverage level of 50%.

### Epidemiology/Public Health Measuring the impact of HPV vaccination

#### Equity in HPV Vaccination Uptake?

Presenter: Madelief Mollers, MSc

Investigators/Collaborators: Madelief Mollers, Karin Lubbers, Kor Spoelstra, Willibrord Weijmar, Schultz Toos, Daemen Tjalke, Westra Nynke, Koelma Marianne van der Sande, Hans Nijman Hester de Melker, Adriana Tami

Country: Netherlands

**Objectives:** In the Netherlands, the HPV vaccination (Cervarix) is part of a state funded national programme and should therefore be equally accessible for all girls invited for vaccination. The objective of this study was to investigate whether vaccinated girls are different from unvaccinated girls with regard to demographics, such as education and ethnicity (both associated with nonattendance in the Cervical Cancer Screening programme), sexual behaviour and knowledge of HPV and cervical cancer. **Method:** Online questionnaires were sent to approximately 20,000 randomly selected 16-17 year old girls, which were targeted in the catch-up vaccination campaign in 2010. Out of these girls, 2,982 participated (65% vaccinated, 35% unvaccinated). Proportional differences between vaccinated and unvaccinated girls were tested by  $\chi^2$ . A knowledge scale composite score was calculated based on answers to 7 general knowledge questions (0-7) and 11 questions on HPV transmission knowledge (0-11). Mean scores were compared for vaccinated and unvaccinated girls by a t-test. **Results:** Vaccinated and unvaccinated girls were similar with regard to ethnicity, education level and knowledge of HPV transmission. However, vaccinated girls had slightly more general knowledge of HPV (2.0 vs. 1.9,  $p < 0.001$ ), were from more urbanized areas (53% vs. 47%,  $p < 0.01$ ) and were less likely to have a religious background (46% vs. 54%,  $p < 0.0001$ ). Vaccinated girls were less aware of the Cervical Cancer Screening programme (48% vs. 57%,  $p < 0.0001$ ), although they were more inclined to participate in the future (71% vs. 66%,  $p < 0.03$ ). A higher percentage of vaccinated girls were sexually active (56% vs. 52%,  $p < 0.04$ ) and amongst them, a higher number of lifetime partners was identified (2.2 vs. 1.9,  $p < 0.01$ ). With regard to age of sexual debut, condom use and history of STIs, there were no differences amongst vaccinated and unvaccinated sexually active girls. Irrespective of vaccination status, 81% of the girls knew about the causal relationship between HPV and cervical cancer, but only 20% knew about the relationship between HPV and genital warts. **Implications and Impact:** Routine HPV vaccination in the Netherlands reduces the inequity of prevention of cervical cancer. For example, vaccination uptake is not associated with education and ethnicity. Vaccinated girls were slightly more sexually active indicating that the impact of vaccination is not overestimated in for example modelling studies.

### Epidemiology/Public Health, Measuring the impact of HPV vaccination

#### HPV-Genotype Distribution in Urine Samples from 17-Year Old Girls in Norway in a Nonvaccinated Age-Cohort

Presenter: Christine Jonassen, PhD

Investigators/Collaborators: Christine M. Jonassen<sup>1</sup>, Mona Hansen<sup>1</sup>, Berit Feiring<sup>2</sup>, Ellen Myrvang<sup>1</sup>, Thu Nguyen<sup>1</sup>, Roger Meisal<sup>1</sup>, Elisabete Weiderpass<sup>3</sup>, Lill Trogstad<sup>2</sup>

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Country: Norway

**Objectives:** The HPV vaccine was included in the Norwegian childhood immunisation programme from September 2009. The quadrivalent vaccine is offered to girls aged 12 years. No catch up vaccination for older girls is offered. As part of a national surveillance programme of the HPV-vaccination, HPV testing in urine was proposed as a surrogate sample for cervical infection in prescreening age cohorts to monitor the impact of the HPV immunisation programme on the occurrence and HPV type distribution in young women. Two age-cohorts were selected for surveillance; 17 and 22 year old girls. Cross-sectional HPV prevalence studies will be performed first in non-vaccinated cohorts, later in vaccinated cohorts as they reach 17 and 22 years of age. The objective of this study was to monitor HPV genotype distribution in urine samples from 17-year old girls in a non-vaccinated age cohort in Norway. **Method:** The whole cohort of girls born in 1994 ( $n = 25\,400$ ) was invited by mail to participate in the surveillance programme. Sampling materials were sent to the girls who had accepted to participate by returning the informed consent letter. Urine samples were analysed for HPV using a modified GP5+/6+ PCR protocol followed by Luminex-based genotype detection, a method genotyping 37 different HPV genotypes. Cell-content was tested for all samples through a beta-globin PCR. **Results:** A total of 5 433 of the 25 400 girls invited (21%) participated in the study by providing an urine sample. 3 179.

samples have been tested and validated to date. the results show an overall prevalence for HPV of 14%%, with the main HPV types detected being HPV 16 (18.3% of the HPV positive samples), followed by HPV 90 (14% of the HPV positive samples), HPV 42 (13.4% of the HPV positive samples), HPV 6 (13.1% of the HPV positive samples), HPV 18 (10.7% of the HPV positive samples) and HPV51 (10.2% of the HPV positive samples). HPV 11 was only detected in 1.5% of the positive samples, i.e in 0.2% of the screened population. Multiple infections were detected in more than 46% of the positive samples. **Implications and Impact:** In this population based study, HPV infection was highly prevalent among 17-year old girls. HPV 16 and 18, in addition to HPV 6, are among the most prevalent types, and the vaccine is therefore expected to significantly reduce the overall HPV prevalence in this population.

#### Epidemiology/Public Health Measuring the impact of HPV vaccination

### Burden of Disease Due to Non-Cervical HPV-Related Cancers in Spain

Presenter: Javier Cortés, PhD MD, FIAC

Investigators/Collaborators: Xavier Castellsagué<sup>1</sup>, Javier Cerdán<sup>2</sup>, Javier Cortés<sup>3</sup>, Pepi Hurtado<sup>4</sup>, Carmen Morillo<sup>5</sup>, Miquel Quer<sup>6</sup>, Jesús Salinas<sup>7</sup>

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Country: Spain

**Objectives:** To estimate the burden of non-cervical HPV-related cancers in Spain in 2009 and the cost of treatment of these cancers from both the National Health System and social perspectives during five years' follow up period. **Method:** Data needs were identified by conducting a bibliographic search on management of pathologies, epidemiologic data and direct and indirect costs of oral cavity and pharyngeal, anal, vulvar, vaginal and penis cancer. Cases attributable to HPV-16 and HPV-18 were calculated by means of the fractions attributable to each type, using estimates with greater evidence in the medical literature and data obtained from interviews with scientists in the field. Cost of non-cervical HPV-related cancers included direct and indirect costs. Direct costs were added to the monetary value of diagnosis, hospitalization and surgery, ambulatory treatment, including chemo and radiotherapy, and follow up costs, together with recurrence treatment. Indirect costs included potential years of work life lost (PYWLL). **Results:** Between 30-75% of new annual cases can be directly attributable to HPV-16/18. Direct costs were higher in advanced stages of cancer, with the exception of anal cancer. Indirect costs were 55-75% of the total cost depending on the type of cancer. Total costs of non-cervical HPV-related cancers were estimated at 355,748,285€. the fraction attributable to HPV was 137,751,910€ and the fraction attributable to HPV-16/18 was 56,758,762€. There was the difficulty in the estimation of the underlying indirect costs as well as the intangible costs of these cancers concerning quality of life and psychological impact on patients and their families. **Implications and Impact:** These tumors could be of interest in Public Health and primary prevention strategies. Currently established vaccination programs for the prevention of cervical cancer may have an eventual impact in the reduction of the incidence and burden of non-cervical HPV-related cancers.

#### Epidemiology/Public Health, Measuring the impact of HPV vaccination

### Impact of a 9-Valent Vaccine in HPV Related Cervical Disease

Presenter: Laia Alemany, MD MPH

Investigators/Collaborators: Serrano B<sup>1</sup>, Alemany L<sup>1,2</sup>, Tous S<sup>1</sup>, Bruni L<sup>1</sup>, Clifford GM<sup>3</sup>, Weiss T<sup>4</sup>, Bosch FX<sup>1</sup>, de Sanjosé S<sup>1,2</sup>

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Country: Spain

**Objectives:** We estimated the relative contribution (RC) of the nine HPV types (HPV 6/11/16/18/31/33/45/52 and 58) included in a developmental HPV vaccine, in invasive cervical cancer (ICC) and precancerous cervical lesions. **Method:** Estimations on ICC were based on an international study of 8,977 HPV/DNA positive cases and estimations on precancerous cervical lesions were extracted from a published meta-analysis including 115,789 HPV/DNA positive women. Globocan 2008 and 2010 World Population Prospects were used to estimate current and future projections of new ICC cases. **Results:** RC of the 9 HPV types in ICC was 89.4% with 18.5% of cases positive for HPV 31/33/45/52 and 58. Regional variations were observed. RC varied by histology, ranging between 89.1% in squamous cell carcinomas and 95.5% in adenocarcinomas. HPV 16/18 and 45 were detected in 94.2% of adenocarcinomas. RC of the 9 types altogether decreased with age (trend test  $p < 0.0001$ ), driven by the decrease in older ages of HPV 16/18 and 45. in contrast, HPV 31/33/52 and 58 were more frequent in older ages. Due to population growth alone, projected estimates of ICC cases attributable to the 9 HPV types are expected to rise from 493,770 new cases in 2012 to 560,887 in 2025. the addition of HPV 31/33/45/52 and 58 to HPV types included in current vaccines could prevent almost 90% of ICC cases worldwide. If the nine-valent vaccine achieves similar efficacy of existing HPV vaccines, world incidence rates could be reduced to 1.7 new cases per 100,000 women per year, driving cervical cancer from the 3rd to 19th most common female

cancer. Differences in the RC of each high risk HPV type in precancerous cervical lesions were large for most cytological and histological categories, with RC increasing in higher grades cervical lesions. **Implications and Impact:** Although HPV 16 is the most common type in all cervical cancer and pre-cancerous lesions, there is an under representation of HPV 18 and 45 in women with precancerous cervical lesions compared to the high contribution in ICC. At the meeting more detailed data regarding the impact of nine-valent vaccine (RC of 9 types) on pre-neoplastic cervical lesions will also be presented.

#### Epidemiology/Public Health Measuring the impact of HPV vaccination

### Condyloma Protection of Quadrivalent HPV-Vaccine: Population Cohort Analysis of Dose Effectiveness

Presenter: Par Sparen, PhD Professor

Investigators/Collaborators: Amy Leval, RN<sup>1</sup>; Eva Herweijer, MSc<sup>1</sup>; Alexander Ploner, PhD<sup>1</sup>; Sandra Eloranta, MSc<sup>1</sup>; Julia Fridman Simard, ScD<sup>2</sup>; Professor Joakim Dillner, MD<sup>1</sup>; Eva Netterlid, PhD<sup>3,4,5</sup>; Professor Pär Sparén, PhD<sup>1</sup>; Lisen Arnheim-Dahlström, PhD<sup>1</sup>

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5 Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden

Country: Sweden

**Objectives:** The aim of this study is to examine quadrivalent HPV-vaccine effectiveness against condyloma per dose level. **Method:** To assess condyloma incidence in relation to vaccine dose level for females first vaccinated before age 20, an open cohort of all females living in Sweden between 2006-2010 (n = 1 045 083) were linked to numerous Swedish nationwide registers. Time-to-event analyses generating incidence rate ratios (IRR) of condyloma were estimated using Poisson regression with dose as a time-dependent exposure, adjusting for attained age, parental education and stratifying on age-at-first-vaccination for two age groups (ages 10-16 and 17-19). **Results:** For girls vaccinated between ages 10-16, maximum effectiveness was seen with three doses 79% (95% CI 75-83). There was a significant difference between three versus two doses in this younger age group (p-value 0.007), with three doses offering 37% more effectiveness (95% CI 12-54). For individuals vaccinated between ages 17-19, maximum effectiveness (70%, 95% CI 63-76) was also seen with three-doses, offering 26% (95% CI 0-46) more effectiveness than two-doses (p-value 0.061), but with borderline significance. No differences in effectiveness were found for girls who received two-doses between ages 10-16 with that of individuals who received three-doses between ages 17-19 (p-value 0.633). **Implications and Impact:** Maximum protection against condyloma was found with three doses for younger girls and two doses are less effective than three.

#### Epidemiology/Public Health Measuring the impact of HPV vaccination

### Quadrivalent HPV-Vaccine Effectiveness on Genital Warts: Population Cohort Study on over 2.2 Million Girls and Women

Presenter: Par Sparen, PhD Professor

Investigators/Collaborators: Amy Leval, RN<sup>1</sup>; Eva Herweijer, MSc<sup>1</sup>; Alexander Ploner, PhD<sup>1</sup>; Sandra Eloranta, MSc<sup>1</sup>; Julia Fridman Simard, ScD<sup>2</sup>; Professor Joakim Dillner, MD<sup>1</sup>; Cecilia Young, PhD<sup>3</sup>; Eva Netterlid, PhD<sup>4,5,6</sup>; Professor Pär Sparén, PhD<sup>1</sup>; Lisen Arnheim-Dahlström, PhD<sup>1</sup>

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Country: Sweden

**Objectives:** When assessing the effectiveness of human papillomavirus (HPV) vaccination strategies, genital warts (GW) incidence is the earliest disease outcome possible to measure. This study was conducted to assess GW incidence after vaccination with the qHPV vaccine in Sweden using individual-level data from the entire Swedish population. **Method:** An open cohort of the entire population of 10-44 year old women living in Sweden between 2006 and 2010 (n > 2.2 million) was linked to the national HPV Vaccination Register, the Patient Register, the Prescribed Drug Register, the Multi-generation Register and the Education Register to identify incident GW and parental education level in relation to HPV vaccination. Self-selection for vaccination in relation to GW risk was assessed by studying GW rates over time among the unvaccinated. Incidence rate ratios of GW were estimated using time-to-event analyses adjusting for attained age, parental education and stratifying on age-at-first vaccination. **Results:** 124000 women were vaccinated between 2006 and 2010, 90% of whom were in the subsidized target group (coverage 25-33%). High education-level of parents compared to low was a strong determinant of vaccination (OR: 15.3; 95% CI 14.5; 16.1). Above age 20, GW rates declined among unvaccinated, suggesting that HPV vaccines were preferentially used by women at high GW risk. Vaccination effectiveness for women below 20 was 76% and highest below age 14 (effectiveness = 93%; 95% CI 71-99). **Implications and Impact:** Above age 20, self-selection to women at high GW risk may have impaired effectiveness. Below age 20, there was considerable effectiveness. However, the on-demand vaccination strategy used during this time had substantial social inequity.

**Epidemiology/Public Health Measuring the impact of HPV vaccination****A Registry-Based Long-Term Follow-up Study of the Safety of the Quadrivalent HPV (qHPV) Vaccine in Scandinavia**

Presenter: Alfred Saah, MD

Investigators/Collaborators: Laufey Tryggvadóttir, Christian Munk, Mari Nygård, Bo Terning Hansen, Maria Hortlund, Lara G. Sigurdardóttir, Jack Smith, Joakim Dillner and Susanne Krüger Kjaer

Country: United States

**Background:** The long-term follow-up (LTFU) study is an ongoing extension of a pivotal randomized, placebo-controlled, double-blind, 4-year study, FUTURE II, to investigate the safety, immunogenicity, and effectiveness of qHPV vaccine on the incidence of HPV 16/18-related CIN 2+ in young women. Long term assessment of safety is presented. **Methods:** Upon completion of FUTURE II, the National Research Study Centers of Denmark, Iceland, Norway and Sweden systematically searched their respective national registries for information on deaths, cancers, hospitalizations, and other outcomes for safety assessment. the full Intention to Treat (ITT) population (all subjects who received at least one dose of qHPV vaccine and consented to safety follow-up) was used for the analysis in this study. the second search of the hospital discharge registries covered the time period from the subject's last base protocol study visit through 01-Mar-2011 (approximately 48 months follow up after the end of the base study). **Results:** There were no signals or changes in the new medical conditions that would indicate any change in the safety profile of the qHPV vaccine. the number of subjects with cancer, conditions of potential autoimmune etiology, or who died was varied and small. Overall, there was no specific pattern of new medical conditions. Data will be presented from an extended follow-up time not available at the time of abstract submission. **Implications and Impact:** The qHPV vaccine continues to be generally safe and well tolerated in young women 8 years following vaccination.

**Epidemiology/Public Health Measuring the impact of HPV vaccination****Catching up or Missing out? HPV Vaccine Acceptability among 18-26 Year Old Men who Have Sex with Men in a U.S. National Sample**

Presenter: Nathan Stupiansky, PhD

Investigators/Collaborators: Nathan W. Stupiansky, PhD; Joshua G. Rosenberger, PhD; Gregory D. Zimet, PhD; David S. Novak, MSW Susan L. Rosenthal, PhD

Country: United States

**Objectives:** Men who have sex with men (MSM) have higher HPV infection rates than those in the general population and also face disproportionately high rates of anal cancer, yet HPV vaccine uptake among young MSM is minimal. the purpose of this study was to examine the factors associated with HPV vaccine acceptability among a U.S. national sample of young MSM. **Method:** All U.S. users between the ages of 18-26 years ( $M = 22.5$ ,  $SD = 2.4$ ) of an online social and sexual networking site for MSM were invited to complete an anonymous online survey of HPV vaccine history, attitudes, and acceptability. a total of 1,457 participants provided complete data including sociodemographics, HPV vaccine history, HPV vaccine acceptability, HPV-related health beliefs, and barriers to vaccination. among those not previously vaccinated, HPV vaccine acceptability was assessed from 0-100 at a cost condition of US \$30 per dose to reflect the likely amount that would be paid out of pocket. **Results:** In this sample 6.7% (98/1457) reported receipt of one or more doses of HPV vaccine, and 2.7% (39/1457) reported series completion. For those who were unvaccinated ( $n = 1,359$ ) there were several factors that related to HPV vaccine acceptability ( $M = 62.2$ ,  $SD = 32$ ). in multivariate models, safety concerns ( $B = -.137$ ), cost ( $B = -.186$ ), the feeling that one is not at risk for HPV ( $B = -.098$ ), and the belief that the vaccine is for men who are promiscuous ( $B = -.084$ ) were associated with decreased vaccine acceptability. Conversely, worry about getting infected with HPV ( $B = .230$ ), agreeing to receive a shot in the future that a doctor would say is necessary ( $B = .10$ ), and the belief that they may have already been exposed to the virus ( $B = 0.88$ ) were associated with increased vaccine acceptability. Young men who had been tested in the past year for HIV ( $p = .01$ ) or STDs ( $p = .01$ ) and those who reported having a primary health care provider ( $p = .03$ ) also rated the vaccine as more acceptable, as did those who had achieved higher levels of education ( $p = .01$ ) and those who self-reported better health ( $p = .001$ ). the majority of men who had not received vaccination had not been offered the vaccine by a doctor (96.3%). **Implications and Impact:** Overall, young MSM represent an at-risk group with generally high HPV vaccine acceptability. Men's reports of better overall health and sexual health behaviors (i.e. STD/HIV testing) were indicative of more favorable attitudes towards the HPV vaccine. Our findings suggest that structural interventions (e.g. offering vaccination in HIV testing venues), as well as interventions that address health beliefs may help to increase HPV vaccination rates among MSM.

**Epidemiology/Public Health Measuring the impact of HPV vaccination****HPV Types Associated with High Grade Cervical Dysplasia: Impact of Vaccination in California, 2008-2011**

Presenter: Heidi Bauer, MD MPH

Investigators/Collaborators: Heidi M. Bauer<sup>1</sup>, Ellen Luecke<sup>1,2</sup>, Sharon McDonnell<sup>1,2</sup>, Erin Whitney<sup>1,2</sup>, Lauri Markowitz<sup>3</sup>, Elizabeth R. Unger<sup>4</sup>, Susan Hariri<sup>3</sup>

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Country: United States

**Objectives:** HPV vaccination is expected to reduce disease related to vaccine types and change the distribution of HPV types in high grade cervical disease. the CDC-funded HPV-Impact project, comprising five sentinel sites in the U.S., initiated ongoing surveillance of histologically defined high-grade cervical dysplasia, specifically cervical intraepithelial neoplasia (CIN) grade 2 or 3 and adenocarcinoma in situ (AIS). Our objective was to examine trends in disease rates and distribution of HPV vaccine types 16/18. **Method:** The California catchment area includes over 317,000 adult women residents. Case reports are generated by laboratories and health care organizations. Representative cervical histology specimens from women age 18-39 years diagnosed in 2008-2011 underwent HPV typing using with L1 Consensus PCR. We compared HPV type distribution over time, by age, by high-grade diagnosis, and by vaccination status (defined as at least one dose). **Results:** From 2008-2011, 1,328 cases of CIN2/3/AIS were identified among women 18-39 years of age. the annual rate of disease declined 17% from 279 to 231 per 100,000 in that time period (P for trend = 0.04). Diagnoses included CIN2 (42%), CIN2/3 (22%), CIN3 (34%), and AIS (2%); these proportions were unchanged over time. of the 576 specimens tested, 553 (96%) were considered adequate and typed for HPV. of these, 96% were HPV-positive; 51% had types 16/18 and 20% had multiple types. the proportion of specimens with 16/18 did not vary by the year of diagnosis or the age of the patient. Higher grade lesions were more likely to have HPV 16/18: 46% of CIN2 and CIN2/3, 59% of CIN3, and 88% of AIS (P < .05). Only 27 (4.9%) specimens were from women who had received any HPV vaccine; notably 44% of these women received the vaccine after their diagnosis. the proportion of specimens with HPV 16/18 did not vary by vaccination status. **Implications and Impact:** The decline in incident lesions soon after vaccine introduction emphasizes the complexity of detecting the early endpoints of HPV vaccine impact and highlights the need for ongoing surveillance of HPV type distribution in cervical lesions. Ongoing measurement of vaccine coverage as well as cervical cancer clinical prevention practices will be critical for interpreting trends.

#### Epidemiology/Public Health, Measuring the impact of HPV vaccination

### Long-Term Extension Study of GARDASIL in Adolescents; Results through Month 96

Presenter: Alfred Saah, MD

Investigators/Collaborators: on behalf of the Protocol 018 investigators

Country: United States

**Objectives:** Quadrivalent HPV vaccine has previously been shown to be safe and immunogenic in adolescents though 72 months after vaccination. We describe the first interim effectiveness data for a long-term immunogenicity, safety, and effectiveness study of GARDASIL™ among adolescents. **Method:** In the base study, 1781 sexually naïve boys and girls were assigned (2:1) to GARDASIL or saline placebo at day 1, months 2 and 6. At the end of the base study (month 30), the placebo group received GARDASIL™ following the same regimen. Those vaccinated with GARDASIL in the base study are the early vaccination group (EVG). Those vaccinated with GARDASIL during months 30-36 are the catch-up vaccination group (CVG). As this extension study does not have a placebo arm, effectiveness was assessed by calculating the incidence of the primary endpoints (HPV6/11/16/18 persistent infection or related disease) and comparing these rates with those from previous phase 3 studies in men and women aged 16-26. the median follow-up time for effectiveness was 6.8 years in EVG and 4.7 years in the CVG. **Results:** For each of HPV types 6, 11 and 16, the vaccination-induced anti-HPV response persisted long-term. Depending on HPV type, 88%-97% remained seropositive through Month 96. the lower vaccination-induced anti-HPV 18 response over time observed in V501-018-11 is consistent with the persistence profile observed in other studies in the GARDASIL™ program. No cases of HPV 6/11/16/18-related disease were observed. One serious adverse event was reported between months 72-96 (tonic-clonic movements) and was deemed not related to vaccine. **Implications and Impact:** Vaccine-type anti-HPV 6, 11, 16, and 18 responses generated through administration of GARDASIL™ among preadolescents and adolescents persist over the long-term, in accordance with expectations from previous GARDASIL™ studies. No breakthrough cases of disease related to vaccine HPV types 6, 11, 16, and 18 have been observed among preadolescents and adolescents vaccinated with GARDASIL™.

#### Epidemiology/Public Health the human element: Sociocultural and psychosocial factors related to cervical cancer prevention

### Is the World Ready to Vaccinate Boys against HPV? Socio-Cultural and Psychosocial Lessons from the Implementation of the HPV Vaccine Programs for Girls

Presenter: Margaret Heffernan, OAM, PhD OAM: Order of Australia Medal

Authors: No conflict of interest

Investigators/Collaborators: Heffernan ME<sup>1</sup>, Daley EM<sup>2</sup>, Garland SM<sup>3,4</sup>, Zimet GD<sup>5</sup>

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Country: Australia

**Objectives:** Sound arguments can be made for HPV vaccination of males, but much of the world is not prepared for male HPV vaccination programs. Female HPV vaccination programs globally overlooked critical social and system ramifications, and have proven to be complex and challenging. If crucial system, educative, psycho-social and cross-cultural factors are unaddressed, challenges will be posed for adoles-

cent male HPV vaccination across diverse nations. **Method:** (a) Results from an Australian cross-cultural qualitative study on parental and general medical practitioners (GPs) attitudes toward adolescent HPV vaccination. Participants for the qualitative semi-structured interviews were purposively selected: (i) parents of Anglo, Aboriginal, and Chinese descendency (n = 166) (ii) practicing GPs (n = 15). Recruitment was through hospital clinics and cultural networks; (b) a literature review of global HPV vaccination programs 2007-2012. **Results:** The study showed parental consent was based on passive acceptance and emotional vulnerability toward cancer, despite concerns about the vaccine's characteristics, relevance for young adolescents and psychosocial factors of 'shame' and 'stigma'. Public HPV education resources, derived from assumptive conclusions and ethnocentric discourses, ignored diverse socio-cultural paradigms and health practices. Dissatisfaction was held with protectionist discourses by the health sector which limited overall public awareness about HPV infection, and especially for males. Cultural and religious norms influenced parental and GPs' differing attitudes. The literature shows that the message framing of HPV vaccines and minimisation of HPV as an STI contributed to confusion about HPV infection and vaccination for males. Implementation strategies for female HPV vaccination programs, typically treated as different from other vaccines, failed to take advantage of findings from prior adolescent vaccination strategies and studies. **Implications and Impact:** The introduction of boys' HPV vaccination programs should not mimic that of girls and current implementation strategies require a system-change review. To aid support for male vaccination, an unmitigated education approach undertaken pre-vaccination should inform about male and female sexual acquisition and HPV diseases. Diverse resources, expanded time frames and public sexual discourses are required to change the social paradigms toward stigma and taboo in relation to HPV and other STIs. This comprehensive and socio-ecological approach to HPV-STI education programs and male vaccination considers conflicting values and will optimise delivery and uptake.

**Epidemiology/Public Health the human element: Sociocultural and psychosocial factors related to cervical cancer prevention**  
**Parents' Human Papillomavirus Vaccine Decision-Making for their Young Daughters: the Role of Vaccination Safety**

Presenter: Andrea Krawczyk, PhD

Investigators/Collaborators: Bärbel Knäuper, Vladimir Gilca, Eve Dubé, Zeev Rosberger

Country: Canada

**Objectives:** Vaccination against the human papillomavirus (HPV) is an effective primary prevention measure for HPV-related cancers and associated diseases. For children and young adolescents, the uptake of the vaccine is contingent on parental vaccination consent. This study sought to identify key differences between parents who accept and parents who refuse the HPV vaccine for their daughters. **Method:** In the context of a free, universal, school-based HPV vaccination program, a random sample of 2,500 Québec parents of 9-10 year old girls were invited to participate in the study by mail. Participants completed a questionnaire based on the theoretical constructs of the health belief model (HBM) and additional relevant factors identified in the literature. **Results:** Of the 834 parents who completed the questionnaire (33% response rate), 88.2% reported accepting the HPV vaccine for their daughter. The HBM constructs distinguishing parents who have accepted and parents who have refused the HPV vaccine included: perceived susceptibility of daughters to HPV infection (OR = 1.12 CI = 1.06, 1.18), perceived benefits of the vaccine (OR = 1.27 CI = 1.20, 1.36), perceived barriers (OR = 0.92 CI = 0.90, 0.95), and cues to action (OR = 1.23 CI = 1.18, 1.28). In particular, parental perception of vaccine safety was the strongest factor associated with acceptance (OR = 2.30 CI = 1.96, 2.71). Further, perceived safety was a significant independent contributor beyond all other HBM constructs (OR = 1.73, CI = 1.36, 2.21). Other significant factors associated with parental vaccination acceptance were positive vaccination attitudes (OR = 1.13 CI = 1.08, 1.18), negative vaccination attitudes (OR = 0.89 CI = 0.86, 0.92), anticipated regret (OR = 0.61 CI = 0.54, 0.69), adherence to other routinely recommended vaccines (OR = 1.96 CI = 1.24, 3.10), social norms (OR = 1.65 CI = 1.43, 1.91), and media influence (OR = 1.64 CI = 1.43, 1.90). **Implications and Impact:** Parental perception of vaccine safety is a critical factor for HPV vaccination acceptance. The HBM provided a useful, but incomplete framework to identify the factors related to parental vaccination decision making. Comprehensive theories of vaccination decision making that include additional behavioural, social, and cognitive factors are warranted.

**Epidemiology/Public Health, the human element: Sociocultural and psychosocial factors related to cervical cancer prevention**  
**Effects of Condom Use on Genital Human Papillomavirus (HPV) Incidence and Clearance in Men: The HPV in Men Study**

Presenter: Christine Pierce Campbell, PhD

Investigators/Collaborators: Christine M. Pierce Campbell<sup>1</sup>, William Fulp<sup>1</sup>, Hui-Yi Lin<sup>1</sup>, Mary R. Papenfuss<sup>1</sup>, Eduardo Lazcano-Ponc<sup>2</sup>, Luisa L. Villa<sup>3</sup>, and Giuliano AR<sup>1</sup>

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Country: United States

**Objectives:** Male condoms offer substantial protection against many sexually transmitted infections; however, data supporting the efficacy of male condoms against HPV infection have been limited. The goal of this study was to determine if consistent condom use among certain groups of high-risk men would reduce the risk of acquiring genital HPV infections, or decrease the duration of HPV infections, compared with men who never use condoms. **Method:** A prospective analysis was conducted within the HPV in Men (HIM) Study, an ongoing co-



hort study of the natural history of HPV infections among men in the US, Brazil, and Mexico. the analytic cohort consisted of 3,323 men aged 18–70 years who reported recent sexual activity (3–6 months prior to baseline visit). All men completed risk factor questionnaires and underwent clinical examinations at baseline and subsequent follow-up visits. Genital HPV was assessed using the Roche Linear Array genotyping test. To assess under which circumstances condoms might impact HPV acquisition and clearance, men were categorized according to their risk potential for HPV infection (single, monogamous, or non-monogamous). Sex act- and partner-specific measures of condom use (always, sometimes, or never) were used to evaluate risk of HPV acquisition and median time to clearance. **Results:** Men (N = 3,323) were followed for a median of 17.3 months (range = 0.3–55.6). Risk of HPV acquisition and clearance varied significantly by risk group and condom use. the 12-month incidence of any HPV was higher among non-monogamous men (53.8%) than single (40.8%) or monogamous men (34.6%) (log-rank  $p < 0.001$ ). among single men, those who always used condoms during vaginal sex had the lowest risk of acquiring any HPV within 12 months (32.2%) (sometimes [50.3%] and never [49.9%]; log-rank  $p = 0.014$ ). the median time to clear an incident HPV infection was shorter among monogamous men (6.6 months) than single (7.2 months) or non-monogamous (7.6 months) men (log-rank  $p = 0.008$ ). among non-monogamous men, those who always used condoms with non-steady partners cleared oncogenic HPV infections more quickly (median = 6.4 months) (sometimes [8.1 months] and never [11.1 months]; log-rank  $p = 0.014$ ). No protective effects of condom use were observed among monogamous men. **Implications and Impact:** Consistent condom use may reduce the risk of acquiring some, but not all, grouped HPV infections and decrease the duration of these infections among high-risk men. Condom use is a cost-effective risk-reduction strategy that should be promoted in combination with population-based vaccination to prevent HPV infection, reduce HPV transmission, and decrease the burden of HPV-related diseases.

### **Epidemiology/Public Health the human element: Sociocultural and psychosocial factors related to cervical cancer prevention Psychosocial Impact of Genital Warts and Other HPV-Related Diseases in South Korea**

Presenter: Smita Kothari, PhD, MBA, RPh

Investigators/Collaborators: JuW<sup>1</sup>, LeeTS<sup>2</sup>, Yee KS<sup>3</sup>, Kothari S<sup>4</sup>, Lara N<sup>5</sup>, Montse R<sup>5</sup>, Giuliano A<sup>6</sup>, Garland S<sup>7</sup>

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Country: United States

**Objectives:** To assess the psychosocial impact of genital warts (GW) in males and select HPV-related diseases in females in South Korea. **Method:** During September 2011 through December 2011, male and female patients, 20-60 years of age from 4 different provinces (Seoul, Busan, Daegu and Daejeon) in South Korea were invited by their physicians to complete questionnaires to assess healthcare seeking and sexual activity behavior and the psychosocial impact of GW (males) and selected HPV-diseases (females). Patients diagnosed with GW or HPV-condition, without any significant comorbid condition or a concurrent/active sexually transmitted infection within the last 3 months of completing the questionnaire, were included in the study. Patients without diagnoses of GW or HPV-related diseases within the last 3 months were also included. Psychosocial impact was assessed using HPV Impact Profile (HIP), disease specific Questionnaire for Condylomata Acuminata (CECA) which was administered only to patients with GW, and EQ-5D in 250 females with (200) and without (50) HPV disease and 150 males with (75) and without GW (75). HIP and EQ-5D questionnaire scores were compared between male GW patients and females with HPV vs. those without. the CECA scores were compared between males and females with GW only. **Results:** The total HIP scores (range 1 (best) -100 (worst)), were statistically significantly higher in both males with GW ( $p < 0.001$ ) and females with HPV ( $p < 0.001$ ) than those without GW or HPV-related diseases, respectively. in males, the HIP scores were significantly higher than those without GW in all domains except "control-life impact." the HIP domain scores for females with HPV diseases was significantly higher in the worries/concerns ( $p < 0.0001$ ), emotional impact ( $p < 0.0001$ ), and partner issues/transmission ( $p = 0.0001$ ) than the no HPV group. in GW patients, the CECA scores ((range 1 (worst) -100 (best)), for "emotional" ( $p < 0.0001$ ) and "sexual activity" ( $p < 0.0001$ ) domains were both statistically significantly higher in males than females. in females, EQ-5D anxiety/depression ( $p = 0-0078$ ) domain was significant for the HPV disease group compared to no HPV group. **Implications and Impact:** In our study sample, there is a significant psychosocial impact on male patients with GW as compared to those without. in females, HPV disease including GW has high impact on worries/concerns, emotional and partner issues/transmission related issues than no HPV disease.

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