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CONFERENCE REVIEW

Making Education Easy

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In this review:

Abbreviations used in this review
CIN/VIN/VAIN = (cervical/vulvar/vaginal) intraepithelial neoplasia
HIC = high-income country
HIV = human immunodeficiency virus
HPV = human papillomavirus
HSIL = high-grade squamous intraepithelial lesion
MSM = men who have sex with men

Welcome

to this review of the 32nd IPVC (International Papillomavirus Conference) 2018, in conjunction with AOGIN (Asia-Oceania Research Organisation in Genital Infection and Neoplasia), held recently in Sydney with the theme of 'Towards global control of HPV disease'. Delegates were able to attend a range of workshops, invited lectures and oral and poster sessions covering the latest research topics from basic science to global health impact, with particular focus on control of HPV in the most vulnerable populations. Among those who attended were myself (Min Lo) and Helen Petousis-Harris, and together we have provided the commentary for this review.

We hope you find this Conference Review enlightening and helpful, and we invite you to send any comments or feedback you have.

Kind regards

Dr Min Karen Lo
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INTRODUCTION BY HELEN PETOUSIS-HARRIS, INVITED SPEAKER ON 'HPV VACCINE SAFETY: SCIENCE AND COMMUNICATION'

Wouldn't you love to go to a 5-day international conference on one virus? The overriding theme of the 2018 IPVC was not about vaccine efficacy, safety or coverage. We know it works. The main issues affecting us today relate to vaccine hesitancy and social media. Those of you who have traditionally shied away from these areas should now be sitting up and paying attention because this is so important.

Reaching and informing: effective engagement methods to support HPV vaccine uptake

Presenter: Tiro J

Summary: The following two trends hinder HPV vaccine uptake globally: i) increased vaccine hesitancy (delay in acceptance or refusal of vaccination when the services are available); and ii) spread of misinformation regarding the HPV vaccine via social media. US data showed that 40% of parents either refused or delayed ≥1 vaccine for their children in 2009, and 88% of healthcare providers more recently reported that parents had asked for vaccines to be delayed. This has led to: i) more parents questioning guideline-based vaccination schedules; ii) providers becoming more uneasy when discussing vaccinations with parents; and iii) vaccination coverage falling short of goals. Furthermore, it has become apparent that informational campaigns and educational materials based on facts are not reliably effective, and the application of the latest science in decision-making, such as nudge theory, is needed. How nudge theory principles have been used by the antivaccine movement and public health practitioners to reach parents was covered in this presentation, along with challenges that lie ahead.

Public health workshop 1: Moving forward with HPV vaccination in high income countries
Abstract

Communicating HPV messages

Presenter: Leask J

Summary: Parental hesitancy and HPV vaccine refusal for their adolescent are frequently encountered by health professionals. Based on behavioural and communication science, this presentation provided practical strategies for health professionals who are faced with these issues. A structured approach based on enhancing professionals' existing skills was described for maintaining the balance between the therapeutic relationship and encouraging vaccination.

Clinical workshop 6: HPV vaccination in clinical practice
Abstract

Independent commentary by Helen Petousis-Harris

Helen is Senior Lecturer in the Department of General Practice and Primary Health Care at the University of Auckland and the Academic Lead for Immunisation Research and Vaccinology at the Immunisation Advisory Centre. **For full bio CLICK HERE.**

Effective tactics for creating a vaccine supportive media environment: a history of the stop the AVN movement

Presenter: McDermott T

Summary: Social media platforms available via the internet have enabled the antivaccination movement to spread its messages to a wider audience. Australia's most prominent antivaccination organisation (AVN; Australian Vaccination-risks Network) was formed in 1994, and with a yearly income of ~$300,000 and regular media appearances, it has expanded to a position of power, including harassment by its president on a national television show of parents of an infant who died of pertussis in 2009. This action led to the formation of the SAVN (Stop the Australian (Anti) Vaccination Network) Facebook group, the actions of which have led to a reduction in the AVN's media profile and a ~90% drop in their income.

Public health workshop 6: Lifting our game: Communication and engagement strategies about HPV vaccination to overcome the organised anti vaccination movement

Abstract

Comment (HPH): Why don't some people want the HPV vaccine? The safety of the HPV vaccine has been extensively assessed since it became available, and there is a mind-boggling amount of quality safety data. After over 270 million doses, the clear consensus is that this is one of the safest vaccines ever developed. As soon as the vaccine hit the fridges the opposition to HPV vaccines brought weapons of mass destruction. Powerful anecdotes of death and disability that scared people away from vaccinating. The antivaccine lobby was globally co-ordinated and well-funded – 'A lie can travel halfway around the world while the truth is still putting on its shoes.' The horrible truth is that on social media lies spread faster and further than truths.

Parents all share a desire to keep their children healthy, but can differ in how they evaluate information about evidence due to a whole range of cognitive biases. There are certain traits that predispose to accepting antivaccine rhetoric as fact. Research suggests that conspirational thinking, reactance (don't tell me what to do), disgust (such as fear of needles or chemicals) and individualistic world views are at the root of antivaccination attitudes. While we still do not have a reliable map with which to negotiate these complex cognitive quirks, what we do know is that understanding these underlying psychologies better along with establishing and maintaining trust and transparency could help us better communicate the science.

It is reassuring to know that the 'hard core' antivaxxers are actually a small group that should be avoided, as trying to communicate with them only strengthens their resolve. The more important and bigger group that we need to connect with are the 'vaccine hesitants' who are normal people looking for information, easily swayed by family, 'what their friends said' or what they are reading. Parents consistently rank their child's doctor as their most trusted source of vaccine information. Most people appreciate having the scientific consensus reinforced, and correcting misinformation is very important, so don't stop doing it! For some it is not helpful to just give more and more information and expect them to change their mind, in fact it can backfire.

Here are some key tips. Consider the ASK approach (Acknowledge the persons concerns, Steer your conversation, Knowledge (know the facts)):

1. Rather than tacking it on at the end of a consultation, include a conversation about HPV vaccination in the middle of your consultation and together with other routine vaccines.
   - "now that Sophie is 11, she is due for her vaccines. She should have her HPV vaccine in school and she is due for her tetanus, diphtheria, whooping cough".
2. Keep things very simple. Instead of providing too much information, ask for questions. If parents have concerns, your willingness to listen to their concerns will play a major role in building trust.
   - "HPV virus is very common and can cause a variety of cancers. The vaccine is very effective at preventing infection with this virus. Do you have any questions for me?"
3. Understand where they are coming from, acknowledge concerns and resist the temptation to 'jump in and correct misinformation'. Address concerns and myths like a sandwich. Start and end with facts.
   - Acknowledge: "I hear what you're saying, that is a common concern. Tell me more about what you have heard."
   - Steer: "I understand how you want what's best for your child and you have worries about neurotoxins/aluminium/autism, etc."
   - Knowledge: "let's work through your concerns"
   - "Is it OK for me to bring this up at the next visit?"

The CDC provides some very useful resources for clinicians on how to talk (and how to say it) about HPV vaccination, which I highly recommend:

- #HowIRecommend HPV vaccination video series
- Paed talks to vaccine-hesitant coffee group (US CDC) (https://www.youtube.com/watch?v=3uVvq7dbf4s&feature=channel_page)
- Provider resources for vaccine conversations (US CDC) (https://www.cdc.gov/vaccines/hcp/conversations/index.html)
- In NZ, do you need to ring for advice? Immunisation specialist – 0800 IMMUNE

WHERE IS NZ UP TO?

Implementation of two dose, nonavalent, gender neutral vaccination in New Zealand

Presenter: Turner N

Summary: HPV4 (Gardasil) was introduced on NZ's national schedule in 2008 for females aged 12 years with a catch-up programme for those aged up to 20 years. HPV9 (Gardasil9) replaced HPV in 2017, with a two-dose regimen for those aged <15 years, and extended to males as well as females aged 9–26 years, delivered mainly through schools at year 8, with catch-up in primary care. Coverage rates for females aged 12 years started out at around 52% for the first 3 years of the programme, with lower rates in the catch-up programme. This has increased steadily to 65–67% for full immunisation of 12-year-olds since 2012, although there is variability among DHBs. No formal evaluation of the effectiveness of the programme for young males has been conducted, but uptake rates have been almost identical to those for females. Provider feedback on the strengths and challenges of the current programme were presented.

Comment (ML): It has been nearly 2 years since NZ started the HPV9 (Gardasil9). National coverage is about 70%, which is a lot better than when we first started with Gardasil4, 10 years ago. We did have a problem with vaccine supply, but that is currently being rectified. The uptake for boys is as high as for girls, which has been very positive. Adding young men has certainly changed the perception of HPV and helped normalise the vaccine. The primary care catch-up programme has been affected by provider fatigue and vaccine hestitancy. In some DHBs, the difference between school-based and primary care based programmes has been plainly obvious, with primary care having much lower coverage.

Public Health Workshop 1: Moving forward with HPV vaccination in high income countries.

Abstract

WHAT'S HAPPENING IN THE REST OF THE WORLD

Hidden inequalities in HPV vaccine uptake. Who is missing out on HPV vaccine in HIC, why, and what can we do about it?

Presenter: Zimet G

Summary: There is considerable variability in HPV vaccination rates across HICs, with some rapidly achieving high rates and others struggling to vaccinate their targeted populations, and some achieving high initial rates followed by setbacks. There is also high variability among HICs regarding how the vaccine is administered, the target population, the target age and vaccination policies, with different groups missing out in some countries. This presentation focussed on differences between the US and the UK. In the US, lower vaccination rates are seen for whites and populations living in a rural area or with higher incomes, whereas in the US, rates are lower for ethnic minorities and males (particularly young MSM).

Public Health Workshop 1: Moving forward with HPV vaccination in high income countries.

Abstract

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Update on HPV vaccine development and implementation in China

Presenter: Zhao F

Summary: Based on clinical trial evidence, 2- and 4-valent HPV vaccines have been approved in China over the past 2 years, while 9-valent HPV vaccine has received conditional approval following a vastly reduced regulatory timeline. The availability of international HPV vaccines in China is an important advancement, but challenges remain. The demand for the vaccine in China exceeds supply by a considerable degree, and there are also financial issues regarding high uptake. At the time of reporting, there were 20 domestic HPV vaccines under investigation in clinical trials, with a phase 3 trial of the first of these almost completed. Based on clinical trial data, a three-dose schedule is used in China, with two- and single-dose noninferiority studies to be conducted in the near future.

AOGIN plenary 2: HPV vaccination
Abstract

The role of communication in public health: the HPV experience in India

Presenter: Godinho N

Summary: With India used as a case study, the role of communication efforts in shaping the environment around HPV vaccine introduction was discussed. Although HPV vaccines have being licensed in India since 2008, coverage remains low, partly due to HPV vaccine not being included in the government's UIP (Universal Immunization Programme) and partly due to limited awareness regarding the value and efficacy of the vaccine among political, technical and community stakeholders. Despite this, several communication efforts made over recent years have resulted in progress toward introduction of HPV vaccination, including pilot programmes, and in 2017, India's National Technical Advisory Group on Immunization recommended that HPV vaccine be included in the UIP.

Structured scientific session 1: vaccine safety and communication
Abstract

Comment (ML): An interesting trend around the world is that ethnic minorities and rural and lower income groups are consistently achieving higher vaccine coverage rates than white and/or urban groups. The same trend is also seen in Australia and NZ where Indigenous Australians, NZ Māori and Pacific Islanders have consistently higher coverage than other groups. What this shows is that groups that are 'well informed' are talking themselves out of vaccination, and how social media is continuing to fuel vaccine hesitancy.

Some countries have achieved and maintained high vaccination rates. Australia is powering on and aims to be the first country in the world to eliminate cervical cancer. Some countries achieved high rates, but then had significant setbacks from antivaccination lobby groups and poor media reporting, e.g. Japan, Austria, and Ireland. Some countries struggle; e.g. in the US, low vaccine coverage is dogged by lack of cohesive policy, lack of school immunisation programmes (you have to go to a paediatrician to get the vaccine) and by high levels of vaccine hesitancy. In many countries where school-based programmes are implemented (including NZ), pockets of low uptake reflect the significant influence that schools that decline to take part have on the local community.

Asian countries are just starting to implement HPV vaccination. In most places, vaccines are very expensive and only available on a self-funded basis. It is perhaps disappointing that countries such as Singapore, China and India are marketing the vaccine as a 'cervical cancer vaccine'. This is where Australia and NZ started 10 years ago, and we have since learnt that HPV vaccine should be gender neutral; including boys increases community confidence, and it is frankly not ethical if the male population are not able to benefit.

IS ONE DOSE IS ENOUGH?

One dose of human papillomavirus vaccine is as effective as three for prevention of high-grade cervical lesions: national cohort study

Presenter: Brotherton J

Summary: The effectiveness of quadrivalent HPV vaccine by number of doses administered against CIN 2 or 3 adenocarcinoma *in situ* was evaluated by analyses of linked data from 250,648 eligible screened Australian women aged ≤15 years. Compared with unvaccinated women (n=48,845), those who received one (n=8613), two (n=18,190) and three (n=174,995) vaccine doses had lower likelihoods of histologically confirmed CIN 2 or 3 adenocarcinoma *in situ* (respective hazard ratios 0.63 [95%CI 0.51–0.79], 0.60 [0.51–0.71] and 0.60 [0.55–0.66]), with no significant differences among the dose groups, leading the authors to conclude that *"one dose was as effective as three"*.

Comment (ML): Yes, one dose is enough. HPV vaccine is highly immunogenic with sustained antibody levels observed after one dose. This preliminary analysis of data from Australia shows that one dose of Gardasil4 was as effective as three doses. The outcomes of 'one-dose' RCTs are pending. What this means is that in poorly resourced countries, one-dose regimens should be considered for early implementation. We should still follow the vaccination guidelines in NZ.

Scientific stream 4: vaccination evaluation
Abstract

HPV SCREENING AND DISEASE IN IMMUNE-COMPROMISED PEOPLE

HPV screening and disease in immune-compromised women

Presenter: Moscicki A

Summary: The risk of HPV-associated cancers (specifically cervical and anal) is increased in immunocompromised women. The most studied immunocompromised women in this respect are those with HIV infection; others include solid organ or hematopoietic stem cell transplant recipients and those with autoimmune diseases. Life expectancy of immunocompromised patients is improving, although treated HIV-infected women are likely to have better immune health than women with iatrogenic immunosuppression. Current cervical cancer recommendations include: i) starting screening within 1 year of onset of sexual debut; ii) annual screening with cytology until three consecutive normal screens have been obtained, and then every 3 years with cytology alone, or >30 years of age, with co-testing (cytology plus HPV) and iii) continued lifetime screening. The available skills and tools for detection and treatment affect recommendations for anal cancer screening. Recommendations for screening for both cervical and anal cancer were covered in this workshop.

Clinical workshop 4: clinical perspectives in specific populations
Abstract

HPV vaccination in HIV infection

Presenter: Lacey C

Summary: Despite many patients with HIV infection living normal lifespans with combination antiretroviral therapy, even those with undetectable viral loads have persistent subtle immunological, metabolic and tissue abnormalities. Persons with HIV infection have increased rates of HPV acquisition, persistence and multiple genotype infections, and higher rates of HPV disease and disease progression, including to invasive cancers. Due to memory TFH-cell function defects resulting in abnormal B cell responses, HIV-infected patients often exhibit suboptimal immune responses to vaccination, with more rapid declines in vaccine-induced antibody levels. While studies have demonstrated the immunogenicity of HPV vaccines in HIV infection (Papillomavirus Res 2017;4:35–8), few have reported HPV disease endpoints. Evidence and directions for future research in HPV vaccination in patients with HIV infection were presented.

IPVC 2018 plenary session 2
Abstract

Comment (ML): HPV causes significant morbidity in immunocompromised people. HIV-positive women as well as women with solid organ transplants and autoimmune disease require more frequent screening than the general population. The best studies are in those with HIV infection. Other groups include solid organ transplants and autoimmune disease. Current recommendations in the US CDC guidelines include starting screening 1 year after first sexual intercourse or 1 year of immunosuppression and continuing throughout life (not stopping), then annual screening with cytology until three consecutive normal screens then every 3 years. This may differ from the NZ screening guidelines. The efficacy of the HPV vaccine is unknown, but the vaccine is safe, immunogenic and recommended. These populations are also at risk of disease from HPV types other than HPV 16/18, so vaccination with Gardasil9 is recommended, even for patients who are already sexually active.

VACCINATION OF 'OLDER' PEOPLE

Evidence of efficacy for older women

Presenter: Skinner R

Summary: While HPV vaccination programmes have focussed on adolescent females (and more recently males), there is now evidence that where catch-up vaccination to age 26 years has occurred, the impact of vaccination programmes on HPV infection and related disease has accelerated. Older women are at higher risk of HPV-related cancer than their younger counterparts, but are unlikely to have been vaccinated. This presentation summarised the key data relevant to this age group with the aim of providing an understanding of: i) HPV infection and related disease epidemiology and natural history in older women; ii) HPV vaccine clinical efficacy in this age group as well as women with previous HPV infection and related disease; and iii) indications for vaccination of older women.

Clinical workshop 6: HPV vaccination in clinical practice
Abstract

Targeted MSM HPV vaccination program in the UK: why, how and lessons learned

Presenter: Jit M

Summary: This was a presentation on the UK's targeted HPV vaccination programme for MSM aged ≤45 years who attend sexual health and HIV clinics. After analyses deemed it would be cost effective and result in substantial declines in HPV-related disease among MSM, the programme was introduced in 2016 in Wales, Scotland and Northern Ireland, with a 2-year pilot preceding introduction in England in 2018. The overall first-dose uptake was just under 50%, although there was considerable variability across clinics, with some achieving uptake of >80%. The vaccine refusal rate was 3.4%, and there were anecdotal reports suggesting issues with data recording leading to underestimation of vaccination uptake at some clinics. For the pilot programme, it was concluded that acceptable and equitable delivery of HPV vaccine could be achieved through sexual health and HIV clinics.

Moving forward with HPV vaccination in HIC
Abstract

Comment (ML): Well, I thought I would get final enlightenment on the data at the conference. The trial data have always been extremely confusing, and I now realise that to remain contained by the 'evidence' is limiting. What seems clear is that there are two ways of approaching the question of whether or not vaccinating 'older' people is beneficial: i) follow the 'evidence'; or ii) be pragmatic. The data available are difficult to untangle from the studies and complicated by methodological and confounding problems. In particular, if you are already sexually active and are seropositive to HPV, naturally acquired antibodies can provide some immune protection that 'masks' the potential effect of vaccination, thus making vaccine efficacy outcomes difficult to understand and less clear.

We should not limit our conversations. HPV vaccine has probably more potential than we realise that goes beyond its current indications; for example, it may decrease viral shedding or make virions less infectious. There are many countries routinely providing vaccination to those already sexually active; i.e. catch-up programmes (age 15–26 years) and approving use to 'older' ages of ~55 years (which is self-funded). Data so far from countries are showing some benefit in these age groups even though they are already sexually active. Vaccination is also generally recommended in high-risk groups, even if they are sexually active or older (i.e. will have to self-fund). The UK has a targeted MSM programme in its sexual health clinics for all MSM up to age 45 years.

Several studies are reporting that vaccination at or near to the time of treatment for high-grade cervical disease can help to reduce future recurrence. There is no doubt that vaccination when a person is already sexually active has lower efficacy. However, the potential benefit will ultimately depend on the individuals previous lifetime exposure and ongoing risk exposure, and women (and men) on the 'young' side of old will benefit more.

(References: J Infect Dis 2018;217:1590–600 & J Infect Dis 2018;218:84–94)

ANAL CANCERS

Clearance of anal HSIL is inversely related to persistent high-risk HPV – three-year follow up results from the Study of Prevention of Anal Cancer (SPANC)

Presenter: Poynten I

Summary: Anal cytological and histological assessments and HPV genotyping were performed at baseline, at 6 months and at three annual visits in 617 gay and bisexual men in the SPANC trial; this analysis included 377 men who had attended all annual visits by April 2018, for whom the median age was 50 years, the HIV-positivity rate was 40.1% and the baseline composite (cytological and/or histological) HSIL rate was 39.0%. Eighty-five men experienced composite HSIL clearance (26 per 100 person-years). No significant association was seen between HSIL clearance and HIV status, cigarette smoking, recent sexual behaviour, lesion size or prevalent HPV18 infection. Factors significantly associated with reduced clearance were increasing age, higher number of lifetime male partners, higher lesion grade (hazard ratio 0.50 [95% CI 0.32–0.79]), baseline HPV16 (0.50 [0.06–0.36]), persistent HPV16 (0.21 [0.09–0.45]) and persistent non-HPV16 high-risk HPV infection (0.38 [0.18–0.81]).

Comment (ML): Anal cancer, although rare, is clustered in a few populations. These include gay and bisexual men, HIV-positive people, organ transplant recipients and women who have had a previous history of high-grade anogenital HPV disease (CIN, VIN or VAIN). In treated HIV-positive people who have undetectable viral loads, there are subtle immunological, metabolic and tissue abnormalities, resulting in increased rates of HPV acquisition, persistence and multiple genotypic infections, and increased rates of HPV disease and disease progression. Women with a history of high-grade cervical, vulval or vaginal disease make up a significant group of the population. These women have a risk of developing anal cancer, which usually arises 5–10 years after a history of high-grade CIN.

There is no screening test for high-grade anal disease in NZ. At the current time, anal pap smears (cytology) and high-resolution anoscopy (colposcopy of the anal canal) are done in Sydney and some parts of the US, but we still don't know yet if these procedures are resulting in true benefit. We await the outcomes of ongoing research. In NZ, we recommend talking to your patients so that they are alert to any symptoms such as pain, bleeding or lump, and offering an annual digital anal-rectal examination to detect any palpable irregularity. Anal cancer is very curable if detected early.

(Reference: Lancet Infect Dis 2018;18:198–206)

Scientific stream 5: anogenital disease
Abstract

Independent commentary by Dr Min Karen Lo

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Min is a Sexual Health Specialist working in private practice in Auckland. Her interests include vulvo-vaginal disease, HPV, HSV and genital dermatology. Min is a forensic physician in the area of sexual assault medicine and is the chair of the board of MEDSAC Medical Sexual Assault Clinicians Aotearoa. She has previously been a consultant at Auckland Hospital, clinical lead of the Adult Sexual Assault Service and also a consultant at Middlemore Hospital Colposcopy Unit.

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