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VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

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Extending Australian national HPV vaccination program to males

Georgousakis et al. Population-wide vaccination against human papillomavirus in adolescent boys: Australia as a case study. Lancet Infect Dis *2012 [Epub ahead of print].*

Extension of the Australian National Immunisation Program to include vaccination against the human papillomavirus (HPV) to males has been shown to be cost-effective and is under consideration by the Australian government, according to the National Centre for Immunisation Research Surveillance (NCIRS), Westmead, New South Wales.

"Australia was the first country to introduce a government-funded national HPV vaccination programme aimed at reducing the incidence of cervical cancer in women," confirmed lead author Dr. Melina Georgousakis of the NCIRS. Through this program, the quadrivalent HPV vaccine, which also protects against HPV types 6 and 11, is delivered to schools for girls between the ages of 12 and 13. In mid 2010, the Therapeutic Goods Administration, the Australian regulatory agency, extended registration of the quadrivalent vaccine to include its use in boys and men up to the age of 26 for the prevention of external genital lesions and infection with HPV types 6, 11, 16 and 18. (Both Canada and the US have similarly recommended quadrivalent HPV vaccination of adolescent boys and young men with the quadrivalent vaccine.)

In consideration of how best to use the vaccine in males, investigators identified factors that need to be taken into account when making decisions around the introduction of population-based vaccination programs, including local disease burden, vaccine efficacy and safety and cost-effectiveness. "As in women, most HPV infections in men are transient, asymptomatic and resolve spontaneously," they noted. Unlike women, however, the risk of acquiring HPV infection in men is evident at all ages and remains stable over time. The most important risk factor for men to acquire external genital HPV infection is the number of sexual partners which is also true for women.

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As with women, men also develop HPV-attributable cancers of the anus, the oral cavity and the oropharynx, as well as non-cancerous lesions such as genital warts and recurrent respiratory papillomatosis. The estimated annual incidence of anogenital warts among Australian men is only marginally lower than that for women.

The only HPV-associated disease unique to men is penile intraepithelial neoplasia which progresses to cancer of the penis in fewer than 1% of cases. Both HPV 16 and 18 account for approximately 90% of all HPV-attributable cancers in men. Overall, "the incidence of HPV-associated cancers in Australian men is low compared with that for cervical cancer before the introduction of HPV vaccination," the authors observed.

Incidence of cancers of the oropharynx associated with HPV has increased in men but not in women, while the estimated number of new cases of cancer associated with HPV 16 and 18 in Australian men before the female vaccination program was started was around a quarter of the total number of diagnosed cancers associated with HPV 16 and 18, investigators added. In contrast, the incidence of anal cancer in men who have sex with men (MSM) is reported to be more than 30 times higher than it is in other men and is estimated to be similar to the incidence of cervical cancer prior to introduction of the cervical cancer screening program.

MSM are also at increased risk of developing HPV-related cancers in the oral cavity and oropharynx compared with other men, and MSM have almost 10 times the estimated incidence of anogenital warts than in the general population. Quadrivalent vaccine efficacy against external genital lesions has been well established in men between the ages of 16 and 26; in MSM, efficacy of the vaccine was also demonstrated for the combined end point of anal intraepithelial neoplasia and anal cancer. "The immunogenicity of the quadrivalent vaccine in sexually-naive boys aged 9 to 15 years is similar to that in age-matched girls and young adult women," investigators noted. No safety signals have been seen in clinical trials evaluating the quadrivalent vaccine in adolescent boys and men.

"In addition to the direct benefit that HPV vaccination may provide to male recipients, a population benefit to unvaccinated members of both sexes through herd immunity seems likely," the authors stated. Herd immunity has already been documented against new cases of genital warts among heterosexual men and women but not in MSM. If HPV vaccine uptake is high among young girls, the greatest benefit of HPV vaccination will be achieved through vaccination of girls alone, the authors noted: where vaccine coverage is less extensive, "male vaccination might have greater benefits." In the one study in which cost-effectiveness of female-only vaccination was compared with male and female vaccination in the Australian setting, "the incremental cost-

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effectiveness ratio almost doubled when vaccination of boys was included compared with female-only vaccination," investigators reported.

In late 2011, an application was made to include the quadrivalent vaccine for administration to boys between 12 and 13 years of age via the National Immunisation Programme along with an appropriate catch-up program. The final decision is currently awaited. In the absence of a universally funded program for adolescent boys, "clinical trial data suggest that vaccination of adolescent boys or young adult men before sexual activity begins would be of potential benefit on an individual level... while vaccination seems particularly compelling for MSM," as the authors concluded.

Herpes zoster vaccine effective, well tolerated in subjects 50 to 59 years of age

Schmader et al. Efficacy, safety and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis *2012;54(7): 922-8.*

The herpes zoster vaccine (ZV) substantially reduces the incidence of herpes zoster (HZ) in middle-aged individuals, among whom the burden of illness from HZ is significant and the acute pain equal to that experienced by older individuals.

Dr. Kenneth Schmader, Duke University, North Carolina, and multicentre colleagues randomized 22,439 subjects between the ages of 50 and 59 years to either a single dose of the licensed ZV or to placebo and followed them for the occurrence of HZ for a mean of 1.3 years. Subjects were also followed for all adverse events (AEs) from day 1 to day 42 post-vaccination and for serious AEs for a total of 182 days.

At the end of follow-up, there were 30 cases of HZ in the vaccine group (1.99/1000 person-years) compared with 99 cases in placebo controls (6.57/1000 person-years), for a vaccine efficacy approaching 70%. "The mean severity-by-duration pain score among all subjects in the ZV group was lower (0.13) than the placebo group (0.49)," investigators reported, where the estimated relative reduction in the pain score between the 2 groups was 73%.

However, among individuals who developed HZ despite having received the vaccine, the mean severity-by-duration scores were similar to those reported by placebo patients who also developed HZ. "This indicates that most of the vaccine effect on acute pain was due to the prevention of HZ and there was no significant attenuation of the severity of cases," the authors observed.

They also noted that the acute pain in individuals in this age group who developed HZ was similar to that experienced by older people. "This is important," as the authors suggested, "because a large proportion in the younger age group are regularly employed and HZ results in significant loss of work time as well as diminished productivity in those remaining at work." Indeed, a survey of working individuals in this age group who developed herpes zoster reported the equivalent of over 71 hours of lost productivity due to the zoster episodes.

AEs occurred more frequently in the vaccine group at a rate of approximately 73% compared with approximately 42% in the placebo group, the difference primarily due to higher rates of injection-site AEs and headache. However, when headache was excluded from the analysis, there was no difference in vaccine-related systemic AEs.

Researchers also noted that the study provided no data on the effect of the ZV on postherpetic neuralgia. Nevertheless, the vaccine effect was stable over an average of 1.3 years and that it could be expected to be at least as long as that observed in the Shingles Prevention Study because response to the vaccine is more robust in younger individuals.

"This study demonstrated that the ZV reduced the incidence of HZ by nearly 70% in persons aged 50 to 59 years," the authors stated. "[Since] approximately 20% of cases of HZ occur in adults aged 50 to 59, this study result will be of interest to clinicians who take care of patients aged 50 to 59 and to patients in that age group who may be interested in reducing their risk of zoster."

HPV infection rates in young British females prior to mass HPV immunization

Howell-Jones et al. Prevalence of human papillomavirus (HPV) infections in sexually active adolescents and young women in England prior to widespread HPV immunisation. Vaccine *2012;30:3867-75.*

There was a high prevalence of human papillomavirus (HPV) infections among young, sexually-active females in England prior to the introduction of mass HPV vaccination in 2008 and both the type-specific and prevalence of multiple infections closely reflected age and sexual activity.

Dr. Rebecca Howell-Jones, Health Protection Agency, London, UK, and UK multicentre colleagues examined residual vulvar-vaginal swab samples from young women under the age of 25 who had undergone chlamydia testing as part of either the National Chlamydia Screening Programme (NCSP) or the Prevention of Pelvic Infection (POPI) trial. Samples were screened for HPV using a specific DNA test, including high-risk and low-risk probes. A total of 3829 samples were included: 2369 from 16- to 24-year-old NCSP participants, 275 from 13- to 15-year-old NCSP participants and 1185 from 16- to 24-year-old POPI participants.

"Overall, 50% of women included in our study reported [having] multiple sexual partners," investigators observed. Screening results revealed that among the 16- to 24-year-old NCSP participants, HPV prevalence was 34.6%. It was significantly lower (22.6%) in the 13- to 15-year-old NCSP participants as well as for POPI participants (18.3%). Regarding exclusively HPV 16 or 18 or both, HPV was prevalent in 17.6% of samples in the 16- to 24-year-old NCSP participants, in 11.5% of 13- to 15-year-old NCSP participants and in 7.2% of the 16- to 24-year-old POPI participants.

Assuming the prevalence of HPV to be zero in young females who were sexually naive—about 17% of 16- to 24-year-olds included in the survey—the population–weighted HPV prevalence estimate was 26.8% based on NCSP data and 13.3% based on POPI data, while the population–weighted prevalence of HPV 16/18 was 13.1% based on NCSP data and 4.9% based on POPI data, the authors added.

"In our samples of young women undergoing chlamydia screening prior to mass HPV immunization, HPV—particularly types 16, 18 and 51—multiple HPV infections were common," investigators reported. The strongest and most consistent associations for type-specific and multiple infections were found for increasing age up to the age of 19, multiple sexual partners and the presence of chlamydia infection, they added.

"The steep increase in HPV prevalence between the ages of 13 and 16 years supports the decision to deliver routine HPV

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immunization at age 12 to 13 years," investigators observed. They remarked that their data might now be used to inform vaccination policies as a baseline against which to measure the impact of the national HPV immunization program.

Candidate herpes simplex virus vaccine prevents HSV-1 genital disease

Belshe et al. Efficacy results of a trial of a herpes simplex vaccine. N Engl J Med *2012;366:34-43.*

A candidate vaccine against herpes simplex was not efficacious overall in a cohort of herpes simplex virus (HSV)-1 and HSV-2-seronegative women but it was reasonably effective in the prevention of HSV-1 genital disease and infection which has important public health implications.

Dr. Robert Belshe, Saint Louis University, St. Louis, Missouri, and multicentre colleagues involved in the Herpevac Trial for Women conducted a randomized, double-blind efficacy field trial involving 8323 women 18 to 30 years of age who were negative for antibodies to both HSV-1 and HSV-2 on study enrolment. "At months 0, 1 and 6, some subjects received the investigational vaccine," investigators noted. The candidate vaccine was an HSV-2 vaccine that contains 20 µg of truncated glycoprotein D from HSV-2 strain G combined with an adjuvant. Regarding the primary end point, 2 doses of the HSV vaccine did not effectively prevent genital disease caused by either HSV-1 or HSV-2, with an overall vaccine efficacy of 20%, as the authors observed. Yet the vaccine was 58% effective after 2 doses against genital disease caused by HSV-1. As investigators explained, HSV-1 was a more common cause of genital disease in the control group than HSV-2. Furthermore, 3 doses of the candidate vaccine were 77% efficacious against HSV-1 disease but not against HSV-2 disease, at an efficacy rate of -40%. Solicited reports of adverse events included redness, swelling and pain at the injection site as well as fatigue, fever, headache and malaise.

As the authors noted, a small cohort with HSV-2 infection collected anogenital swabs on 60 consecutive days beginning 3 to 6 months after disease onset. "Analysis of these swabs showed that the rate of viral shedding was higher among the HSV vaccine recipients than among controls (29% vs. 19%)," they stated, although the mean quantity of HSV DNA on days with shedding did not differ between the 2 groups. Interestingly, the HSV vaccine was immunogenic and was able to stimulate neutralizing antibodies.

Geometric mean gD-2 ELISA titres were 21 at baseline and 6809 at month 7 after 3 doses of the HSV vaccine; however, titres waned to 769 by month 20. HSV-2 neutralizing antibodies also developed after 2 doses of the vaccine but the median value fell to an undetectable level by study month 6 and again to undetectable levels after the third dose by study month 16.

As investigators acknowledged, "Our findings of vaccine efficacy against HSV-1 and lack of efficacy against HSV-2 are puzzling," given that previous studies showed the same gD-2 vaccine against HSV-2 was efficacious. They suggested that this difference in efficacy might be due to some factor in the populations studied. "Attack rates of HSV-2 genital disease in the prior studies of the gD-2 vaccine were high among uninfected women in discordant couples (13.9% for 19 months or 8.4% per year)," they noted, and were reduced by over 70% in previous trials. Nevertheless, the efficacy of the gD-2 candidate vaccine against HSV-1 seen in the current study is important, they added, because studies suggest that sexual transmission of HSV-1 is increasing in the US: it is the most common cause of genital herpes in college students and young heterosexual women, rivalling HSV-2 as a cause of neonatal herpes disease.

Fewer small-for-gestational age infants and higher mean birth weights in pregnant mothers vaccinated against the influenza season

Steinhoff et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ *2012;184(6):645-53.*

The proportion of small-for-gestational age infants born to mothers who received the influenza vaccine during a period when the virus was circulating was lower and the mean birth weight was greater than in controls who received the pneumococcal vaccine, according to a randomized controlled trial.

Dr. Mark Steinhoff, University of Chicago, Illinois, and multicentre colleagues carried out a secondary analysis of data from the Mother's Gift project involving 340 pregnant women in Bangladesh who received either inactivated influenza vaccine or the 23-valent pneumococcal polysaccharide vaccine as a control. "The study was performed from August 2004 through to December 2005," the authors noted. "We performed a secondary analysis of outcomes following maternal influenza immunization during 2 periods: when influenza virus was not circulating (September 2004 through January 2005) and when influenza virus was circulating (February through October 2005)."

As they reported, during the period with limited virus circulating, the proportion of infants who were small for gestational age was similar at 29.1% for the vaccine group vs. 34.3% for the control group. "In contrast, during the period with circulating virus and increased clinical effect of the influenza vaccine, the proportion of infants who were small for gestational age was 25.9% in the influenza vaccine group and 44.8% in the control group"—a 57% reduction in the risk of the small-for-gestational-age end point in favour of the influenza vaccine, as they noted.

Again during the period of limited circulating virus, the mean birth weight in the influenza vaccine group at 3053 g vs. 3083 g in the control group was not significantly different. In contrast, during the period with circulating virus, the mean birth weight in the influenza vaccine group at 3178 g was 7% higher than the mean birth weight of 2978 g in the control group, they added. Since the overall absolute reduction in the proportion of infants who were small for gestational age was 0.1, every 10 maternal influenza immunizations prevents the birth of 1 small-for-gestational-age infant. The number needed to vaccinate to prevent 1 small-for-gestational-age birth is 6 during the period when the local influenza virus is circulating.

"We found that immunization against influenza during pregnancy had a substantial effect on mean birth weight and the proportion of infants who were small for gestational age but only during the period of increased circulating influenza virus in the community," investigators observed. "Our data suggest that the prevention of infection with seasonal influenza in pregnant women by immunization can influence fetal growth."

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Canadian physician acceptance of new vaccines

Dubé et al. Clinicians' opinions on new vaccination programs implementation. Vaccine *2012;30:4632-7.*

According to a recent survey of pediatricians and family physicians, Canadian physicians appear to be overwhelmingly in favour of most of the new vaccines, with the exception of vaccines against rotavirus infection and the human papillomavirus (HPV).

Dr. Ève Dubé, Institut national de santé publique du Québec, Québec City, and multicentre colleagues assessed clinicians' opinions regarding new vaccines in a survey involving 1283 physicians from across most provinces. Responses to 8 statements regarding the frequency and severity of diseases, the efficacy and safety of the vaccine and the feasibility of immunization programs were scored; responses were divided into "strongly agree or agree" and all others. "Almost all respondents strongly agreed (74%) or agreed (23%) that vaccines generally recommended by public health authorities are very useful," investigators reported.

However, this proportion varied depending on which vaccine was being assessed, from 77% for the seasonable influenza vaccine to 99% for the DCaT-IPV-Hib vaccine. Over three-quarters of respondents indicated that they felt it was important to vaccinate children against moderately severe but frequent disease whereas 91% felt it was important to vaccinate them against very severe but rare disease. With the exception of the HPV and rotavirus vaccines, "more than 75% of respondents strongly agreed or agreed that the health and economic burdens of diseases prevented by new vaccines were important and more than 90% considered new vaccines to be safe and effective," investigators added.

More than 70% of respondents also felt that the new vaccines would be or are currently well accepted by the public; the exceptions again were the HPV and rotavirus vaccines where less than one-third of physicians strongly agreed or agreed that either vaccine was accepted by the public.

Physicians' intention to recommend new vaccines to their patients also varied from 52% for the rotavirus vaccine to 95% for the MMRV vaccine. These intentions were associated with perceived acceptability of the vaccines by vaccine providers, self-assessed sufficiency of knowledge of the vaccines and perceived acceptability of the vaccines by the public.

As the authors discussed, Canadian nurses and family physicians have shown a lower level of support for the rotavirus vaccines with fewer than half having a strong intention to recommend them to their patients. "The fact that rotavirus vaccination is not getting a high level of support among health professionals could be explained, at least partially, by the fact that rotavirus diseases nearly never result in long-term sequelae or death in Canada," the authors suggested.

HPV vaccines in turn came out in sixth position out of the 7 vaccines assessed, despite the fact that publicly funded HPV vaccination programs were in place in all Canadian provinces at the time of the study. As the authors noted, HPV vaccines were perceived by physicians as less safe and less effective than other new vaccines and their perception of the acceptability of the HPV vaccines by the public was also very low. Negative media attention may well have helped shape their opinion of public acceptance of the HPV vaccines, but it may again be partially explained by lack of familiarity with these vaccines due to the fact that they are administered through school-based programs.

"The social and professional demand and acceptability for new vaccination programs is a very powerful argument for decision-makers at the political level," investigators observed, "and without health professional support, the introduction of new vaccination programs may be unsuccessful."

Over 90% of survey respondents also felt that currently recommended vaccination schedules should be uniform across Canada and the majority indicated they would like to see money invested to develop and implement a National Vaccination Registry. □

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http://eci-glasgow2012.com/

International Conference on Allergy and Immunology
October 8-9, 2012 / Dubai, UAE
http://www.waset.org/conferences/2012/dubai/icai/

Infectious Diseases Week 2012
October 17-21, 2012 / San Diego, California
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