July-September 2010

VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Quadrivalent HPV vaccine: strong, sustained protection against low-grade lesions

Dillner J and the FUTURE I/II Study Group. Four-year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low-grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ *2010;341:c3493.*

According to a longer-term follow-up of two pivotal trials, the quadrivalent human papillomavirus (HPV) vaccine provides strong and sustained protection for up to four years against condyloma and low-grade cervical and vulvovaginal intraepithelial neoplasia related to HPV types 6, 11, 16 and 18. Dr. Joakim Dillner, Lund University, Malmö, Sweden, and multicentre colleagues carried out a combined analysis of the FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical Disease) I and II trials, focusing on the efficacy of the quadrivalent HPV vaccine in preventing low-grade cervical and vulvovaginal lesions (grade I neoplasia and condyloma) after an average of 42 months of follow-up. "We also sought to describe the proportion of the low-grade disease burden that can be prevented by vaccination against HPV types 6, 11, 16 and 18," researchers added.

In the FUTURE I and II trials, a total of 17,599 females between the ages of 16 and 26 years were randomized to the quadrivalent vaccine or placebo. The day 1 prevalence for one or more of the HPV vaccine types was 14.7% by polymerase chain reaction and 19.8% by serology.

In the per-protocol susceptible population (the only population that received all three doses), the vaccine was 96% effective against the four HPV types of grade 1 cervical intraepithelial neoplasia (CIN 1). Stratified by HPV type, vaccine efficacy against CIN 1 ranged from 94% for HPV 16 to 100% for HPV 6 and 11. There were no cases of vulvar or vaginal intraepithelial neoplasia (VIN/VaIN) attributable to HPV vaccine types, for an efficacy of 100% against these low-grade neoplasias. Two cases of condyloma attributable to vaccine HPV types (both HPV 6) were documented among vaccine recipients vs. 190 cases in placebo females, giving a vaccine efficacy of 99%. Of note, HPV types 6 and 11 were found in 98% of condyloma among placebo recipients.

"As expected, compared with the per-protocol susceptible population... more cases of low-grade CIN or VIN and condyloma were documented in the unrestricted susceptible and intention-to-treat [ITT] populations," the authors observed.

The vaccine remained statistically significantly effective for all four disease end points, ranging from 90% for VIN to 100% for VaIN in the unrestricted susceptible population, and from 69% for CIN 1 to 83% for VaIN in the ITT population.

Regardless of HPV type, the vaccine was 30% effective in the generally HPV-naive population against CIN 1, 75% effective against VIN grade 1, 48% effective against VaIN 1 and 83% effective against condyloma. Corresponding efficacy in the ITT population was 20% against CIN 1, 32% against VIN 1, 31% against VaIN 1 and 62% effective against condyloma. As the authors observed, efficacy against low-grade HPV-related lesions is important to document for several reasons. "Firstly, these lesions occur shortly after infection, and a reduction in these lesions will be the earliest clinically noticeable health gain to be realized by HPV vaccination," they reported. Additionally, condyloma and CIN 1 occur at "substantially higher" rates than CIN 2/3 and the absolute number of cases of CIN 1 prevented by vaccination is expected to be very high when vaccine coverage is high. The data also provide "important confirmatory evidence" of the proportion of low-grade disease that is positive for HPV types 6, 11, 16 or 18, investigators noted.

Low-grade cervical and vulvovaginal lesions are important from a public health perspective as the diagnosis, follow-up and treatment of these common lesions are associated with substantial patient anxiety, morbidity and health care costs. "The high incidence of low-grade disease seen in the placebo group and the estimated benefits of vaccination on total disease burden, regardless of HPV type, suggest that an important portion of the clinical benefit seen in the early years after deployment of the quadrivalent HPV vaccine will be through reductions of CIN 1 and condyloma," the authors concluded.

Herpes zoster vaccine safe, effective in patients with HZ history

Mills et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. Vaccine *2010;28(25):4204-9.*

The pivotal Shingles Prevention Study demonstrated that a single dose of the HZ vaccine reduced the incidence of HZ by 51%, post-herpetic neuralgia by 67% and the burden of illness associated with HZ pain by 61% in adults ≥60 years of age vs. placebo controls.

New findings confirm that the herpes zoster (HZ) vaccine is safe and effective in patients with a prior history of HZ, thereby supporting the Advisory Committee on Immunization Practices' (ACIP) recommendation for routine zoster vaccination in all immunocompetent patients ≥60 years of age irrespective of their HZ history. Dr. Richard Mills, Palmetto Medical Research, Mount Pleasant, South Carolina, and colleagues evaluated the safety and immunogenicity of the zoster vaccine in patients ≥50 years of age who reported a previous episode of HZ. As the

FEATURING SELECTED SUMMARIES FROM:

BMJ: *www.bmj.com/*

Vaccine: *www.sciencedirect.com*

J Adolesc Health: *http://jahonline.org*

authors pointed out, this patient group is usually excluded from clinical trials so there is very limited data on vaccine efficacy in this particular population.

A total of 101 recipients, mean age approximately 68 years, were randomized to receive the vaccine initially on day 1 (group I) followed by placebo at week 4 while group II received placebo initially followed by the vaccine at week 4. "Subjects were followed for adverse experiences [AEs], exposure to varicella or HZ and development of any varicella/varicella-like or HZ/HZ-like rashes, for 28 days after each injection," investigators stated. "Blood samples were obtained prior to study injection on day 1 and week 4, and at week 8." Patients were also stratified by time since prior HZ episode: either five to nine years or ≥10 years.

As investigators reported, the estimated geometric mean titre (GMT) ratio (vaccine:placebo) was 2.07 while the geometric mean fold-rise (GMFR) from prevaccination to week 4 post-vaccination was 2.1 in zoster vaccine recipients vs. 1.0 among placebo recipients. "No subjects reported a serious AE during the 28-day safety follow-up period post-vaccination," investigators noted, "and no subjects discontinued due to an AE." The proportion of participants reporting systemic AEs was similar between the two groups and low following receipt of either the vaccine or placebo. As the authors discussed, this particular group of individuals with a prior HZ episode had numerically higher baseline varicella-zoster virus (VZV) antibody levels, on average, than patients enrolled in the Shingles Prevention Study who had not experienced a prior HZ episode.

Baseline GMTs in vaccine recipients whose previous episode of HZ was at least 10 years ago were also numerically lower than GMTs in recipients who had a shorter interval between their prior episode and vaccination, "suggesting that the strong boost in VZV-specific immune response provided by an HZ episode continues to wane over time," investigators observed. Conversely, the VZV GMFR from prevaccination to week 4 post-vaccination was higher in the zoster vaccine group than in placebo recipients regardless of time since prior HZ episode or age. Consistent with previous studies, those between the ages of 50 and 59 years had a greater GMFR than those who were ≥60 years of age.

Majority of physicians involved in HPV vaccination in females recommending vaccination for males

Weiss et al. Human papillomavirus vaccination of males: attitudes and perceptions of physicians who vaccinate females. J Adolesc Health *2010;47(1):3-11.*

Results of a large survey of US-based practitioners showed that >90% of pediatricians and family physicians involved in vaccinating females against human papillomavirus (HPV) would also recommend the vaccine for males between the ages of 13 and 18 years as well as those from 19 to 26 years of age.

Dr. Thomas Weiss, West Point, Pennsylvania, and multicentre colleagues sought to evaluate the attitudes of US-based physicians towards vaccinating males and whether they would recommend the vaccine to their male patients. Surveys were distributed to a stratified random sample of 2714 eligible physicians, from which investigators received 1158 responses. Some 1094 surveys were included in the final analysis, including 595 from pediatricians and 499 from family practitioners. A slightly higher proportion of pediatricians participated in the survey than family practitioners but nearly equal numbers of male and female physicians responded.

Virtually all respondents agreed that males are at risk for HPV infection and that genital and anal warts can cause serious physical, emotional and financial consequences for male patients. "Likewise," investigators added, "most agree that HPV infection may contribute to anal, penile or head and neck cancers in males." Most physicians also strongly agreed or somewhat agreed that males should be vaccinated to prevent them from getting genital and anal warts and that it would be important to vaccinate males to prevent them from getting anal and penile cancers. "Consistent with this," the authors stated, "physicians disagreed [35.8% strongly and 31.7% somewhat] that HPV causes too few cancers among males to make it worthwhile to vaccinate them."

Most survey participants also disagreed with the statement that vaccinating males does not make sense because genital and anal warts can be managed in other ways. Similarly, most physicians either strongly or somewhat disagreed with the statement that it is too late to vaccinate against HPV if an adolescent male is already sexually active. Regarding why they agreed that males should be vaccinated, the overwhelming majority of respondents indicated that males should be vaccinated to protect their future partners from cervical cancer and other consequences of HPV as well as to prevent females from getting infected with HPV.

In contrast, they again overwhelmingly disagreed with the statement that there is no need to vaccinate males as well as females because females are already being vaccinated against HPV. The majority (97.8%) also recommended HPV vaccination for females between the ages of 13 and 18 years while only about 18% recommended it for 9- to 10-year-old girls.

A similar pattern was seen for recommendations to males, with over 93% of respondents indicating that they would recommend it for boys between the ages of 13 and 18 years but only about 24% indicated that they would recommend vaccination for boys between 9 and 10 years of age. Among the other benefits that physicians saw in recommending the HPV vaccine for males is that it would represent an opportunity to discuss sexual health with their adolescent male patients and/or their parents, especially at any earlier age.

Survey respondents did not have strong opinions on how a "gender-neutral" vaccine recommendation would affect attitudes towards and acceptance of HPV vaccination. They were also ambivalent about whether a gender-neutral vaccination program would improve female vaccination rates or make it easier for them to recommend the vaccine to girls. As the authors pointed out, a "novel finding" of this survey was that significantly more physicians would recommend the HPV vaccine to boys between the ages of 9 and 10 years than girls in the same age group. Although this may be because physicians believe males become sexually active at an earlier age than females, "It may also be related to physicians' belief in the direct benefits of HPV vaccination of males, that is, protection against genital warts and anogenital cancers," the authors suggested.

Immune memory against tetanus toxoid does not persist

Posfay-Barbe et al. Frequency failure of adolescent booster responses to tetanus toxoid despite infant immunization: waning of infancy-induced immune memory? Vaccine *2010;28(27):4356-61.*

Immune memory elicited by infant immunization against tetanus toxoid (TT)—one of the most potent of all vaccine antigens—did not persist at a sufficient level to allow reactivation by a single booster in most 10- to 15-year-old students, according to a multicentre study. Dr. Klara Posfay-Barbe, University Hospitals of Geneva, Switzerland, and multicentre colleagues recruited children from nine classes in four primary schools and four classes in secondary schools to whom they administered a TT booster.

A total of 381 healthy students were enrolled and immunization records indicated that 89.5% of them had received at least one dose of the infant diphtheria-tetanus-pertussis (DTP) vaccine. The primary cohort for the analysis included adolescents who had three recorded doses of infant DTP. In this cohort, baseline anti-TT antibodies were low and >92% of them had very low anti-TT concentrations of <0.10 IU/mL.

One week after a single booster, mean anti-TT concentrations had increased by over elevenfold. Nevertheless, only slightly over half (55%) of this group of adolescents who had three recorded doses of the infant DTP achieved the 0.10 IU/mL threshold which is protective against tetanus infection. Fewer than half (46%) of the same group responded to the tetanus booster with a fourfold or greater increase in their anti-TT concentrations. Among adolescents who had received only one recorded dose of infant DTP, 94% had <0.10 IU/mL baseline titres. One week after receiving their booster vaccination, anti-TT GMTs were similar to those of the primary cohort, where approximately 48% achieved protective antibody levels.

As for the younger cohort of children between 10 and 11 years of age, 97% of those who had three recorded doses of infant DTP still had anti-TT <0.10 IU/mL prior to boosting. One week following the booster, 53% achieved anti-TT concentrations >0.10 IU/mL. As the authors pointed out, the low anti-TT antibody levels seen in most adolescents primed with DTP in infancy was not unexpected, as the duration of immunity after a three-dose primary infant vaccination regimen was calculated to be only about five years.

In contrast, "We did not expect that such a large proportion of infant-primed adolescents would fail to raise anamnestic responses to a TT booster," investigators noted, "[to the point where] half of the participants did not generate anamnestic responses after boosting." The observation that boosting failed to reactivate infant-driven anti-TT immune responses in most adolescents, in fact, runs against the current belief that immune memory is lifelong, they added.

It also contradicts current official national and international recommendations which state that booster responses can still be elicited after intervals of 25 to 30 years, demonstrating the persistence of immunological memory.

"As the risk of tetanus persists lifelong, concluding that infant immunization with a vaccine as potent as TT may not induce immune memory persisting at a sufficient level to be reactivated 10 to 15 years later provides strong support to the recent World Health Organization recommendation to implement childhood DTP boosters," the authors concluded, "and it indicates that such boosters should be given prior to the waning of immune memory."

Nasal spray prevents viral respiratory infections in high-risk military recruits

Gao et al. A randomized controlled trial of low-dose recombinant human interferons alpha-2b nasal spray to prevent acute viral respiratory infections in military recruits. Vaccine *2010;28:4445-51.*

A novel recombinant human interferon nasal spray has been shown to prevent a variety of common acute viral respiratory infections in military recruits who are at high risk for acute respiratory tract infections, according to results of a randomized controlled trial carried out in China.

Dr. Lulu Gao, Southern Medical University, Guangzhou, and colleagues from the China Center for Disease Control and Prevention, Beijing, carried out the study during the basic training period of new military recruits at 12 recruit training units located in different districts in China. In each unit, there were from 120 to 150 new recruits, eight to 10 recruits per barrack (30 m2) where they resided during their three-month training interval. A total of 721 recruits were randomized to the experimental group where they received a newly developed low-dose recombinant human interferon a-2b (rIFNa-2b) twice daily for five consecutive days.

The control group (n=728) received placebo formulation of the nasal spray. ELISA assays were used to test IgM antibodies against adenovirus species B (ADV), respiratory syncytial virus (RSV), influenza A virus (Flu-A), influenza B virus (Flu-B) and parainfluenza viruses 1-3 (PIV 1-3).

In the per protocol analysis, the nasal spray was found to prevent approximately 60% of infections caused by ADV, 72% of infections due to RSV and at least 75% of infections due to Flu-A, Flu-B and PIV 1-3. All reductions were significantly relative to placebo except for infections caused by RSV. In the intent-to-treat analysis, the same rIFNa-2b nasal spray afforded similar protection rates at approximately 60% against ADV, approximately 72% against RSV and at least 75% against Flu-A, Flu-B and PIV 1-3. The number needed to treat to prevent one case of ADV-related infection was 24 but was much lower at between seven and nine to prevent one episode of respiratory infection from either Flu-A, Flu-B or PIV 1-3.

"No participants withdrew from the trial due to intolerance of the spray," the authors observed, "and on the whole, the intranasal rIFNa-2b with relative low-dose and short-term administration [1.8 x 106 IU daily for five days] was well tolerated."

Protective antibody levels against hepatitis A/B persist out to five years

Marshall et al. Long-term (5-year) antibody persistence following two- and three-dose regimens of a combined hepatitis A and B vaccine in children aged 1 to 11 years. Vaccine *2010;28(27):4411-5.*

A long-term follow-up study of the persistence of antibodies against hepatitis A (HAV) and hepatitis B (HBV) following primary vaccination with either a two- or three-dose regimen of the combined hepatitis A and B vaccine indicates that protective antibody levels persist in most recipients out to five years.

Dr. Helen Marshall, University of Adelaide, Australia, and multicentre colleagues evaluated the long-term persistence of anti-HAV and anti-HBV antibodies in study participants who had received either three doses of the pediatric formulation or two doses of the adult formulation of the combined hepatitis A and B vaccine at the ages of 1 to 11 years. "The study was also designed to evaluate the persistence of immune memory to the HAV and HBV antigens in subjects whose antibody concentrations had dropped below 15 mIU/mL for HAV and 10 mIU/mL for HBV," the authors added. A total of 511 subjects participated in the primary study which concluded in July 2002.

At the end of five years, 206 subjects were included in the long-term immunogenicity cohort. "One month after the completion of the primary vaccination course, all subjects in both groups had anti-HAV antibody concentrations ≥15 mIU/mL," investigators observed. Following primary vaccination, antibody concentrations decreased "relatively fast" in the first year of follow-up, then gradually levelled off. Nevertheless, even at the end of five years, 100% of subjects in both the three- and the two-dose groups continued to have anti-HAV antibodies ≥15 mIU/mL.

Anti-HBV antibody concentrations ≥10 mIU/mL were also seen in 94.1% of the two-dose group and 97% in the

three-dose group at the same five-year end point. "None of the subjects included in this study became seronegative for anti-HAV antibodies and only a small minority reached anti-HBV antibody concentrations <10 mIU/mL," the authors added.

In order to evaluate whether these subjects still retained immune memory to the HBsAg, they were given a challenge dose of the HB vaccine. One month later, an anamnestic response was observed in all subjects in both dose groups.

"The results of the present long-term follow-up studies confirm that good long-term immunogenicity is also induced by the two-dose schedule," the authors concluded. "The advantages of good safety, immunogenicity and long-term immune memory with a lesser number of injections makes the combined hepatitis A and B vaccine [adult formulation] in a two-dose regimen an effective intervention for prevention of HAV and HBV diseases."

Influenza vaccine uptake low in UK future health care workers

Blank et al. Influenza vaccination of future healthcare workers: a cross-sectional study of uptake, knowledge and attitudes. Vaccine *2010;28(29):4668-72.*

Uptake of the influenza vaccine among future health care workers (HCWs) in the UK is extremely low and falls drastically short of government targets set for HCWs who have contact with patients.

Dr. Debra Blank, University of Birmingham, UK, and colleagues assessed influenza vaccine uptake in future HCWs and compared it to vaccine uptake among current HCWs. "We conducted a cross-sectional survey among future HCWs for the season 2008 to 2009 at the College of Medical and Dental Sciences at the University of Birmingham, West Midlands, and selected participants to represent a population of future HCWs who have direct patient contact and therefore who are eligible to receive the influenza vaccination," investigators noted. Specifically, undergraduates were chosen from every year of medicine, nursing, physiotherapy and dentistry and were classified into "pre-clinical" and "clinical" groups depending on their exposure to patients.

Out of 519 returned questionnaires, investigators determined that only 8% of future HCWs were vaccinated against influenza during the 2008 to 2009 season. The best uptake rate was seen in future nurses (12.7%) followed by future physiotherapists (8.2%), future doctors (8.1%) and future dentists (0%). Slightly <4% of pre-clinical students and slightly >10% of clinical students indicated they had received the influenza vaccine in the previous season. Uptake rates in future HCWs were even lower than uptake rates among current HCWs where, over the 2007 to 2008 campaign, 13.4% reported they received the influenza vaccine.

In contrast, vaccination uptake among future nurses was higher (12.7%) than that reported for current nurses (11.1%). As investigators pointed out, knowledge about influenza vaccination among future HCWs was high, with about three-quarters of respondents being able to correctly identify specific knowledge about influenza morbidity and mortality and almost all of them about its infectivity.

Despite this, "Uptake was low, suggesting that knowledge alone is insufficient in encouraging HCWs to get vaccinated," the authors noted. "This suggests the need for promotional campaigns to emphasise directly the importance of vaccination in terms of personal and patient protection and to eliminate misconceptions about the vaccine." □

UPCOMING EVENTS

American Academy of Pediatrics National Conference
October 2-5, 2010/San Francisco, California
http://www.aapexperience.org/

48th Annual Meeting of the Infectious Diseases Society of America
October 21-24, 2010/Vancouver, British Columbia
http://www.idsociety.org/IDSA2010.htm

59th Annual Meeting of the American Society of Tropical Medicine and Hygiene
November 3-7, 2010/Atlanta, Georgia
http://www.astmh.org/home.htm

9th Canadian Immunization Conference
December 5-8, 2010/Quebec City, Quebec
http://www.publichealth.gc.ca/immunconf/2010

Your feedback is important to us!

Please take a moment to return the enclosed postage-paid business reply card with your comments.

Thank you!