



VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

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Malaria vaccine halves clinical, severe disease in African children

The RTS,S Clinical Trial Partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011 Oct 18.

A candidate vaccine against malaria has been found to reduce clinical episodes of malaria and severe malaria by approximately half during 12 months of follow-up in children between 5 and 17 months of age, according to ongoing findings from the RTS,S Clinical Trials Partnership.

"From March 2009 through January 2011, we enrolled 15,460 children in 2 age categories—6 to 12 weeks of age and 5 to 17 months of age—for vaccination with either RTS,S/AS01 or a non-malaria comparator vaccine," investigators explained. The trial included 3 study groups in each age category: children who received all 3 doses of the RTS,S/AS01 vaccine at 1-month intervals and a booster dose at 18 months; those who received the RTS,S/AS01 primary vaccination series without a booster; and a control group who received a non-malaria comparator vaccine. Children 5 to 7 months were given the rabies vaccine as a control, while those between 6 and 12 weeks were given a meningococcal serogroup C conjugate.

During 12 months of follow-up in the first 6000 children in the older age category, the incidence of the first or only episode of clinical malaria was 0.44/person-year in the malaria vaccine groups vs. 0.83/person-year in the control group for a vaccine efficacy of 55.8%. Vaccine efficacy against all clinical malaria episodes was 55.1%, they added. "Among children in the combined age categories, at least 1 episode of severe malaria... occurred in 149 of 8597 children or 1.7% of the RTS,S/AS01 groups vs. 116 of 4364 children or 2.7% in the control group," investigators observed, for a vaccine efficacy against severe malaria in the pooled age categories of 34.8%. The mean follow-up was 18 months in the older age group after the first dose of study vaccine and 9 months in the younger age group.

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Serious adverse events occurred in 17.6% of the older RTS,S/AS01 age group vs. 21.6% for the control group and 13.1% and 13.4% of the younger RTS,S/AS01 and control groups, respectively. The incidence of generalized convulsive seizure within 7 days after vaccination was 1.04/1000 doses in the malaria vaccine group and 0.57/1000 doses in the control group receiving rabies vaccine for a risk ratio of 1.8. "All seizures occurred in children with a history of fever," investigators pointed out.

In the younger age group, the incidence of generalized convulsive seizures within 7 days after vaccination was 0.16/1000 doses in the malaria vaccine group and 0.47/1000 doses in the control group receiving meningococcal vaccine for a risk ratio of 0.3. Malaria-specific mortality was very low in the trial. It is noteworthy that level of protection provided by the RTS,S/AS01 vaccine among the older age group was lower at the end of the 12-month surveillance period than shortly after vaccination.

Vaccine efficacy will be presented for the younger age category in approximately 1 year after the first 6000 children in that age category have completed 12 months of follow-up.

Quadrivalent HPV vaccine reduces AIN rates, condyloma in men

Palefsky et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011;365:1576-85.

Anic et al. Incidence and human papillomavirus (HPV) type distribution of genital warts in a multinational cohort of men: The HPV in Men study. J Infect Dis 2011;204:1886-92.

The quadrivalent human papillomavirus (qHPV) vaccine has been shown to reduce rates of anal intraepithelial neoplasia (AIN), including grade 2 or 3 AIN, among men who have sex with men (MSM) in a substudy of a large randomized, placebo-controlled trial involving both heterosexual males and MSM.

Dr. Joel Palefsky, University of California at San Francisco, and multicentre colleagues enrolled 3463 heterosexual men and 602 MSM into the study between September 3, 2004, and August 29, 2008. Vaccine efficacy was measured in the per-protocol population (PPP), i.e. subjects who were seronegative and had HPV DNA-negative swab and biopsy specimens at day 1 for relevant vaccine types; were negative for vaccine-type DNA through month 7; and did not violate the protocol. The intent-to-treat (ITT) population consisted of those who were or were not seropositive or DNA-positive for vaccine HPV types on enrolment; who received at least 1 dose of vaccine or placebo; and who returned for follow-up.

"The prespecified primary efficacy end point was HPV 6-, 11-, 16- or 18-related AIN or anal cancer," investigators noted.

Some 432 MSM or slightly less than 72% completed the 36-month follow-up, roughly two-thirds of whom were included in the PPP with a mean follow-up of 2.2 years after month 7. In this population, vaccine efficacy against HPV 6-, 11-, 16- or 18-related AIN was 77.5%. The vaccine was efficacious against both grade 1 AIN (including condyloma) at 73% and grade 2 or 3 AIN at 74.9%, the authors reported.

In the ITT population, vaccine efficacy against vaccine-type related AIN was 50.3% and 25.7% against AIN due to any HPV type. The authors also observed “significant reduction” in grade 1 AIN at 49.6% as well as grade 2 or 3 AIN at 54.2%. Significant reductions were also seen in persistent infection rates. In the PPP, there was a 94.9% reduction in persistent anal HPV 6, 11, 16 or 18 infection, while in the ITT population, the vaccine reduced persistent infection with the same 4 vaccine types by 59.4%.

No vaccine-related serious adverse events or death were reported in either group. “Our study suggests that qHPV vaccination could be a tool for preventing anal HPV-related disease, potentially even cancer,” investigators observed. As expected, there were no cases of anal cancer in this young cohort. “Just as prevention of cervical intraepithelial neoplasia of grade 2 or 3 is expected to reduce the risk of cervical cancer in vaccinated women, prevention of AIN grade 2 or 3 is expected to reduce the risk of anal cancer among vaccinees,” the authors remarked, adding that the vaccine also reduced the incidence of anal condyloma—a substantial added benefit of vaccination.”

As reported by Dr. Gabriella Anic, Moffitt Cancer Center and Research Institute, Tampa, Florida, and multicentre colleagues, the most common HPV types detected in newly acquired genital warts (GW) in another large-scale HPV in Men study were types 6 and 11. At baseline, almost 65% of men tested positive for HPV DNA on genital skin and 5% tested positive for HPV types 6 and 11.

Over a median follow-up of 17.9 months, 112 men out of 2487 developed incident GWs, some 13 of whom developed multiple warts. As the authors noted, HPV 6 and/or 11 was detected in slightly over 53% of the 112 incident GWs—HPV 6 in almost 44% of GWs and HPV 11 in almost 11%. All other HPV types were found in ≤10% of GWs, they added.

The overall incidence rate for a newly acquired GW was 2.35 cases/1000 person-years but the highest incidence rate was among men between the ages of 18 and 30 at 3.43 cases/1000 person-years. The 24-month cumulative incidence of GWs among men with incident HPV 6/11 infections was 14.6%. Furthermore, the time from an incident HPV infection to GW detection was significantly shorter at 6.2 months among men with HPV 6/11 infection vs. 18.2 months for men with an infection with types other than 6 and 11.

“This study is one of the first to examine progression from HPV infection to GW development including men from across the lifespan,” the authors wrote, “and HPV 6/11 appears to play an important role in GW development, with the highest incidence and shortest time to GW development observed among men with incident HPV 6/11 infection.”

Mortality due to rotavirus-related diarrhea in preschool children

Glass R, Patel M, Parashar U. Lessons from the US rotavirus vaccination program. *JAMA* 2011;306(15):1701-2.

Tate et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2011 Oct 24.

Each year, 1 in every 260 children dies from diarrhea caused by rotavirus infection by their fifth birthday, according to an updated estimate of the number of deaths caused by rotavirus (RV) infection worldwide.

Dr. Jacqueline Tate, and coworkers from the Centers for Disease Control and Prevention, Atlanta Georgia, in collaboration with the WHO-coordinated Global Rotavirus Surveillance Network, reviewed recently published work and data from the surveillance network to estimate the number of deaths in children <5 years attributable to RV infection in 2008. “Specimens from 151,172 children younger than 5 years in 65 countries were tested as part of 131 studies that met our inclusion criteria,” the authors noted. Based on these data, the authors estimated that worldwide RV-related diarrhea results in 453,000 deaths in children <5 years each year. This accounts for 37% of diarrhea-related deaths and 5% of all deaths in this age group, they added. The greatest proportion of deaths from RV-related diarrhea was in India, where the authors estimated that 99,000 children <5 years die from RV-related diarrhea each year.

“Introduction of effective and available RV vaccine could have a substantial effect on diarrhea-related deaths worldwide,” investigators concluded. A significant reduction in RV infections has already been documented in many countries where vaccine uptake has been widespread such as in the US.

The first new RV vaccine was licensed in 2006; by 2010, nearly 60% of American children between 19 and 35 months of age had been immunized against RV, as noted by Dr. Roger Glass, National Institutes of Health and CDC colleagues in Bethesda, Maryland. Already in 2008, the number of RV detections by the CDC surveillance program had decreased by 64%, while hospitalizations for acute gastroenteritis declined by 45% during the 2008 winter RV season, averting approximately 50,000 hospitalizations nationwide. “An unanticipated finding was that hospital admissions for diarrhea also declined among unvaccinated individuals aged 5 through 24 years, suggesting that the vaccine was having a herd effect,” the authors reported.

A series of recent independent regional studies have also documented an 85% to 90% reduction in hospital admissions and visits to emergency departments following introduction of the RV vaccines. In Mexico, use of RV vaccines for only 3 years has reduced the number of deaths due to childhood diarrhea by about 700 per year, “reaffirming the life-saving potential of these vaccines,” as the authors observed.

WHO recommends routine use of RV vaccines in all countries, particularly in those individuals with high mortality attributable to diarrheal disease.

Introduction of PCV7 and PCV13 conjugate vaccines predicted to reduce overall AOM episodes

Shea et al. Modeling the decline in pneumococcal acute otitis media following the introduction of pneumococcal conjugate vaccines in the US. *Vaccine* 2011;29:8042-8.

Introduction of the pneumococcal conjugate vaccines PCV7 and PCV13 in the US is predicted to reduce the proportion of children colonized with *Streptococcus pneumoniae* who would develop pneumococcal acute otitis media (AOM) by variable degrees.

Analyses by Dr. Kim Shea, Boston University School of Public Health, Massachusetts, and multicentre colleagues indicate that during the pre-PCV7 vaccine period, 31% of children colonized

with *S. pneumoniae* would have developed an episode of pneumococcal AOM based on the distribution and invasive potential of *S. pneumoniae* serotypes at that time. A change in the serotype distribution from primarily vaccine-specific type (VST) to non-VSTs (NVSTs) in 2007 caused this proportion to decrease to 27%; using a predicted serotype distribution for 2013 further decreased this proportion to 20%.

"These decreases in the proportions of colonized children who develop AOM following pneumococcal colonization correspond with a 12% reduction in the number of episodes of pneumococcal AOM in 2007 compared with 2000, and an additional 27% reduction from 2007 to 2013," the authors observed. Furthermore, the proportion of PCV7-VST AOM cases among all pneumococcal AOM episodes decreased from 62% in 2000 to 5.5% in 2007, "corresponding to a 91% decrease in the proportion of PCV7-VST from 2000 to 2007," investigators stated. This decrease was offset by an increase in AOM episodes caused by NVST pneumococci, they added.

NVST organisms were estimated to cause only 38% of pneumococcal AOM episodes in 2000 compared with 95% of all pneumococcal episodes in 2007, or a 151% increase in the percentage of pneumococcal AOM attributable to NVT pneumococci during this time period. As the authors noted, if colonization with PCV13 serotypes and serotype 6C similarly decline and the remaining non-PCV13 serotypes proportionally increase as predicted by their model, "we estimate that universal PCV13 vaccination will further decrease the proportion of children colonized with *S. pneumoniae* who would develop pneumococcal AOM an additional 27% and PCV13-VST and serotype 6C-AOM an additional 65%," the authors stated. They added that such a reduction would result in an approximately 35% decrease in pneumococcal AOM and an 11 to 16% decrease in all-cause AOM from 2000 to 2013, assuming that 30 to 45% of AOM is due to *S. pneumoniae*.

ACIP policy expansion of routine influenza vaccination reduces pediatric hospital visits

Hoen et al. Effect of expanded US recommendations for seasonal influenza vaccination: comparison of two pediatric emergency departments in the United States and Canada. CMAJ 2011; 183(13):E1025-E32.

King Jr, et al. Direct and indirect impact of influenza vaccination of young children on school absenteeism. Vaccine 2011 Nov 12.

Expansion of the US Advisory Committee on Immunization Practices (ACIP) policy in 2006 to include children between the ages of 2 and 4 years for routine influenza vaccination led to an estimated 34% decline in influenza-like illness visits to a pediatric hospital in Boston, relative to a pediatric hospital in Montréal starting in the 2006-2007 influenza season.

Research fellow Anne Gatewood Hoen, PhD, Children's Hospital Informatics Program, Boston, Massachusetts, and colleagues examined data for the 2000-2001 through 2008-2009 influenza seasons to estimate the relative change in emergency department visits for influenza-like illness at 2 pediatric hospitals, Children's Hospital Boston and The Montreal Children's Hospital. Patterns of virologic isolates were similar between the 2 regions. "Of 1,043, 989 visits to the emergency departments of the 2 hospitals for any reason during the study period, 114,657 visits were related to influenza-like illness," the authors recorded.

The estimated 34% decline in rates of influenza-like illness among children between the ages of 2 and 4 in the Boston hospital relative to the Montréal hospital was accompanied by more modest but significant declines of between 11 and 18% for non-target age groups. In Canada, the National Advisory Committee on Immunization (NACI) did not recommend children between 2 and 4 years of age be routinely vaccinated against influenza until the 2010/2011 season and not all Canadian provinces have adopted their recommendation.

"Our findings provide evidence that, in our US study community [i.e. Boston], the recommendation of the ACIP to routinely vaccinate preschool-aged children against seasonal influenza is improving pediatric influenza-related outcomes, as evidenced by a reduction in emergency department visits, and this adds to existing evidence that broadening vaccination recommendations toward inclusion of young children reduces the number of influenza cases and associated complications," the authors concluded.

There is also evidence that special mass influenza vaccination programs targeting elementary school-aged children significantly decrease the usual rise in absenteeism seen in schools during influenza outbreaks. As reported by Dr. James King, Jr., University of Maryland School of Medicine, and Baltimore-based colleagues, during the fall seasons of 2005-2007, mass influenza programs reached between 3% to 46% of elementary school-aged children.

Results showed that for every 20% increase in vaccination rates during these special programs, there was an estimated 4% decrease in usual absenteeism rates in both elementary and upper schools during influenza outbreaks, "suggesting both direct and indirect benefits of influenza vaccination of young children," the authors observed.

Strong association between acute herpes zoster and family history of the disease

Hernandez et al. Family history and herpes zoster risk in the era of shingles vaccination. J Clin Virol 2011;52:344-8.

A strong association has been identified between acute herpes zoster and a family history of the disease, suggesting a genetic predisposition to develop herpes zoster is more pronounced than previously believed.

Dr. Paul Hernandez, University of Texas School of Medicine, San Antonio, and Texas-based colleagues carried out a case-control study involving 1103 patients with acute herpes zoster and 523 controls. "Case patients were more likely to report blood relatives with a history of herpes zoster than controls (43.5% vs 10.5%; $P<0.001$)," investigators reported.

Cases were also 6.55 times more likely than controls to report any relative including a first-degree and non-first-degree blood relative with a history of herpes zoster, they add. They also calculated an odds ratio of 5.24 for cases reporting a single relative with a history of herpes zoster and an odds ratio of 17.15 for cases reporting multiple relatives, suggesting a dose-dependent effect of having a blood relative with a history of herpes zoster.

The study also suggested that having a genetic predisposition to develop herpes zoster may be more frequently inherited from the mother. Of some 535 cases with recorded data designating a maternal or paternal family history, 20.9% reported a maternal blood relative vs 8.5% a paternal blood relative. Importantly as well, cases reported a lower mean age of herpes zoster onset at 51.7 years than has been previously reported—a "highly relevant" finding, as the authors pointed out, given the recent FDA approval

of the herpes zoster vaccine for individuals between 50 and 59 years of age (in Canada, the vaccine is approved for patients \geq 50 years old). In 2006, the herpes zoster vaccine was licensed in the US for the prevention of shingles and post-herpetic neuralgia.

As investigators note, emerging epidemiologic data and the identification of new risk factors will allow policy makers to tailor the herpes zoster vaccine for those most at risk for the disease.

Pharmacists effective at identifying, delivering pneumococcal vaccine

Taitel *et al.* *Pharmacists as providers: Targeting pneumococcal vaccinations to high risk populations.* Vaccine 2011;29:8073-6.

Pharmacists have been shown to be effective at not only identifying individuals at risk for pneumococcal disease but also at delivering the pneumococcal vaccine at a higher rate than that achieved by usual care.

Michael Taitel, Clinical Outcomes & Analytic Services, Walgreens Co., Deerfield, Illinois, and colleagues evaluated the impact of pharmacists educating at-risk patients on the importance of receiving pneumococcal vaccination. "Between August 1, 2010, and November 14, 2010, 2,095,748 patients received influenza immunizations at Walgreens, of which 1,343,751 persons met the ACIP (Advisory Committee for Immunization Practices) recommendation for PPSV (pneumococcal vaccination)," the authors recorded. Of these, 921,624 patients were at risk for pneumococcal disease because they were 65 years of age and older. The remaining 422,127 patients were at risk because they had 1 of the ACIP-defined comorbid conditions and were between 2 and 64 years of age.

Among the 1.3 million at-risk patients, 65,598 (4.88%) received a pneumococcal vaccine from a pharmacist. "This vaccination rate was significantly higher ($P<0.001$) than the benchmark rate of 2.9% representing traditional care," the authors noted, "and patients aged 60 to 70 years had the highest vaccination rate (6.6%) of any age group. Concurrent administration of PPSV and influenza vaccination by pharmacists has potential to improve PPSV coverage." □

UPCOMING EVENTS

19th Conference on Retroviruses and Opportunistic Infections

February 5-8, 2012 / Washington, Seattle
www.retroconference.org/

68th Annual Meeting of the American Academy of Allergy, Asthma and Immunology

March 2-6, 2012 / Orlando, Florida
<http://annualmeeting.aaaai.org/>

8th International Conference on Emerging Infectious Diseases

March 11-14, 2012 / Atlanta, Georgia
www.iceid.org/

8th International Symposium on Pneumococci and Pneumococcal Diseases

March 11-15, 2012 / Iguaçu Falls, Brazil
www2.kenes.com/isppd2012/Pages/home.aspx

22nd Annual Meeting of the Society for Virology

March 14-17, 2012 / Essen, Germany
www.conventus.de/index.php?id=gfv-welcomenote

Vaccinology in the Tropics 2nd International Conference

March 14-17, 2012 / Panama City, Panama
www.hscweb3.hsc.usf.edu/health/publichealth/panama/?p=64

1st National Immunization Conference Online

March 26-28, 2012 / Online
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