

VACCINE

RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Rotavirus causes over half of all gastroenteritis in Canadian children

Sénécal et al. Measuring the Impact of Rotavirus Acute Gastroenteritis Episodes (MIRAGE): A prospective community-based study. Can J Infect Dis Med Microbiol 2008;19(6):397-404. MMWR 2008;57(46):1255-7.

Rotavirus (RV) causes over half of all gastroenteritis episodes in Canadian children and can be more severe than gastroenteritis from other causes. According to a prospective community-based study by Canadian investigators, RV is associated with considerably more parental work loss.

Martin Sénécal, MSc, Université Laval, Quebec City, Quebec, and multicentre colleagues in the MIRAGE study group collected data on symptoms, healthcare utilization, parental work loss and additional household episodes of gastroenteritis among children under the age of 3 years who presented with gastroenteritis in Canadian outpatient settings. “Cohort inception took place between January 1 and June 31, 2005—the expected epidemic RV season in Canada,” the authors noted. Children were enrolled from 59 practices across Canada; approximately half were from family physician practices and the remainder from pediatric practices. A total of 395 children were recruited, most of whom had their stools tested for RV antigen.

Of 336 evaluable children, 55.4% tested positive for RV infection while 44.6% tested negative. The age distribution of children with RV-positive vs. RV-negative gastroenteritis differed significantly, with a higher proportion of infants under the age of 6 months testing negative for RV. During the course of illness, “diarrhea was observed in all RV-positive children, while vomiting and fever were observed in 89.3% and 67.2%, respectively,” the authors reported.

Almost two-thirds of children with RV gastroenteritis experienced all three symptoms of diarrhea, vomiting and fever, they added. Children with RV gastroenteritis who were vomiting at presentation also vomited significantly more frequently compared to children with gastroenteritis from other causes. Duration of vomiting and fever was similar for both groups of children, but episodes of diarrhea were longer in children whose gastroenteritis was not caused by RV.

Nevertheless, gastroenteritis caused by RV was definitely more severe than gastroenteritis from other causes, with 12.9% of children with RV gastroenteritis requiring hospitalization vs. 3.9% of children who had RV-negative disease. RV-positive children were also more likely to visit an emergency room or to be hospitalized at 29.3% vs. 15.7% of RV-negative children and to require intravenous rehydration (13.2% vs. 3.2%).

Importantly, from a parental standpoint, parents whose children had RV gastroenteritis were more likely to miss work because of their child’s illness, while 21% of parents with RV-positive children who took time off from work missed more than four days of work. The same was true for 14.3% of parents whose children did not have RV gastroenteritis.

In both groups, approximately half of the families reported at least one other household member experienced gastroenteritis over the study interval, most commonly infants under the age of 2 years. As the authors pointed out, RV was detected in over half of children included in this particular study—about twice as high as previously reported incidence rates in Canadian children of the same age.

The same phenomenon appears to be happening elsewhere. According to a surveillance report between 2001 and 2008, World Health Organization networks reported that approximately 40% of hospitalizations for diarrhea among children under the age of 5 worldwide were attributed to RV infections, the most common strains being G1, G2, G3, G4 and G9.

“This percentage is greater than those percentages reported in two literature reviews,” commented the editor of this CDC report. According to studies published between 1986 and 1999, the median RV detection rate for diarrheal hospitalizations among children under the age of 5 years was 22%. Similarly, studies conducted between 1990 and 2004 showed a median RV detection rate of 29% in the same cohort of young children.

More recent studies reported a median detection rate of 39%, “comparable to the overall rate observed in the surveillance data presented in this report,” the editor observed, adding, “The substantial health burden of RV diarrhea in the world underscores the need for effective

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interventions [e.g. vaccines] for the control of this disease as part of a comprehensive approach for prevention and control of diarrhea.”

Uptake of herpes zoster vaccine among US adults still low

Lu et al. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007: Uptake of the first new vaccine to target seniors. Vaccine 2008;27(6):882-7.

Stein et al. Herpes zoster burden of illness and health care resource utilization in the Australian population aged 50 years and older. Vaccine 2009;27(4):520-9.

According to findings from the first study to assess national herpes zoster (HZ) vaccination coverage since the vaccine became available, uptake of the HZ vaccine in the US among adults 60 years of age and older, for whom the vaccine is indicated, is still low.

Dr. Peng-jun Lu, Centers for Disease Control and Prevention, Atlanta, Georgia, and colleagues analyzed vaccine uptake rates among 3662 adults 60 years of age and older, among whom two-thirds were between the ages of 60 and 74 and the remainder 75 years of age and older. “Overall, 1.9% [of] persons aged 60 years of age and older reported having had HZ vaccination,” the authors noted. Importantly, 77.8% of unvaccinated individuals indicated that they would get the vaccine if their physician recommended it, and most recipients shared this view regardless of educational level, medical insurance status or any other demographic variable.

While over 93% of respondents stated they had heard of HZ, only about 27% of the same respondents indicated they were aware there was a vaccine that targeted the HZ virus. Stated reasons for not accepting the vaccine included feeling that they did not need the vaccine (34.8%); that they were not at risk for HZ (12.5%); that they did not trust doctors or medicine (9.5%); and were concerned about side effects (5.7%). As investigators pointed out, physicians are the most important reason why patients accept vaccines. “Our study suggests that doctors have not been actively recommending the HZ vaccination, based on our results indicating that over three-quarters of persons would have accepted the vaccination if their doctors had, in fact, been recommending it,” the authors stated. “With high uptake, this vaccine has the potential to prevent an enormous burden of disease resulting from HZ and its primary complication, PHN [post-herpetic neuralgia].”

A separate study in which Australian investigators assessed the burden of illness of HZ and PHN among adults 50 years of age and older—for whom the vaccine is indicated in Australia—found that the burden of disease among younger adults was also substantial. Using data from BEACH (Bettering the Evaluation and Care of Health), a cross-sectional paper-based national study of general practice (GP) clinical activity, analyses indicated that HZ was managed at 632 of some 298,492 encounters recorded in the BEACH database between April 2000 and September 2006.

“These numbers were extrapolated to an estimated annual average of 58,350 new HZ cases among individuals 50 years and older,” they added. Other HZ-related healthcare resource utilization for the same cohort included the following:

- Antivirals were prescribed for 71.7% of incident HZ cases.
- The average number of new cases of PHN managed by GPs per year was 8800.
- There was a yearly average of 4058 cases of HZ requiring hospitalization between 1998 and 2005.
- The average length of hospital stay for HZ hospitalizations was 6.8 days at an average estimated cost of \$4764.
- An average of 1885 emergency room visits occurred per year, which did not require hospital admission, at an average annual total cost of approximately \$562,000.
- HZ and PHN resulted in an estimated 139,000 GP consultations per year.

“This study shows that the burden of HZ and PHN in the Australian population aged 50 years and above is substantial, highlighting the potential benefit of HZ vaccination in this age group,” the authors concluded.

Influenza-like illness accounts for large proportion of work loss/ impaired work performance in older adults

Nichol et al. Burden of influenza-like illness and effectiveness of influenza vaccination among working adults aged 50-64 years. Clin Infect Dis 2009;48(3):292-8.

Influenza-like illness (ILI) is not only common among working adults between the ages of 50 and 64, but it also accounts for a large proportion of work loss and impaired work performance during the influenza season, according to a Minnesota-based study.

Dr. Kristin Nichol, University of Minnesota, Minneapolis, and colleagues carried out a prospective cohort study to clarify the burden of ILI as well as the benefits of vaccination among working adults between the ages of 50 and 64. A total of 497 participants were involved in the study, 17.1% of whom indicated that they had experienced an ILI during the influenza season between November 2006 and April 2007.

“Persons with ILI were sick for approximately eight days, missed approximately 1.5 days of work because of illness and worked for less than four days while still symptomatic,” researchers observed. Some 31% of those with an ILI indicated they visited a health care provider while 24% of them received a prescription antibiotic. During the days when participants with an ILI worked, the median level of work effectiveness was estimated at between 70% and 75%. Importantly as well, ILI was responsible for 45% of all days of illness, 39% of all workdays lost because of illness and 49% of days working while ill.

Following vaccination with the influenza vaccine, “We demonstrated a substantial reduction in the risk of ILI of approximately 45% and reductions of 60% or greater in the numbers of days of illness, days of work lost, days of working while ill and days in bed because of ILI.” As the authors pointed out, a recent study estimated the annual economic burden of influenza in the US to be \$87 billion, with lost productivity due to work absenteeism and premature mortality comprising the bulk of the economic burden.

With several recent health economic studies indicating that vaccination of individuals between the ages of 50 to 64 may be cost-effective, “Our study provides additional evidence of the substantial disease burden associated with ILI among working adults in this age group and the substantial benefits that can be achieved with vaccination,” study authors concluded.

Three-shot series of hepatitis B vaccine provides protection against infection for 22 years

But et al. Twenty-two years follow-up of a prospective randomized trial of hepatitis B vaccines without booster dose in children: Final report. Vaccine 2008;26(51):6587-91.

After 22 years of follow-up, primary vaccination against hepatitis B (HBV) with both the plasma-derived and the recombinant DNA-yeast HBV vaccine continues to provide protection against chronic HBV infection, according to the longest prospective follow-up of HBV vaccination in children ever reported.

Dr. David Yiu-Kuen But, The University of Hong Kong, and colleagues extended their previous report of an 18-year follow-up of different HBV vaccines and schedules in 318 high-risk children who received the HBV series between November 1984 and February 1986. Group A received two 5-mcg doses of a recombinant DNA yeast vaccine given one month apart; group B received three 5-mcg doses of the same vaccine at 0, 1 and 6 months of age; and group C received three 10-mcg doses of a plasma-derived HBV vaccine given at 0, 1 and 6 months. No booster was given over the course of the study except to those who did not achieve protective antibody levels against HBV following vaccination. This small group were given a booster but were excluded from the study. As the authors reported, there were no statistically significant differences in geometric mean titres (GMTs) in anti-HBV levels throughout the 22 years of follow-up between subjects in groups B and C.

In contrast, those in group A had lower GMTs than those in groups B and C. These differences were statistically significant up to year 18, after which they became insignificant. “Similarly, the GMTs of the subjects between groups A and C showed significant differences at years 1, 5, 10, 16 and 17,” investigators added, after which point they became insignificant. A higher proportion of subjects in groups B and C also developed protective levels of anti-HBV compared with group A from years 1 to 18 and there was a similar trend at years 20 and 22.

Relatively equal numbers of participants in all three groups demonstrated at least one episode of an anamnestic response over the course of the 22-year study and there was no difference between the three groups in the development of this response. Most importantly, in the 22 years of follow-up, no subject became positive for HBsAg, the authors stressed. They also reported that the two-dose HBV regimen was less immunogenic than the three-dose regimens but long-term protection from HBV carriage was not inferior. This suggests that a two-dose regimen given in childhood without subsequent booster may be adequate for prevention against chronic HBV infection, although this cannot be firmly concluded because

of the small numbers of remaining subjects in the study at the end of the 22-year follow-up.

Candidate malaria vaccine approximately halves disease risk in young children

Bejon et al. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. N Engl J Med 2008;359(24):2521-32.

Results from a randomized, double-blind trial carried out in young children in Kilifi, Kenya, and Korogwe, Tanzania, have demonstrated that a candidate malaria vaccine, RTS,S/AS01E, reduces the risk of malaria by approximately half compared to a control vaccine.

Dr. Philip Bejon, Kenya Medical Research Institute, Kilifi, Kenya, and multicentre colleagues evaluated the efficacy of the new RTS,S vaccine administered with a more immunogenic adjuvant system (AS01E) in 894 children between five and 17 months of age. Children received either three doses of the RTS,S/AS01E vaccine or a control rabies vaccine, with one dose given each month for three months. “The primary end point was a clinical episode of malaria, defined as an axillary temperature of 37.5°C or higher with a *Plasmodium falciparum* density of more than 2500 parasites per microlitre,” researchers explained.

A secondary end point was the presence of any falciparum parasitemia density with the same body temperature. Analysis of data over a mean of eight months, beginning two weeks after the final vaccination, showed that the cumulative incidence of the first or only malarial episodes (the primary end point of the study) was 8% (32 out of 402 subjects) in the malaria vaccine arm vs. 16% (66 of 407 subjects) in the control arm, for an adjusted vaccine efficacy rate of 53%.

In the intent-to-treat analysis, which included data collected over a mean of 10.5 months beginning with the first vaccination, the cumulative incidence of the first or only episode of malaria meeting end point criteria was 9% (42 out of 447 subjects) in the RTS,S/AS01E arm vs. 17% (78 out of 447) in the rabies vaccine arm, for an unadjusted efficacy rate of 49%. “The rate of efficacy against all clinical episodes meeting the criteria for the primary end point was 56%... which was similar to the rate of efficacy against first or only episodes,” the authors indicated.

Estimates of efficacy according to the secondary end point were similar to those achieved for the primary end point, they added. Some 47 out of the 447 children who received the malaria candidate vaccine experienced one or more serious adverse events (11%) compared to 82 out of the 447 children receiving the rabies vaccine (18%). The lower rate of serious adverse events in the malaria vaccine arm was only partly accounted for by a reduction in admissions related to falciparum malaria, investigators observed.

They concluded, “The RTS,S/AS01E malaria vaccine has significant efficacy against clinical malaria in the field in a target group for licensure [i.e., children 5 to 17 months of age. Our findings indicate that the RTS,S/AS01E vaccine should be further tested in a phase III multicentre trial.”

Pneumococcal vaccination does not appear to prevent pneumonia

Huss et al. *Efficacy of pneumococcal vaccination in adults: a meta-analysis*. CMAJ 2009;180(1):48-58.

Andrews R, Moberley SA. *The controversy over the efficacy of pneumococcal vaccine*. CMAJ 2009;180(1):18-9.

Pneumococcal vaccination does not appear to prevent pneumonia, even in populations for whom the vaccine is currently recommended, according to results from a meta-analysis of 22 clinical trials.

Dr. Anke Huss, Institute of Social and Preventive Medicine, University of Bern, Switzerland, and multicentre colleagues carried out a systematic review of clinical trials in which the efficacy of pneumococcal polysaccharide vaccination on outcomes was evaluated, taking the quality of the trials into account. "Depending on the outcome, from two to 19 trials were included in our meta-analyses," investigators noted, "and there were between 794 and 82,665 study participants in each analysis."

Without taking trial quality into account, the combined relative risks (RRs) indicated that the vaccine reduced the risk of pneumococcal pneumonia by 36% (RR 0.64) and all-cause pneumonia by 27% (RR 0.73). However, as investigators stressed, there was "pronounced heterogeneity" between the trials analyzed, and trials of higher quality (e.g. double-blind or adequate concealment of allocation) showed no benefit of the vaccine. Results from 19 trials that examined the risk of all-cause pneumonia again revealed little evidence for a difference in RR of all-cause pneumonia between vaccine recipients and non-recipients, even among the elderly and those with chronic respiratory diseases, for whom the vaccine is indicated.

Trials of higher quality generally showed little evidence of a protective effect regardless of the study population and setting. As the authors pointed out, a recent Cochrane review found strong evidence supporting a beneficial effect of the pneumococcal vaccine against invasive pneumococcal disease, a finding which they suggest is largely explained by the inclusion of two studies in the Cochrane review which the current meta-analysis did not include due to perceived design weaknesses in both trials.

In an accompanying editorial, Dr. Ross Andrews and Sarah A. Moberley, Child Health Division, Menzies School of Health Research, Casuarina, Northern Territory, Australia, co-authors of the same meta-analysis, disagreed with the conclusions reached by Huss et al. As they pointed out, Dr. Huss and colleagues suggested that countries with childhood immunization programs that include the pneumococcal conjugate vaccine should reconsider the recommended use of the pneumococcal polysaccharide

vaccine in adults. But as they commented, "The implication that the polysaccharide vaccine should be withdrawn in such settings exceeds the scope of their evidence." This is because outcomes examined by the meta-analysis—namely, invasive pneumococcal disease, definite pneumococcal pneumonia and bacteremia—were rare in the trials evaluated and the confidence intervals in those studies were as a result extremely wide.

Andrews and Moberley also suggested that the basis upon which the authors excluded several studies from their meta-analysis were "questionable." The editorialists did not dispute the potential for childhood immunization to provide indirect protection to adults due to herd immunity but they insisted that this conclusion is beyond the scope of the meta-analysis by Dr. Huss and colleagues. They also pointed out that the authors did not consider data from other observational studies on the direct impact of the pneumococcal polysaccharide vaccine on invasive pneumococcal disease. Given that the epidemiology of the disease varies by age, "it seems unlikely that childhood vaccination alone will be adequate to prevent invasive pneumococcal disease in adults," they suggested. They added that recommendations from the World Health Organization (WHO) on the 23-valent vaccine did not change when they took the findings from the meta-analysis into consideration.

"The position of the WHO is that randomized trials, meta-analyses of randomized trials and most observational studies are consistent with a protective effect against invasive pneumococcal disease among healthy adults and, to a lesser extent, among individuals aged 65 years or more. In the absence of any new data to the contrary, we support that position," the editorialists concluded. □

UPCOMING EVENTS

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April 3-6, 2009 / Whistler, British Columbia

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April 27-30, 2009 / Cannes, France

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