

## **Chapter 5 Citations**

### **1. "A calculated risk": the Salk polio vaccine field trials of 1954**

#### **Abstract**

"The polio vaccine field trials of 1954, sponsored by the National Foundation for Infantile Paralysis (March of Dimes), are among the largest and most publicised clinical trials ever undertaken. Across the United States, 623 972 schoolchildren were injected with vaccine or placebo, and more than a million others participated as "observed" controls. The results, announced in 1955, showed good statistical evidence that Jonas Salk's killed virus preparation was 80-90% effective in preventing paralytic poliomyelitis.<sup>1</sup>

The statistical design used in this great experiment was singular, prompting criticism at the time and since. Eighty four test areas in 11 states used the textbook model: in a randomised, blinded design all participating children in the first three grades of school (ages 6-9) received injections of either vaccine or placebo and were observed for evidence of the disease. But 127 test areas in 33 states used an "observed control" design: participating children in the second grade (ages 7-8) received injections of vaccine; no placebo was given, and children in all three grades were then observed for the duration of the polio "season."<sup>1</sup>

The use of the dual protocol illustrates both the power and the limitations of the randomised clinical trial to legitimate therapeutic claims. The placebo controlled trials were necessary to define the Salk vaccine—introduced by a lay organisation that has taken an activist position against the counsel of its virological advisers—as the product of scientific medicine. The observed control trials were essential to maintaining public support for the vaccine as the product of lay faith and investment in science. Here I examine the process by which the trial design was negotiated and the roles of the several actors."

#### **Links**

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1114166/>

#### **References**

Meldrum, M. "'A Calculated Risk': The Salk Polio Vaccine Field Trials of 1954." *Bmj* 317.7167 (1998): 1233-236.

## 2. Acute Gastroenteritis Hospitalizations Among US Children Following Implementation of the Rotavirus Vaccine

### Abstract

### Links

<http://jama.jamanetwork.com/article.aspx?articleid=2319155>

### References

Leshem, Eyal, Jacqueline E. Tate, Claudia A. Steiner, Aaron T. Curns, Ben A. Lopman, and Umesh D. Parashar. "Acute Gastroenteritis Hospitalizations Among US Children Following Implementation of the Rotavirus Vaccine." *Jama* 313.22 (2015): 2282.

## 3. Association between type 1 diabetes and *Haemophilus influenzae* type b vaccination: birth cohort study

### Abstract

#### “Objectives:

To determine the effect of *Haemophilus influenzae* type b vaccination and its timing on the risk of type 1 diabetes in Finnish children.

#### Design:

Cumulative incidence and relative risk of type 1 diabetes was compared among three birth cohorts of Finnish children: those born during the 24 months before the *H influenzae* type b vaccination trial, those in the trial cohort who were vaccinated at 3 months of age and later with a booster vaccine, and those in the trial cohort who were vaccinated at 24 months of age only. The probability of type 1 diabetes was estimated using regression analysis assuming that there were no losses to 10 year follow up and no competing risks.

#### Setting:

Finland (total population 5 million and annual birth rate 1.3%).

#### Subjects:

128 936 children born from 1 October 1983 to 1 September 1985, and 116 352 children born from 1 October 1985 to 31 August 1987.

#### Main outcome measures:

Probability of type 1 diabetes among children vaccinated with *H influenzae* type b and non-vaccinated children.

### **Results:**

No statistically significant difference was found at any time during the 10 year follow up in the risk of type 1 diabetes between the children born before the vaccination period and those vaccinated at the age of 24 months only (relative risk 1.01). The difference in the risk between the cohort vaccinated first at the age of 3 months and the cohort vaccinated at the age of 24 months only was not statistically significant either (1.06).

### **Conclusion:**

It is unlikely that *H influenzae* type b vaccination or its timing cause type 1 diabetes in children.“

### **Links**

<http://www.bmj.com/content/318/7192/1169>

### **References**

Karvonen, M., Z. Cepaitis, and J. Tuomilehto. "Association between Type 1 diabetes and Haemophilus Influenzae Type B Vaccination: Birth Cohort Study." *Bmj* 318.7192 (1999): 1169-172.

## **4. Childhood Intussusception: A Literature Review**

### **Abstract**

#### **“Background**

Postlicensure data has identified a causal link between rotavirus vaccines and intussusception in some settings. As rotavirus vaccines are introduced globally, monitoring intussusception will be crucial for ensuring safety of the vaccine programs.

#### **Methods**

To obtain updated information on background rates and clinical management of intussusception, we reviewed studies of intussusception in children <18 years of age published since 2002. We assessed the incidence of intussusception by month of life among children <1 year of age, seasonality, method of diagnosis, treatment, and case-fatality.

#### **Findings**

We identified 82 studies from North America, Asia, Europe, Oceania, Africa, Eastern Mediterranean, and Central & South America that reported a total of 44,454 intussusception events. The mean incidence of intussusception was 74 per 100,000 (range: 9–328) among

children <1 year of age, with peak incidence among infants 5–7 months of age. No seasonal patterns were observed. A radiographic modality was used to diagnose intussusception in over 95% of the cases in all regions except Africa where clinical findings or surgery were used in 65% of the cases. Surgical rates were substantially higher in Africa (77%) and Central and South America (86%) compared to other regions (13–29%). Case-fatality also was higher in Africa (9%) compared to other regions (<1%). The primary limitation of this review relates to the heterogeneity in intussusception surveillance across different regions.

## **Conclusion**

This review of the intussusception literature from the past decade provides pertinent information that should facilitate implementation of intussusception surveillance for monitoring the postlicensure safety of rotavirus vaccines.”

## **Links**

<http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0068482>

## **References**

Jiang, James, Baoming Jiang, Umesh Parashar, Trang Nguyen, Julie Bines, and Manish M. Patel. "Childhood Intussusception: A Literature Review." PLoS ONE 8.7 (2013)

## **5. Decline of Childhood Haemophilus influenzae Type b (Hib) Disease in the Hib Vaccine Era**

### **Abstract**

*“OBJECTIVE:*

Effective Haemophilus influenzae type b (Hib) conjugate vaccines were first licensed for use in US children at least 18 months old in December 1987 and for infants at least 2 months old in October 1990. We evaluated trends in Hib disease associated with licensure of Hib conjugate vaccines.

*DESIGN:*

Data from two sources, an intensive laboratory-based active surveillance system and the National Bacterial Meningitis Reporting System (NBMRs), were used separately to evaluate disease incidence. Data from vaccine manufacturers on Hib vaccine doses distributed in the United States were compared with trends in Hib disease incidence.

## *RESULTS:*

The age-specific incidence of Hib disease among children less than 5 years old decreased by 71% from 37 per 100,000 persons in 1989 to 11 per 100,000 persons in 1991 (active surveillance data). Haemophilus influenzae meningitis incidence decreased by 82% between 1985 and 1991 (NBMRS data). Increases in doses of Hib vaccine distributed in the United States coincided with steep declines in Hib disease. Both surveillance systems showed decreased rates of Hib disease in infants less than 1 year old before vaccine was licensed for use in this age group. Haemophilus influenzae type b disease incidence in persons at least 12 years old and pneumococcal meningitis incidence in children less than 5 years old did not change substantially during the same period; therefore, decreased Hib disease in children less than 5 years old is not likely to be explained solely by changes in surveillance sensitivity or decreases in bacterial disease due to changes in medical practice.

## *CONCLUSION:*

Our data suggest that conjugate vaccines have already had a marked impact on the incidence of Hib disease in the United States, preventing an estimated 10,000 to 16,000 cases of Hib disease in 1991. The decline of disease in infants less than 1 year old before licensure for this age group warrants further investigation.”

### **Links**

<http://www.ncbi.nlm.nih.gov/pubmed/8417239>

### **References**

Adams, William G. "Decline of Childhood Haemophilus Influenzae Type B (Hib) Disease in the Hib Vaccine Era." JAMA JAMA: The Journal of the American Medical Association 269.2 (1993)

## **6. Discovery of rotavirus: Implications for Child health**

### **Abstract**

“For centuries, acute diarrhea has been a major worldwide cause of death in young children, and until 1973, no infectious agents could be identified in about 80% of patients admitted to hospital with severe dehydrating diarrhea. In 1973 Ruth Bishop, Geoffrey Davidson, Ian Holmes, and Brian Ruck identified abundant particles of a 'new' virus (rotavirus) in the cytoplasm of mature epithelial cells lining duodenal villi and in feces, from such children admitted to the Royal Children's Hospital, Melbourne. Rotaviruses have now been shown to cause 40-50% of severe

acute diarrhea in young children worldwide in both developing and developed countries, and > 600 000 young children die annually from rotavirus disease, predominantly in South-East Asia and sub-Saharan Africa. Longitudinal surveillance studies following primary infection in young children have shown that rotavirus reinfections are common. However the immune response that develops after primary infection is protective against severe symptoms on reinfection. This observation became the basis for development of live oral rotavirus vaccines. Two safe and effective vaccines are now licensed in 100 countries and in use in 17 countries (including Australia). Rotarix (GSK) is a single attenuated human rotavirus, representative of the most common serotype identified worldwide (G1P[8]). RotaTeq (Merck) is a pentavalent mixture of naturally attenuated bovine/human rotavirus reassortants representing G1, G2, G3, G4, and P(8) serotypes. Preliminary surveillance of the numbers of children requiring hospitalization for severe diarrhea, in USA, Brazil, and Australia, after introduction of these vaccines, encourages the hope that rotavirus infection need no longer be a threat to young children worldwide.”

### **Links**

<http://www.ncbi.nlm.nih.gov/pubmed/19799704>

### **References**

Bishop, Ruth. "Discovery of Rotavirus: Implications for Child Health." *Journal of Gastroenterology and Hepatology* 24 (2009)

## **7. Helmet therapy in infants with positional skull deformation: randomised controlled trial**

### **Abstract**

#### **“Objective**

To determine the effectiveness of helmet therapy for positional skull deformation compared with the natural course of the condition in infants aged 5-6 months.

#### **Design**

Pragmatic, single blinded, randomised controlled trial (HEADS, HELmet therapy Assessment in Deformed Skulls) nested in a prospective cohort study.

#### **Setting**

29 paediatric physiotherapy practices; helmet therapy was administered at four specialised centres.

#### **Participants**

84 infants aged 5 to 6 months with moderate to severe skull deformation, who were born after 36 weeks of gestation and had no muscular torticollis, craniosynostosis, or dysmorphic features.

Participants were randomly assigned to helmet therapy (n=42) or to natural course of the condition (n=42) according to a randomisation plan with blocks of eight.

## **Interventions**

Six months of helmet therapy compared with the natural course of skull deformation. In both trial arms parents were asked to avoid any (additional) treatment for the skull deformation.

## **Main outcome measures**

The primary outcome was change in skull shape from baseline to 24 months of age assessed using plagioccephalometry (anthropometric measurement instrument). Change scores for plagioccephaly (oblique diameter difference index) and brachycephaly (cranioproportional index) were each included in an analysis of covariance, using baseline values as the covariate. Secondary outcomes were ear deviation, facial asymmetry, occipital lift, and motor development in the infant, quality of life (infant and parent measures), and parental satisfaction and anxiety. Baseline measurements were performed in infants aged between 5 and 6 months, with follow-up measurements at 8, 12, and 24 months. Primary outcome assessment at 24 months was blinded.

## **Results**

The change score for both plagioccephaly and brachycephaly was equal between the helmet therapy and natural course groups, with a mean difference of  $-0.2$  (95% confidence interval  $-1.6$  to  $1.2$ ,  $P=0.80$ ) and  $0.2$  ( $-1.7$  to  $2.2$ ,  $P=0.81$ ), respectively. Full recovery was achieved in 10 of 39 (26%) participants in the helmet therapy group and 9 of 40 (23%) participants in the natural course group (odds ratio  $1.2$ , 95% confidence interval  $0.4$  to  $3.3$ ,  $P=0.74$ ). All parents reported one or more side effects.

## **Conclusions**

Based on the equal effectiveness of helmet therapy and skull deformation following its natural course, high prevalence of side effects, and high costs associated with helmet therapy, we discourage the use of a helmet as a standard treatment for healthy infants with moderate to severe skull deformation.”

## **Links**

<http://www.bmj.com/content/348/bmj.g2741>

## **References**

Wijk, R. M. Van, L. A. Van Vlimmeren, C. G. M. Groothuis-Oudshoorn, C. P. B. Van Der Ploeg, M. J. Ijzerman, and M. M. Boere-Boonekamp. "Helmet Therapy in Infants with Positional Skull Deformation: Randomised Controlled Trial." *Bmj* 348.May01 8 (2014)

## 8. Intussusception Risk after Rotavirus Vaccination in U.S. Infants

### **Abstract**

#### *“BACKGROUND:*

International postlicensure studies have identified an increased risk of intussusception after vaccination with the second-generation rotavirus vaccines RotaTeq (RV5, a pentavalent vaccine) and Rotarix (RV1, a monovalent vaccine). We studied this association among infants in the United States.

#### *METHODS:*

The study included data from infants 5.0 to 36.9 weeks of age who were enrolled in three U.S. health plans that participate in the Mini-Sentinel program sponsored by the Food and Drug Administration. Potential cases of intussusception and vaccine exposures from 2004 through mid-2011 were identified through procedural and diagnostic codes. Medical records were reviewed to confirm the occurrence of intussusception and the status with respect to rotavirus vaccination. The primary analysis used a self-controlled risk-interval design that included only vaccinated children. The secondary analysis used a cohort design that included exposed and unexposed person-time.

#### *RESULTS:*

The analyses included 507,874 first doses and 1,277,556 total doses of RV5 and 53,638 first doses and 103,098 total doses of RV1. The statistical power for the analysis of RV1 was lower than that for the analysis of RV5. The number of excess cases of intussusception per 100,000 recipients of the first dose of RV5 was significantly elevated, both in the primary analysis (attributable risk, 1.1 [95% confidence interval, 0.3 to 2.7] for the 7-day risk window and 1.5 [95% CI, 0.2 to 3.2] for the 21-day risk window) and in the secondary analysis (attributable risk, 1.2 [95% CI, 0.2 to 3.2] for the 21-day risk window). No significant increase in risk was seen after dose 2 or 3. The results with respect to the primary analysis of RV1 were not significant, but the secondary analysis showed a significant risk after dose 2.



## *CONCLUSIONS:*

RV5 was associated with approximately 1.5 (95% CI, 0.2 to 3.2) excess cases of intussusception per 100,000 recipients of the first dose. The secondary analysis of RV1 suggested a potential risk, although the study of RV1 was underpowered. These risks must be considered in light of the demonstrated benefits of rotavirus vaccination. (Funded by the Food and Drug Administration.)”

## **Links**

<http://www.nejm.org/doi/full/10.1056/NEJMoa1303164#t=article>

## **References**

"Intussusception Risk after Rotavirus Vaccination in U.S. Infants." *Child: Care, Health and Development* Child Care Health Dev 40.3 (2014): 453.

## **9. Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil**

### **Abstract**

*“BACKGROUND:*

Because postlicensure surveillance determined that a previous rotavirus vaccine, RotaShield, caused intussusception in 1 of every 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) with intussusception after routine immunization of infants in Mexico and Brazil.

*METHODS:*

We used case-series and case-control methods to assess the association between RV1 and intussusception. Infants with intussusception were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants from the same neighborhood were enrolled as controls. Vaccination dates were verified by a review of vaccination cards or clinic records.

*RESULTS:*

We enrolled 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1 to 7 days after the first dose of RV1 was identified among infants in Mexico with the use of both the case-series method (incidence ratio, 5.3; 95% confidence interval [CI], 3.0 to 9.3) and the case-control method (odds ratio, 5.8; 95% CI, 2.6 to 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk, albeit smaller than that seen after the first dose in Mexico--an increase by a factor of 1.9 to 2.6 - was seen 1 to 7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51,000 infants) and in Brazil (approximately 1 per 68,000 infants) and of 5 deaths due to intussusception was attributable to RV1. However, RV1 prevented approximately 80,000 hospitalizations and 1300 deaths from diarrhea each year in these two countries.

#### *CONCLUSIONS:*

RV1 was associated with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants. The absolute number of deaths and hospitalizations averted because of vaccination far exceeded the number of intussusception cases that may have been associated with vaccination. (Funded in part by the GAVI Alliance and the U.S. Department of Health and Human Services.).”

#### **Links**

<http://www.nejm.org/doi/full/10.1056/NEJMoa1012952#t=article>

#### **References**

Perlman, Stanley. "Faculty of 1000 Evaluation for Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil." F1000 - Post-publication Peer Review of the Biomedical Literature

### **10. Melaleuca alternifolia (Tea Tree) Oil: a Review of Antimicrobial and Other Medicinal Properties**

#### **Abstract**

“Complementary and alternative medicines such as tea tree (melaleuca) oil have become increasingly popular in recent decades. This essential oil has been used for almost 100 years in Australia but is now available worldwide both as neat oil and as an active component in an array of products. The primary uses of tea tree oil have historically capitalized on the antiseptic and anti-inflammatory actions of the oil. This review summarizes recent developments in our

understanding of the antimicrobial and anti-inflammatory activities of the oil and its components, as well as clinical efficacy. Specific mechanisms of antimicrobial and anti-inflammatory action are reviewed, and the toxicity of the oil is briefly discussed.”

### **Links**

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1360273/>

### **References**

Carson, C. F., K. A. Hammer, and T. V. Riley. "Melaleuca Alternifolia (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19.1 (2006): 50-62.

## **11. Parental Tdap Boosters and Infant Pertussis: A Case-Control Study**

### **Abstract**

#### **“BACKGROUND:**

Although recommended for almost a decade, evidence for field effectiveness of vaccinating close adult contacts of newborn infants against pertussis (“cocooning”) is lacking. We evaluated the impact of a government-funded cocoon program during a pertussis epidemic in New South Wales, Australia.

#### **METHODS:**

We matched all New South Wales laboratory-confirmed pertussis cases aged <4 months with onset between April 1, 2009, to March 30, 2011 to controls from the state birth register by date of birth and area of residence. Parental vaccine receipt was by self-report, with a subset verified. Parents were considered “immunized” if vaccinated  $\geq 4$  weeks before case symptom onset. The effectiveness of parental immunization (versus neither vaccinated) was quantified as  $(1 - \text{odds ratio}) \times 100\%$ .

#### **RESULTS:**

Case households had fewer immunized mothers (22% vs 32%) or fathers (20% vs 31%) but were more likely to include additional and older children. After adjustment, when both parents met our

definition of immunized, risk of pertussis at <4 months of age was reduced by 51% (95% confidence interval 10% to 73%). Maternal vaccination prepregnancy and an immunized father reduced the risk by 51% (95% confidence interval 0% to 76%).

## **CONCLUSIONS:**

Timely parental pertussis boosters provided significant protection. Evidence of protection from maternal vaccination prepregnancy is biologically plausible, and more precise data on the magnitude and duration of this is important for future policy recommendations.”

### **Links**

<http://pediatrics.aappublications.org/content/early/2014/09/09/peds.2014-1105>

### **References**

"Parental Tdap Boosters and Infant Pertussis: A Case-Control Study." *Pediatrics* 134.4 (2014)

## **12. Pediatric Invasive Pneumococcal Disease in the United States in the Era of Pneumococcal Conjugate Vaccines**

### **Abstract**

“Invasive infections caused by *Streptococcus pneumoniae* continue to be a major cause of morbidity and mortality worldwide, especially in children under 5 years of age. In the United States, 90% of invasive pneumococcal infections in children are caused by 13 serotypes of *S. pneumoniae*. The licensure (in 2000) and subsequent widespread use of a heptavalent pneumococcal conjugate vaccine (PCV7) have had a significant impact on decreasing the incidence of serious invasive pneumococcal disease (IPD) in all age groups, especially in children under 2 years of age. However, the emergence of replacement non-PCV7 serotypes, especially serotype 19A, has resulted in an increase in the incidence of serious and invasive infections. In 2010, a 13-valent PCV was licensed in the United States. However, the impact that this vaccine will have on IPD remains to be seen. The objectives of this review are to discuss the epidemiology of serious and invasive pneumococcal infections in the United States in the PCV era and to review some of the pneumococcal vaccines that are in development.”

### **Links**

<http://www.ncbi.nlm.nih.gov/pubmed/22763632>

### **References**

Disease in the United States in the Era of Pneumococcal Conjugate Vaccines." *Clinical Microbiology Reviews* 25.3 (2012)

### **13. Tdap Vaccine Effectiveness in Adolescents During the 2012 Washington State Pertussis Epidemic**

#### **Abstract**

#### **“BACKGROUND:**

Acellular pertussis vaccines replaced whole-cell vaccines for the 5-dose childhood vaccination series in 1997. A sixth dose of pertussis-containing vaccine, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap), was recommended in 2005 for adolescents and adults. Studies examining Tdap vaccine effectiveness (VE) among adolescents who have received all acellular vaccines are limited.

#### **METHODS:**

To assess Tdap VE and duration of protection, we conducted a matched case-control study during the 2012 pertussis epidemic in Washington among adolescents born during 1993–2000. All pertussis cases reported from January 1 through June 30, 2012, in 7 counties were included; 3 controls were matched by primary provider clinic and birth year to each case. Vaccination histories were obtained through medical records, the state immunization registry, and parent interviews. Participants were classified by type of pertussis vaccine received on the basis of birth year: a mix of whole-cell and acellular vaccines (1993–1997) or all acellular vaccines (1998–2000). We used conditional logistic regression to calculate odds ratios comparing Tdap receipt between cases and controls.

#### **RESULTS:**

Among adolescents who received all acellular vaccines (450 cases, 1246 controls), overall Tdap VE was 63.9% (95% confidence interval [CI]: 50% to 74%). VE within 1 year of vaccination was 73% (95% CI: 60% to 82%). At 2 to 4 years postvaccination, VE declined to 34% (95% CI: –0.03% to 58%).

#### **CONCLUSIONS:**

Tdap protection wanes within 2 to 4 years. Lack of long-term protection after vaccination is likely contributing to increases in pertussis among adolescents.”

### **Links**

<http://pediatrics.aappublications.org/content/early/2015/04/28/peds.2014-3358>

### **References**

"Tdap Vaccine Effectiveness in Adolescents During the 2012 Washington State Pertussis Epidemic." *Pediatrics* 135.6 (2015)

## **14. Screening of Viral Pathogens from Pediatric Ileal Tissue Samples after Vaccination**

### **Abstract**

“In 2010, researchers reported that the two US-licensed rotavirus vaccines contained DNA or DNA fragments from porcine circovirus (PCV). Although PCV, a common virus among pigs, is not thought to cause illness in humans, these findings raised several safety concerns. In this study, we sought to determine whether viruses, including PCV, could be detected in ileal tissue samples of children vaccinated with one of the two rotavirus vaccines. A broad spectrum, novel DNA detection technology, the Lawrence Livermore Microbial Detection Array (LLMDA), was utilized, and confirmation of viral pathogens using the polymerase chain reaction (PCR) was conducted. The LLMDA technology was recently used to identify PCV from one rotavirus vaccine. Ileal tissue samples were analyzed from 21 subjects, aged 15–62 months. PCV was not detected in any ileal tissue samples by the LLMDA or PCR. LLMDA identified a human rotavirus A from one of the vaccinated subjects, which is likely due to a recent infection from a wild type rotavirus. LLMDA also identified human parechovirus, a common gastroenteritis viral infection, from two subjects. Additionally, LLMDA detected common gastrointestinal bacterial organisms from the Enterobacteriaceae, Bacteroidaceae, and Streptococcaceae families from several subjects. This study provides a survey of viral and bacterial pathogens from pediatric ileal samples, and may shed light on future studies to identify pathogen associations with pediatric vaccinations.”

### **Links**

<http://www.hindawi.com/journals/av/2014/720585/>

### **References**

Hewitson, Laura, James B. Thissen, Shea N. Gardner, Kevin S. Mcloughlin, Margaret K. Glausser, and Crystal J. Jaing. "Screening of Viral Pathogens from Pediatric Ileal Tissue Samples after Vaccination." *Advances in Virology* 2014 (2014): 1-10.

## **15. The Incidence of Positional Plagiocephaly: A Cohort Study**

### **Abstract**

#### **OBJECTIVE:**

The objective of this study was to estimate the incidence of positional plagiocephaly in infants 7 to 12 weeks of age who attend the 2-month well-child clinic in Calgary, Alberta, Canada.

#### **METHODS:**

A prospective cohort design was used to recruit 440 healthy full-term infants (born at  $\geq 37$  weeks of gestation) who presented at 2-month well-child clinics for public health nursing services (eg, immunization) in the city of Calgary, Alberta. The study was completed in 4 community health centers (CHCs) from July to September 2010. The CHCs were selected based on their location, each CHC representing 1 quadrant of the city. Argenta's (2004) plagiocephaly assessment tool was used to identify the presence or absence of plagiocephaly.

#### **RESULTS:**

Of the 440 infants assessed, 205 were observed to have some form of plagiocephaly. The incidence of plagiocephaly in infants at 7 to 12 weeks of age was estimated to be 46.6%. Of all infants with plagiocephaly, 63.2% were affected on the right side and 78.3% had a mild form.

#### **CONCLUSIONS:**

To our knowledge, this is the first population-based study to investigate the incidence of positional plagiocephaly using 4 community-based data collection sites. Future studies are required to corroborate the findings of our study. Research is required to assess the incidence of plagiocephaly using Argenta's plagiocephaly assessment tool across more CHCs and to assess

prevalence at different infant age groups. The utility of using Argenta's plagiocephaly assessment tool by public health nurses and/or family physicians needs to be established.”

### **Link**

<http://pediatrics.aappublications.org/content/early/2013/07/02/peds.2012-3438>

### **Reference**

"The Incidence of Positional Plagiocephaly: A Cohort Study." Pediatrics 132.2 (2013)

## **16. Trends of Diarrheal Disease—Associated Mortality in US Children, 1968 Through 1991**

### **Abstract**

#### **“Objectives.**

To describe temporal patterns in mortality related to diarrheal disease in US children and to assess progress toward its prevention and control.

#### **Design.**

Retrospective analyses of death certificate data on diarrhea of all causes compiled by the National Center for Health Statistics, Centers for Disease Control and Prevention, Atlanta, Ga.

#### **Patients.**

Children aged 1 month through 4 years who died with diarrhea.

#### **Setting.**

United States, 1968 through 1991.

#### **Results.**

A total of 14137 deaths associated with diarrhea among children were reported in the United States between 1968 and 1991. Of these, 78% occurred in infants (ie, aged 1 to 11 months); the median age at the time of death has declined from 5 to 1.5 months. Diarrheal disease mortality dropped by approximately 75% during the first 18 years of the study, but no decline has occurred since 1985. Infant mortality due to diarrhea (per 100 000 live births) averaged 12.8 and was found to be high for blacks (33.1) and for residents of the southern United States (18.5). The infant mortality due to diarrhea from 1986 through 1991 is 5.9. Peaks in winter deaths previously associated with rotavirus were prominent in the early years among infants aged 4 through 11 months. Such peaks have virtually disappeared since 1985. Diarrhea was the principal cause of



death, as the leading associated diagnoses (electrolyte disorders [30%], cardiac arrest [16%], shock [8%], and nausea/vomiting [4%]) were commonly recognized complications of diarrhea. Since 1979, prematurity has emerged as a common associated diagnosis.

## **Conclusions.**

Diarrheal deaths nationwide have declined 75% from 1968 to 1985 but stabilized since then at about 300 deaths per year. Because many of these deaths may still be preventable by early rehydration, future prevention efforts should be directed at educating health care providers about the continuing problem and recognition of the high-risk infant and at teaching mothers of such infants to begin rehydration early and to seek medical attention when their infant develops diarrhea.(*JAMA*. 1995;274:1143-1148)”

## **Link**

<http://jama.jamanetwork.com/article.aspx?articleid=389779>

## **Reference**

Kilgore, P. E. "Trends of Diarrheal Disease--associated Mortality in US Children, 1968 through 1991." *JAMA: The Journal of the American Medical Association* 274.14 (1995): 1143-148.

## **17. Vaccine Policy Changes and Epidemiology of Poliomyelitis in the United States**

### **Abstract**

#### **“Context**

The last case of poliomyelitis in the United States due to indigenously acquired wild poliovirus occurred in 1979; however, as a consequence of oral poliovirus vaccine (OPV) use that began in 1961, an average of 9 cases of vaccine-associated paralytic poliomyelitis (VAPP) were confirmed each year from 1961 through 1989. To reduce the VAPP burden, national vaccination policy changed in 1997 from reliance on OPV to options for a sequential schedule of inactivated poliovirus vaccine (IPV) followed by OPV. In 2000, an exclusive IPV schedule was adopted.

#### **Objective**

To review the epidemiology of paralytic poliomyelitis and document the association between the vaccine schedule changes and VAPP in the United States.

#### **Design and Setting**

Review of national surveillance data from 1990 through 2003 for cases of confirmed paralytic poliomyelitis.

## **Main Outcome Measures**

Number of confirmed paralytic poliomyelitis cases, including VAPP, and ratio of VAPP cases to number of doses of OPV distributed that occurred before, during, and after implementation of policy changes.

## **Results**

From 1990 through 1999, 61 cases of paralytic poliomyelitis were reported; 59 (97%) of these were VAPP (1 case per 2.9 million OPV doses distributed), 1 case was imported, and 1 case was indeterminate. Thirteen cases occurred during the 1997-1999 transitional policy period and were associated with the all-OPV schedule; none occurred with the IPV-OPV schedule. No cases occurred after the United States implemented the all-IPV policy in 2000. The last imported poliomyelitis case occurred in 1993 and the last case of VAPP occurred in 1999.

## **Conclusion**

The change in polio vaccination policy from OPV to exclusive use of IPV was successfully implemented; this change led to the elimination of VAPP in the United States.

In 1952, 3 years before the licensure of the first poliomyelitis vaccine, more than 21 000 cases of paralytic poliomyelitis were documented in the United States.<sup>1</sup> The use of inactivated poliovirus vaccine (IPV) and, later, oral poliovirus vaccine (OPV) led to a precipitous drop in reported cases of poliomyelitis.<sup>2</sup> The last cases of poliomyelitis caused by indigenously acquired wild poliovirus occurred in 1979 during an outbreak following importation from Canada.<sup>3</sup> Genetic studies of poliovirus isolates from the 1970s suggested that endemic circulation of wild polioviruses in the United States may have ceased by the late 1960s, and subsequent sporadic cases and small outbreaks due to wild poliovirus during the 1970s probably represented importations from neighboring countries.<sup>4</sup>

Monovalent OPV type 3 became available in 1961 in the United States. Trivalent OPV (offering protection against the 3 poliovirus serotypes) was licensed in the United States in 1963 and became the vaccine of choice for prevention of poliomyelitis in the United States and most of the world.<sup>5</sup> Oral poliovirus vaccine was considered superior to IPV because of provision of better intestinal immunity, ability to indirectly vaccinate susceptible contacts through transmission of vaccine polioviruses, ease of administration, and lower costs. However, a serious consequence of the use of this live-virus vaccine, vaccine-associated paralytic poliomyelitis (VAPP), was recognized as early as 1962.<sup>6,7</sup> From 1961 through 1989, an average of 9 cases of VAPP (range, 1-25 cases) were confirmed each year.<sup>8, 10</sup>

In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by 2000.<sup>11</sup> Universal implementation of polio eradication strategies substantially reduced the risk of poliovirus importation into the United States.<sup>12</sup> In response to the changing risk-benefit profile associated with OPV use, the Institute of Medicine conducted independent evaluations on polio vaccine policy options in the United States in 1977 and 1988,<sup>13,14</sup> and in 1995, participated in a policy review initiated by the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices.<sup>15</sup> The discussion of changing reliance from OPV to IPV led to national debates in the mid 1990s.<sup>16</sup> It was thought that the potential for reduced compliance due to higher costs and the increased number of injections

associated with IPV, coupled with possible reduced mucosal immunity in IPV recipients, could lead to wild poliovirus outbreaks.<sup>17,18</sup>

However, as the likelihood of wild poliovirus importations declined, the risk of VAPP with routine use of OPV became more difficult to justify. In June 1996, a policy change was made when the Advisory Committee on Immunization Practices recommended a transition to IPV by first introducing a sequential vaccination schedule of 2 doses of IPV followed by 2 doses of OPV.<sup>17</sup> This schedule was predicted to reduce the number of VAPP cases by 53%, with the greatest impact on recipients.<sup>19</sup> However, more flexible policy options were supported by the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) that allowed for an all-OPV schedule or an all-IPV schedule, provided parents were educated about the decision.<sup>18,20</sup> In January 1999, the AAP and AAFP revised their recommendations to state that only IPV should be administered for doses 1 and 2, citing that VAPP continued to be associated with the all-OPV schedule<sup>21</sup> and that the vaccine options were not always presented to patients and parents.<sup>20</sup> Further progress toward global polio eradication and the desire to eliminate VAPP prompted all policy-setting groups to recommend that an all-IPV schedule be implemented in 2000.<sup>22,23</sup>

This report reviews national poliomyelitis surveillance data in the United States from 1990 through 2003, describes the epidemiology of poliomyelitis, and assesses the impact of the poliomyelitis vaccine policy changes on the occurrence of paralytic poliomyelitis in the United States.”

### **Link**

<http://jama.jamanetwork.com/article.aspx?articleid=199583>

### **Reference**

Alexander, Lorraine Niño. "Vaccine Policy Changes and Epidemiology of Poliomyelitis in the United States." *Jama* 292.14 (2004): 1696.

## **18. Viral nucleic acids in live-attenuated vaccines: detection of minority variants and an adventitious virus.**

### **Abstract**

“Metagenomics and a panmicrobial microarray were used to examine eight live-attenuated viral vaccines. Viral nucleic acids in trivalent oral poliovirus (OPV), rubella, measles, yellow fever, varicella-zoster, multivalent measles/mumps/rubella, and two rotavirus live vaccines were partially purified, randomly amplified, and pyrosequenced. Over half a million sequence reads were generated covering from 20 to 99% of the attenuated viral genomes at depths reaching up to 8,000 reads per nucleotides. Mutations and minority variants, relative to vaccine strains, not known to affect attenuation were detected in OPV, mumps virus, and varicella-zoster virus. The anticipated detection of endogenous retroviral sequences from the producer avian and primate cells was confirmed. Avian leukosis virus (ALV), previously shown to be noninfectious for humans, was present as RNA in viral particles, while simian retrovirus (SRV) was present as genetically defective DNA. Rotarix, an orally administered rotavirus vaccine, contained porcine circovirus-1 (PCV1), a highly prevalent nonpathogenic pig virus, which has not been shown to

be infectious in humans. Hybridization of vaccine nucleic acids to a panmicrobial microarray confirmed the presence of endogenous retroviral and PCV1 nucleic acids. Deep sequencing and microarrays can therefore detect attenuated virus sequence changes, minority variants, and adventitious viruses and help maintain the current safety record of live-attenuated viral vaccines.”

### **Link**

<http://www.ncbi.nlm.nih.gov/pubmed/20375174>

### **Reference**

Victoria, J. G., C. Wang, M. S. Jones, C. Jaing, K. Mcloughlin, S. Gardner, and E. L. Delwart. "Viral Nucleic Acids in Live-Attenuated Vaccines: Detection of Minority Variants and an Adventitious Virus." *Journal of Virology* 84.12 (2010): 6033-040.

## **19. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant.**

### **Abstract**

“Scientific data pertaining to vitamin D supplementation during lactation are scarce. The daily recommended intake for vitamin D during lactation has been arbitrarily set at 400 IU/d (10 microg/d). This recommendation is irrelevant with respect to maintaining the nutritional vitamin D status of mothers and nursing infants, especially among darkly pigmented individuals. Our objective was to examine the effect of high-dose maternal vitamin D2 supplementation on the nutritional vitamin D status of mothers and nursing infants. Fully lactating women (n = 18) were enrolled at 1 mo after birth to 1 of 2 treatment arms, ie, 1600 IU vitamin D2 and 400 IU vitamin D3 (prenatal vitamin) or 3600 IU vitamin D2 and 400 IU vitamin D3, for a 3-mo study period. High-dose (1600 or 3600 IU/d) vitamin D2 supplementation for a period of 3 mo safely increased circulating 25-hydroxyvitamin D [25(OH)D] concentrations for both groups. The antirachitic activity of milk from mothers receiving 2000 IU/d vitamin D increased by 34.2 IU/L, on average, whereas the activity in the 4000 IU/d group increased by 94.2 IU/L. Nursing infant circulating 25(OH)D2 concentrations reflected maternal intake and the amount contained in the milk. With limited sun exposure, an intake of 400 IU/d vitamin D would not sustain circulating 25(OH)D concentrations and thus would supply only limited amounts of vitamin D to nursing infants in breast milk. A maternal intake of 2000 IU/d vitamin D would elevate circulating 25(OH)D concentrations for both mothers and nursing infants, albeit with limited capacity, especially with respect to nursing infants. A maternal intake of 4000 IU/d could achieve substantial progress toward improving both maternal and neonatal nutritional vitamin D status.”

### **Link**

<http://www.ncbi.nlm.nih.gov/pubmed/15585800>

### **Reference**

"Maternal Versus Infant Vitamin D Supplementation During Lactation: A Randomized Controlled Trial." *Pediatrics* 136.4 (2015)