# 2013 Research Annual Report

# **Global Child Health**



### **Division Details**

#### **Division Data Summary**

RESEARCH AND TRAINING DETAILS	
Number of Faculty	4
Number of Support Personnel	9
Direct Annual Grant Support	\$2,980,297
Direct Annual Industry Support	\$354,613
Peer Reviewed Publications	17

#### **Division Photo**



M Steinhoff, E Schlaudecker, A Dawodu

## Significant Accomplishments

### Largest Dose Most Effective for Mothers and Infants in Middle East Vitamin D Study

Adekunle Dawodu, MBBS, has completed the first randomized controlled trial of daily vitamin D supplementation in pregnant Arab women, who are reported to have high prevalence of vitamin D deficiency. His group investigated whether high doses were superior to currently recommended 400 IU/day for optimizing vitamin D status of mothers and their infants at birth. The project measured blood vitamin levels during pregnancy and at delivery in 192 women who were randomly assigned to either 400, 2000 or 4000 IU/day vitamin  $D_3$  at approximately 12 weeks of pregnancy and followed monthly until delivery. Vitamin  $D_3$  doses of 4000 IU/day were more effective than 2000 IU/day in optimizing vitamin D status in mothers and their newborn infants. There were no safety concerns during the study. The results indicate that the currently recommended vitamin D intake for pregnant women in the US is inadequate to prevent vitamin D deficiency in the majority of pregnant women in this study. The study has provided valuable new information for designing future larger studies to assess the effect of vitamin supplementation in populations with similar high prevalence of vitamin D deficiency.

### Vaccine Increases Influenza A Antibody Levels in Human Milk

Colleagues in Bangladesh with Elizabeth Schlaudecker, MD, MPH, and Mark Steinhoff, MD, demonstrated that influenza-specific IgA levels in breast milk were significantly higher for at least 6 months postpartum among mothers receiving influenza vaccines during pregnancy compared to a control group that received pneumococcal vaccines. The team also showed that the influenza virus neutralization effect of breast milk was greater in mothers who received influenza vaccine. Greater exclusivity of breastfeeding in the first 6 months of

life also significantly decreased the expected number of respiratory illness with fever episodes in infants of influenza-vaccinated mothers, but not in infants of pneumococcal-vaccinated mothers.

### Study in China Evaluates Medical Cost Burden of RSV Infections

Expanding on a previous evaluation of the epidemiology of laboratory-proven influenza in children hospitalized in Suzhou, China, Steven Black, MD, and Mark Steinhoff, MD collaborated with investigators at Fudan University in Shanghai and Suzhou Children's Hospital to evaluate the epidemiology and medical costs of children hospitalized for respiratory syncytial virus (RSV) infections. RSV was a significant cause of hospitalization in children with rates much higher than for influenza. Medical costs, when put in the context of income levels in Suzhou, represented a significant economic burden to parents. This is one of the first population-based studies of in hospitalized children in the People's Republic of China and the first study to evaluate the economic burden of this disease.

## Research Highlights

Academic Collaboration with Department of Pediatrics, College of Medicine in Malawi

An agreement has been completed to provide faculty and fellows to assist with the pediatric training of third-year medical students in Malawi. Our faculty from Emergency Medicine and other divisions will be involved in bedside clinical teaching, as well as formal lectures to 88 medical students in four groups each year in their pediatric clinical clerkship at Kamuzu Central Hospital in Lilongwe, Malawi. We believe that this collaborative effort will encourage more Malawian medical students to pursue pediatrics. We will continue to work with faculty colleagues at KCH to improve care in the general and neonatal wards. In collaboration with Dr. Mlotha, the Head of Pediatrics, we are designing research projects to assess outcomes of patients admitted to the emergency ward. To support this new program, Cincinnati Children's has arranged local housing and transportation in Lilongwe.

Effect of influenza vaccine in pregnancy on fetal outcomes

Dr. Mark Steinhoff, with colleagues in Emory University, analyzed the effect of receipt of pandemic influenza vaccine in 2009-10 among 3,227 women, of whom 1,125 received vaccine. The analysis showed that mothers who received the pandemic vaccine had 37% lower odds of having preterm infants, and the mean birth weight of infants of vaccinated mothers was 45% greater than that of the unvaccinated mothers.

#### Children with influenza in China

Drs. Steven Black and Mark Steinhoff, working with colleagues in Fudan University, analyzed data from 480 children hospitalized with laboratory-proven influenza between 2005 and 2009. They described the common clinical characteristics, as well as the cost of influenza-related hospitalization. This was the first study of the cost of laboratory-proven influenza hospitalization in China, showing that there is potential for the use of influenza vaccine in children to reduce medical care costs.

Decreased Antibody Response to Influenza Vaccine in Pregnant Women

Elizabeth Schlaudecker, MD, MPH, studied the immunologic response to influenza immunization in pregnant women compared to non-pregnant women. Because the antibody responses (hemagglutination inhibition titers) were significantly decreased in pregnant women compared to non-pregnant women after immunization, Dr. Schlaudecker is currently investigating the IgG isotype responses to influenza immunization in Dr. Sing Sing

Way's laboratory with the mentorship of Dr. Fred Finkelman in the Division of Cellular and Molecular Immunology.

Award for presentation of vitamin D supplementation study in the UAE

A poster presentation on vitamin D supplementation during pregnancy in the UAE received the best poster award during the 7<sup>th</sup> Dubai International Conference for Medical Sciences. December 2012, Dubai, UAE.

Renewal and expansion of Nurturing Children's Development program

The Nurturing Children's Development Program, Cincinnati Children's P&G partnership funded by the Pampers Brand, has been renewed for another three years starting July 1, 2013 to fund research scholars and observers from China, Latin America (Brazil) and Africa (Nigeria). The program will sponsor four research scholars, as well as 18 observers from these countries. The research scholars will spend 12 months in research at Cincinnati Children's and each observer will complete two-month clinical observer programs. It is anticipated that additional funding will be provided for a research scholar from Singapore, the current headquarters of P&G Global Baby Care which funds the program.

The Risk of Narcolepsy following Adjuvanted Pandemic Influenza Vaccine

In this US CDC funded study, Dr. Steven Black and colleagues will evaluate the risk of narcolepsy following adjuvanted influenza vaccines. Three such vaccines were used during the 2009-2010 pandemic and one was associated with an increased risk of narcolepsy in children in several European studies. The goal of this project is to expand the scope of prior studies to include the other two adjuvanted vaccines by performing studies in Brazil, Taiwan, Canada, Israel, the Netherlands, Spain and Argentina. The results of this study will inform the future use and selection of adjuvants for future pandemics.

# Significant Publications

Richards JL, Hansen C, Bredfeldt C, Steinhoff MC, et al. Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age birth. Clin Infect Dis. 2013;56:1216-22.

This paper describes the effect of antenatal influenza vaccine on birth outcomes during the recent H1N1 pandemic season. 3,327 pregnancies were evaluated in the Kaiser Permanente health plan on the East Coast. 1,115 mothers had received influenza vaccine, and their birth outcomes were compared to mothers who did not receive the H1N1 vaccine. After several adjustments to account for underlying differences between the groups, mothers who received the influenza vaccine had a 37% reduction in the odds of a preterm birth, and the weight of their infants was 45 gm greater than the control infants. These data confirm earlier observations that influenza in pregnancy has substantial effects on fetal development, and suggest that maternal immunization with influenza vaccine should be encouraged.

Dawodu A, Akinbi H. Vitamin D nutrition in pregnancy: current opinion. Int. J. Women's Health. 2013. 5:333-343.

This invited review of vitamin D nutrition in pregnancy by the editor of *International Journal of Women's Health* focused on the association between vitamin D status in pregnancy and outcome in the mother, fetus and infant. The authors presented evidence of a high prevalence of low vitamin D status in pregnancy worldwide, with potential adverse effect on the mother and her offspring as well as scant intervention trials to identify optimal vitamin D intake. The findings of two recent RCT by investigators from South Carolina and Cincinnati Children's Hospital indicated that higher vitamin D doses between 2000 and 4000 IU/day were safe and effective

in optimizing vitamin D status in mothers and their newborn infants. Larger studies are needed to further assess safety and the impact of optimal vitamin D supplementation on the health of mothers and their infants.

Baxter R, Ray P, Tran TN, Black S, et al.Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. *Pediatrics*. 2013;131:e1389-96.

Before introduction of routine varicella vaccination of young children, varicella infection was a universal phenomenon in the U.S. The concern with the vaccination program was that if vaccine induced immunity waned, adolescents and adults could become susceptible to varicella at a time in their lives when the risk of complications was much higher. This publication reports on a 14-year follow up of the impact of the vaccination program and documents that vaccine induced protection, especially after two doses, provides long term protection of at least 14 years in almost all individuals.

### **Division Publications**

- Amarasinghe A, Black S, Bonhoeffer J, Carvalho SM, Dodoo A, Eskola J, Larson H, Shin S, Olsson S, Balakrishnan MR, Bellah A, Lambach P, Maure C, Wood D, Zuber P, Akanmori B, Bravo P, Pombo M, Langar H, Pfeifer D, Guichard S, Diorditsa S, Hossain MS, Sato Y. Effective vaccine safety systems in all countries: a challenge for more equitable access to immunization. Vaccine. 2013; 31 Suppl 2:B108-14.
- Baxter R, Ray P, Tran TN, Black S, Shinefield HR, Coplan PM, Lewis E, Fireman B, Saddier P. Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. Pediatrics. 2013; 131:e1389-96.
- 3. Black S, Block SL. Use of MenACWY-CRM in adolescents in the United States. *J Adolesc Health*. 2013; 52:271-7.
- Bonhoeffer J, Black S, Izurieta H, Zuber P, Sturkenboom M. Current status and future directions of post-marketing vaccine safety monitoring with focus on USA and Europe. Biologicals. 2012; 40:393-7.
- Dawodu A, Akinbi H. (2013) Vitamin D nutrition in pregnancy: current opinion. Int J Womens Health. Dove Press. 5:333-343.
- 6. Dawodu A, Saadi HF, Bekdache G, Javed Y, Altaye M, Hollis BW. Randomized Controlled Trial (RCT) of Vitamin D Supplementation in Pregnancy in a Population With Endemic Vitamin D Deficiency. *J Clin Endocrinol Metab*. 2013; 98:2337-46.
- 7. Klein DL, Martinez JE, Hickey MH, Hassouna F, Zaman K, Steinhoff M. Development and characterization of a multiplex bead-based immunoassay to quantify pneumococcal capsular polysaccharide-specific antibodies. *Clin Vaccine Immunol.* 2012; 19:1276-82.
- 8. Lalitha MK, David T, Thomas K, Rapid Antimicrobial Resistance Study G. Nasopharyngeal swabs of school children, useful in rapid assessment of community antimicrobial resistance patterns in Streptococcus pneumoniae and Haemophilus influenzae. *J Clin Epidemiol*. 2013; 66:44-51.
- 9. Modak JK, Steinhoff MC, Zaman K, Islam M, El Arifeen S, Saha SK. **Detection and serotyping of lyophilized nonculturable pneumococcal isolates**. *J Clin Microbiol*. 2012; 50:3388-90.
- Omer SB, Zaman K, Roy E, Arifeen SE, Raqib R, Noory L, Seib K, Breiman RF, Steinhoff MC. Combined
  effects of antenatal receipt of influenza vaccine by mothers and pneumococcal conjugate
  vaccine receipt by infants: results from a randomized, blinded, controlled trial. *J Infect Dis.* 2013;
  207:1144-7.
- 11. Richards JL, Hansen C, Bredfeldt C, Bednarczyk RA, Steinhoff MC, Adjaye-Gbewonyo D, Ault K, Gallagher M, Orenstein W, Davis RL, Omer SB. **Neonatal outcomes after antenatal influenza**

- immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age birth. Clin Infect Dis. 2013; 56:1216-22.
- 12. Schlaudecker EP, Heck JP, Macintyre ET, Martinez R, Dodd CN, McNeal MM, Staat MA, Heck JE, Steinhoff MC. Etiology and seasonality of viral respiratory infections in rural Honduran children. *Pediatr Infect Dis J.* 2012; 31:1113-8.
- 13. Schlaudecker EP, McNeal MM, Dodd CN, Ranz JB, Steinhoff MC. **Pregnancy modifies the antibody response to trivalent influenza immunization**. *J Infect Dis*. 2012; 206:1670-3.
- 14. Schlaudecker EP, Steinhoff MC, Omer SB, Roy E, Arifeen SE, Dodd CN, Altaye M, Raqib R, Breiman RF, Zaman K. **Antibody persistence in mothers one year after pneumococcal immunization in pregnancy**. *Vaccine*. 2012; 30:5063-6.
- 15. Steinhoff MC, MacDonald NE. Influenza pandemics--pregnancy, pathogenesis, and perinatal outcomes. *JAMA*. 2012; 308:184-5.
- 16. Steinhoff MC, Omer SB. A review of fetal and infant protection associated with antenatal influenza immunization. *Am J Obstet Gynecol.* 2012; 207:S21-7.
- 17. Thomas K, Mukkai Kesavan L, Veeraraghavan B, Jasmine S, Jude J, Shubankar M, Kulkarni P, Steinhoff M, Network ISGI. Invasive pneumococcal disease associated with high case fatality in India. *J Clin Epidemiol*. 2013; 66:36-43.

# Faculty, Staff, and Trainees

**Faculty Members** 

Mark Steinhoff, MD, Professor

Leadership Division Director, Global Child Health

Research Interests Maternal Immunization

Steven Black, MD, Professor

Research Interests Vaccine Safety

Adekunle Dawodu, MD, Professor

Leadership Director, International Patient Coordination

Research Interests Vitamin D Supplementation

Elizabeth Schlaudecker, MD, MPH, Assistant Professor

Research Interests Maternal Immunization

### **Division Collaboration**

Neonatology and Pulmonary Biology » Ardythe Morrow, PhD

Research involving Vitamin D supplementation in breastfeeding mothers.

# Grants, Contracts, and Industry Agreements

Grant and Contract Awards Annual Direct

STEINHOFF,M

Mother's Gift 241 Field Trial

Bill & Melinda Gates Foundation

\$3,334,910

Total

### BLACK, S

### Epidemiology and Estimation of Burden of Influenza in Children in China

Centers for Disease Control and Prevention

	03/30/11-09/29/13	\$147,484
	Current Year Direct	\$2,980,297
Industry Contracts		
STEINHOFF, M		
Pfizer		\$34,613
DAWODU, A		
Procter & Gamble		\$320,000
	Current Year Direct Receipts	\$354,613