

Vaccines Statistics News

from the Vaccines Sub-Committee of the ISCB

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Upcoming Statistics Conferences with Vaccine Presentations and Sessions Schedule & Overview

- July 30 - Aug. 4, 2011 The 2011 **Joint Statistical Meetings** will be held July 30 - August 4, 2011, at the Miami Beach Convention Centre, Miami Beach, Florida. The program is now available online and includes 15 papers/roundtable sessions on vaccine topics. [See below for the titles of the papers, authors, and links to the online details.](#) General information is available at <http://www.amstat.org/meetings/jsm/2011/>
- Aug. 21 - 25, 2011 The **32nd Annual Conference of the International Society for Clinical Biostatistics** (ISCB) will be held August 21 - 25, 2011 at the new Ottawa Convention Centre. [Details of Special Mini-Symposium Day on Vaccines below](#)
- Sept. 11 - 12, 2011 **Enterprise-Octave Blended Workshop for Young and Early Career Investigators** will be held in Bangkok, Thailand prior to the AIDS Vaccine 2011 Conference. The Workshop is entitled, "Statistical Methods in HIV Vaccine Trial Design and Evaluation" and will be taught by Peter Gilbert, Don Stablein, Zoe Moodie, and Paul Edlefsen. <http://www.hivvaccineenterprise.org/content/request-applications-workshop-statistical-methods-hiv-vaccine-trial-design-and-evaluation>
- Sept. 19 - 21, 2011 **FDA/Industry Statistics Workshop** will be held September 19 - 21, 2011 at the Marriott, Wardman Park, Washington DC, United States. There will be two vaccine sessions at this year's workshop. [See below for details.](#) General information is posted when available at <http://www.amstat.org/meetings/fdaworkshop>
- Oct. 24 - 28, 2011 **IMS Workshop on the Design and Analysis of Clinical Trials**, National University of Singapore, Singapore. There will be 3 days of technical sessions, a one-half day on specific issues for vaccine clinical trials and another one-half day on pragmatic and regulatory issues for clinical trials

Information on the workshop is available
<http://www2.ims.nus.edu.sg/Programs/011wclinic/index.php#Overview>

Dec. 5 - 9, 2011 **Deming Conference on Applied Statistics**, Atlantic City, New Jersey (<http://demingconference.com/>). Professor Elizabeth Halloran from University of Washington will give a 3-hour tutorial on **Design and Analysis of Vaccine Studies**.

A useful **calendar of statistical conferences** is managed by the International Statistical Institute at <http://isi.cbs.nl/calendar.htm>

If you are organizing or know of a vaccines or infectious disease session or presentation at an upcoming statistics conference, or a statistics session at a vaccines or infectious disease conference, please email details to conferences@iscb-vaccines.info so it may be included in future issues of the newsletter and on the sub-committee's website.

Mini-Symposium on Statistics in Vaccines Research at the 32nd Annual Conference of the ISCB, Ottawa, Canada, 21 - 25 August 2011

The ISCB Vaccines sub-committee has organized a Mini-Symposium on "Current and Emerging Statistical Issues in Vaccines Research" to be held at the annual conference of the **International Society for Clinical Biostatistics (ISCB)** in Ottawa, Canada at the new Convention Centre, from 21 - 25 August 2011. The talks presented will focus on the subject of vaccine safety, including self-controlled methods for vaccine safety surveillance, sequential methods and their application to vaccine safety evaluation, and data mining methods relevant for evaluating vaccine safety. The organizers of the mini-symposium are sub-committee members Jingyee Kou, Jennifer Nelson, Zoe Moodie, Allen Izu, and Kerry Go of Sanofi Pasteur. Invited speakers and their topics include:

- **Bruce Fireman** (Kaiser Permanente Research, USA) who will speak on "Case-based Methods for Vaccine Safety Surveillance"
- **Richard Forshee** (US Food & Drug Administration, Center for Biologics Evaluation & Research, Office of Biostatistics & Epidemiology) who will speak on "A self-controlled series design to evaluate the risk of Guillan-Barre syndrome after receiving the 2009 H1N1 influenza vaccine"
- **Andrea Cook** (Group Health Research Institute, USA) who will speak on "Group sequential methods for observational data incorporating confounding through estimating equations with application in post-marketing vaccine/drug surveillance"
- **Ivan Chan** (Merck Research Laboratories, USA), who will speak on "Sequential methods for evaluation and monitoring of vaccine safety"
- **Thomas Buttolph** (US FDA, CBER, Office of Biostatistics & Epidemiology), who will speak on "Data mining to support product safety evaluation at CBER"
- **Patrick Ryan** (Johnson & Johnson Pharmaceutical Research and Development, USA), who will speak on "Empirical performance of large-scale analysis methods for active surveillance: lessons from the Observational Medical Outcomes Partnership"

For updated information on the annual conference and the Vaccines mini-symposium please visit: <http://www.iscb2011.info/index.html>.

Vaccine Papers/Sessions at JSM 2011
Miami Beach, Florida, July 30 - August 4, 2011

- [Causal Inference of Vaccine Effects on Infectiousness](#). M. Elizabeth Halloran, Fred Hutchinson Cancer Research Center/University of Washington; Michael G. Hudgens, The University of North Carolina at Chapel Hill
- [A Comparative Analysis of Mixed Effects Models and Related Methods to Assess Physical and Mental Functional Status After Receipt of Anthrax Vaccine in a Human Clinical Trial](#). Brock Stewart, Centers for Disease Control and Prevention; Charles Rose, Centers for Disease Control and Prevention; Michael M. McNeil, Centers for Disease Control and Prevention
- [A Mixed-Effects Model to Estimate Duration of Antibody Responses to Anthrax Vaccine in Humans and Non-Human Primates](#). Charles Rose, Centers for Disease Control and Prevention; Lydia Foster, Centers for Disease Control and Prevention; Conrad Quinn, Centers for Disease Control and Prevention
- [Simulation Studies of Self-Controlled Case Series Methods in Vaccine Safety Research](#). Guoying Sun, U.S. Food and Drug Administration; Wei Hua, U.S. Food and Drug Administration; Nick Andrews, Health Protection Agency; Caitlin N. Dodd, Cincinnati Children's Hospital Medical Center; Silvana A. Romio, Erasmus University; Hector Izurieta, U.S. Food and Drug Administration; Heather J. Whitaker, Open University
- [Noninferiority and Superiority Tests for Multiple Immunogenicity Endpoints in Vaccine Clinical Studies](#). Lihan Yan, U.S. Food and Drug Administration
- [The Impact of Individual Decisions on the Equity of H1N1 Vaccine Distribution](#). Jessica L. Heier Stamm, Kansas State University; Nicoleta Serban, Georgia Institute of Technology; Julie Swann, Georgia Institute of Technology
- [Data Mining in Vaccine Manufacturing: Finding Needles in Biological Haystacks](#). Nelson Lee Afanador, Merck Sharp and Dohme Corp.
- [Use of Zero-Inflated Mixture Models to Compare Antibody Titers Among Asthma Subpopulations in Response to the H1N1 Vaccine](#). Leela M. Aertker, Rho; Daniel J. Zaccaro, Rho
- [An Alternative to ANCOVA When Standard Assumptions Are Untenable](#). J. Brooke Marshall, Merck Research Laboratories; Devan V. Mehrotra, Merck Research Laboratories
- [Threshold Methods for Immunological Correlates of Protection](#). Andrew Dunning, Sanofi-Pasteur; Xuan Chen, Sanofi-Pasteur; Huiling Xiong, Sanofi Pasteur; Fabrice Bailleux, Sanofi-Pasteur; Li Qin, Fred Hutchinson Cancer Research Center; Kamal Desai, University of London
- [Evaluation of Immune Response \(gpELISA\) as the Principal Surrogate Endpoint for Protection of Herpes Zoster Afforded by Zostavax](#). Xiaoming Li, Merck Research Laboratories; Xiaopeng Miao, Boston University; Ivan S. F. Chan, Merck Research Laboratories
- [Comparison of TLOVR Algorithm Versus Snapshot Approach for HIV Studies](#). Wei Zhang, Boehringer Ingelheim; Michael Pannucci, Boehringer Ingelheim; Junhai Guo, Boehringer Ingelheim; David Hall, Boehringer Ingelheim

- [Globalization of Clinical Trials: The Development of Treatments and Preventative Products for Diseases, with a Focus on Vaccines](#). Tammy Massie, U.S. Food and Drug Administration – Roundtable Luncheon
- [Sieve Analysis in HIV Vaccine Efficacy Trials with Multivariate and Missing Marks](#). Michal Juraska, University of Washington; Peter B. Gilbert, University of Washington
- [Use of Fixed-Effects Models to Analyze Self-Controlled Case Series Data in Vaccine Safety Studies](#). Stanley Xu, Kaiser Permanente Colorado; Chan Zeng, Kaiser Permanente Colorado; Sophia Newcomer, Kaiser Permanente Colorado; Jennifer Nelson, Group Health Research Institute; Jason Glanz, Kaiser Permanente Colorado

Vaccine Papers/Sessions at FDA/Industry Statistics Workshop Washington DC, September 19 - 21, 2011

Tuesday, Sept. 20; 1:00 - 2:15 PM. **Issues on Correlates of Protection in Vaccine Development**. Organizers: Charles Liss, Merck; Guoying Sun, FDA; Lihan Yan, USFDA. Chairs: Xiaoming Li, Merck Research Laboratories

- [Causal Inference of Vaccine Effects on Infectiousness](#). M. Elizabeth Halloran, Fred Hutchinson Cancer Research Center/University of Washington; Michael G. Hudgens, The University of North Carolina at Chapel Hill
- [Inferences from Tests of Biodefense Vaccines](#). Michael P Fay, NIAID-NIH
- [Experimental Designs and Statistical Methods for Post-licensure Immunological Correlates of Protection](#). Andrew Dunning, Sanofi Pasteur
- [Assessing the Predictive Value of Immunological Markers in Vaccines](#). Ivan Chan, Merck & Co., Inc
- [Correlates of Protection: What have we done, What do we do now?](#) Tsai-Lien Lin, CBER/FDA

Tuesday, Sept. 20; 2:30 - 3:45 PM. **Statistical Challenges Encountered in Assessing Immunogenicity Data from Vaccine Trials**. Organizers: Barbara Krasnicka, FDA; Andrew Dunning, Sanofi Pasteur. Chairs: Mridul K Chowdhury, FDA; Anthony Homer, Sanofi Pasteur

- [Dealing with Missing Data in Vaccine Clinical Trials: from Academics to the Industry](#). Niel Hens, I-BioStat, Hasselt University
- [Application of Recent Guidance on Missing Data to Truncated Immunogenicity Data](#). John Jezowski, Sanofi Pasteur
- [Comparing and Combining Data across Laboratories after Correcting for Inter-laboratory Variation via Integration of Paired-sample Data](#). Yunda Huang, Fred Hutchinson Cancer Research Center
- [Robust Inference from Multiple Statistics via Permutations](#). Jitendra Ganju, Amgen Inc.

Selected Readings in Vaccine Safety

The following selection of readings and links on the statistics of vaccine safety has been prepared by four volunteers and two members of the committee with the intention that it be useful to those new to the field of statistics of vaccines research. There are three sections:

- Methods
- Applications
- Initiatives and Projects

Methods

Shih MC, Lai TL, Heyse JF, Chen J. Sequential generalized likelihood ratio tests for vaccine safety evaluation. *Statistics in Medicine* 2010; 29(26):2698-2708.

Proposes a class of sequential generalized likelihood ratio tests for evaluating adverse event rates in two-armed pre-licensure clinical trials and single-armed post-licensure studies. The approach is illustrated using data from the Rotavirus Efficacy and Safety Trial.

DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *The American Statistician* 1999; 53:177-190.

Describes a data mining method for searching for associations in large data bases.

Kulldorff M, Davis RL, Kolczak M, et al. A maximized sequential probability ratio test for drug and vaccine safety surveillance. *Sequential Analysis* 2011; 30:58-78.

Proposes a maximized sequential probability ratio test to continuously monitor pre-specified safety hypotheses over time. Uses a likelihood ratio test and a flat stopping boundary that holds the Type 1 error rate across all tests performed. The method is illustrated using data from the US Vaccine Safety Datalink and compared with Wald's classical sequential probability ratio test. A reference table of critical stopping values is provided.

Whitaker HJ, Hocine M, Farrington CP. The methodology of self-controlled case series studies. *Statistical Methods in Medical Research* 2009; 18(1):7-26.

Describes the self-controlled case series method, going through the assumptions in detail and how violations may be addressed, such as when an event can influence exposure. Also mentions sequential self-controlled case series methods.

Farrington CP. Control without separate controls: Evaluation of vaccine safety using case-only methods. *Vaccine* 2004; 22:2064-2070.

Considers a number of case only designs along with examples – ecological methods, case-coverage, case-crossover and self-controlled case series.

Glanz JM, McClure DL, Xu S, Hambridge SJ, Lee M, Kolczak MS, Kleinman K, Mullooly JP, France EK. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. *Journal of Clinical Epidemiology* 2006; 59:808-818.

Compares self-controlled case series, cohort, case-control and risk-interval designs using simulation of risks based on the US Vaccine Safety Datalink population. Power, bias and MSE are assessed.

Fine P, Chen R. Confounding in studies of adverse reactions to vaccines. *American Journal of Epidemiology* 1992; 136:121-135.

Looks at the size of bias that unmeasured confounding could introduce to an estimate of the risk of an event after vaccination. Uses as an example diphtheria-pertussis-tetanus vaccination and sudden infant death syndrome.

Applications

Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M. A population-based study of measles, mumps, and rubella vaccination and autism. *New England Journal of Medicine* 2002; 347(19):1477-82.

One of the landmark studies evaluating the claimed association between MMR vaccine and autism. Eight Danish birth cohorts were investigated under a retrospective cohort study design. Outcome and exposure variables were retrieved from six different population-based registries.

Smeeth L, Cook C, Fombonne E, Heavy L, Rodrigues L, Smith P, Hall A. MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* 2004; 364:963-69.

Uses the General Practice Research Database in the UK to explore the relationship between MMR vaccination and autism with a case-control design. Controls were matched on age, sex and general practice, enabling assessment of the association at any time after vaccination.

Niu MT, Erwin DE, Braun MM. Data mining in the US Vaccine Adverse Event Reporting System (VAERS): early detection of intussusception and other events after rotavirus vaccination. *Vaccine* 2001; 19:4627-4634.

A study in the US Vaccine Adverse Event Reporting System to test the utility of an empirical Bayesian data mining approach to detect retrospectively a known side effect of vaccination – intussusception following rotavirus vaccination. Results demonstrate the utility of the method for early detection of significant vaccine-associated events.

Haber P, Patel M, Izurieta HS, et al. Postlicensure monitoring of intussusception after Rotateq vaccination in the United States. *Pediatrics* 2008; 121:1206-1212

Considered rates of intussusception in children following vaccination with RotaTeq™, using data from the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink. Calculated "observed" vs. "expected" rates of intussusception, evaluated whether the rates of intussusception were higher than expected in the two databases, and concluded that the current evidence does not suggest a link between RotaTeq™ and intussusception.

Villumsen M, Sørup S, Jessa T, Ravn H, Relander T, Baker JL, Benn CS, Sørensen TIA, Aaby P, Roth A. Risk of lymphoma and leukaemia after bacille Calmette-Guérin and smallpox vaccination: A Danish case-cohort study. *Vaccine* 2009; 27(49):6950-6958.

A case-cohort study on non-specific effects of bacille Calmette-Guérin and smallpox vaccinations. An example of how the same set of controls (i.e. subcohort) can be used for studying more than one exposure and more than one outcome.

Miller E, Waight P, Farrington P, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. *Archives of Disease in Childhood* 2001; 84:227-229.

An example using the self-controlled case series method for an event where there is a true vaccine risk. It is often used in examples of the method.

Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, Baxter R, Hambidge S, Nordin J, Naleway A, Belongia EA, Lieu T, Baggs J, Weintraub E; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics* 2010; 126(1):e1-8.

A study which identified an increased risk of seizure in infants following receipt of the combination measles-mumps-rubella-varicella vaccine vs. separate injections of measles-mumps-rubella and varicella vaccines. Led to national Advisory Committee on Immunization Practices policy changes around recommended use of measles-mumps-rubella-varicella vaccine.

Initiatives and Projects

The following websites provide information on some initiatives and projects related to post-licensure vaccine safety.

CDC Vaccine Safety Datalink (VSD) Project

Collaborative effort between US Center for Disease Control and Prevention Immunization Safety Office and eight managed care organizations, established in 1990 to monitor immunization safety and address gaps in scientific knowledge about rare and serious adverse events following immunization. Includes a large linked database that uses administrative data sources at each managed care organization.

<http://www.cdc.gov/vaccinesafety/Activities/VSD.html>

FDA Sentinel Initiative

Launched in May 2008 by US FDA, the Sentinel Initiative aims to develop and implement a national electronic proactive system that will complement existing systems the Agency has in place to track reports of adverse events linked to the use of its regulated products.

<http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm>

FDA Vaccine Adverse Event Reporting System (VAERS)

The Vaccine Adverse Event Reporting System is a national vaccine safety surveillance program co-sponsored by the FDA and the Center for Disease Control and Prevention that collects and analyzes information from reports of adverse events that occur after the administration of US licensed vaccines.

<http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/VaccineAdverseEvents/default.htm>

Vaccine Adverse Event Surveillance & Communication (VAESCO)

A European research network with the primary aim of developing guidelines and a sustainable infrastructure for post licensure vaccine safety assessment in the European region. <http://vaesco.net/vaesco.html>

The WHO Programme for International Drug Monitoring

Forum for WHO member states to collaborate in the monitoring of drug safety. Within the Programme, individual case reports of suspected adverse drug reactions are collected and stored in a common database, presently containing over 6 million case reports.

<http://www.who-umc.org/DynPage.aspx>

Selection by Nick Andrews, Xuan Chen, Jennifer Clark-Nelson, Clara Dominguez, Andrew Dunning and Jukka Jokinen for the Vaccines Sub-committee of the ISCB.

Recent Publications in the Statistics of Vaccines Research

Modeling competing infectious pathogens from a Bayesian perspective: Application to influenza studies with incomplete laboratory results. Yang Yang, M. Elizabeth Halloran, Michael J. Daniels, Ira M. Longini, Jr., Donald S. Burke, and Derek A. T. Cummings. *J Am Stat Assoc.* 2010; 105(492):1310-1322.

A Bayesian competing-risk model for multiple cocirculating pathogens is proposed for inference on transmissibility and intervention efficacies under the assumption that missingness in the biological confirmation of the pathogen is ignorable. Using the proposed model, it was found that a nonpharmaceutical intervention is marginally protective against transmission of influenza A in a study conducted in elementary schools.

<http://www.ncbi.nlm.nih.gov/pubmed/21472041>

Statistical efficiency in multiple-to-one comparison trials with optimal allocation ratio. Zhang J., Zhang J.J. J. Biopharm. Stat. 2011; 21:1(125-135).

This paper discusses multiple-to-one comparison trials testing a multivalent vaccine product against multiple comparators with respect to immunologic responses. An optimal subject allocation ratio between the multivalent vaccine group and any of the comparators is introduced. <http://www.informaworld.com/smpp/content~db=all~content=a931668485>

Handling missing data in vaccine clinical trials for immunogenicity and safety evaluation. Li X., Wang W.W.B., Liu G.F., Chan I.S.F. Journal of Biopharmaceutical Statistics 2011; 21:2 (294-310)

This report presents a variety of statistical approaches for analyses of vaccine immunogenicity and safety trials in the presence of missing data. The methods are illustrated with numerical simulations and vaccine trial examples. <http://www.ncbi.nlm.nih.gov/pubmed/21391003>

Statistical interpretation of the RV144 HIV vaccine efficacy trial in Thailand: A case study for statistical issues in efficacy trials. Peter B. Gilbert, James O. Berger, Donald Stablein, Stephen Becker, Max Essex, Scott M. Hammer, Jerome H. Kim, and Victor G. DeGruttola. The Journal of Infectious Diseases 2011; 203:969–75.

Different analyses of the RV144 HIV vaccine efficacy trial seemed to give conflicting results, and a heated debate ensued as scientists and the broader public struggled with their interpretation. First the interpretation of frequentist results is addressed. Second the paper addresses how Bayesian statistics, which provide clearly interpretable statements about probabilities that the vaccine efficacy takes certain values, provide more information for weighing the evidence about efficacy than do frequentist statistics alone. <http://jid.oxfordjournals.org/content/203/7/969.short>

An extension of the single threshold design for monitoring efficacy and safety in phase II clinical trials. Brutti, P., Gubbiotti, S. and Sambucini, V. Statistics in Medicine, 2011, 30: 1648–1664. doi: 10.1002/sim.4229

An extension of a Bayesian two-stage design for treatment efficacy is proposed to incorporate safety considerations by using a criterion based on the joint posterior probability that the true overall toxicity rate and the true efficacy-and-safety rate are, respectively, smaller and larger than conveniently pre-specified target values. <http://onlinelibrary.wiley.com/doi/10.1002/sim.4229/abstract>

HIV-1 vaccine and adaptive trial designs. Lawrence Corey, Gary J. Nabel, Carl Dieffenbach, Peter Gilbert, Barton F. Haynes, Margaret Johnston, James Kublin, H. Clifford Lane, Giuseppe Pantaleo, Louis J. Picker and Anthony S. Fauci. Science Translational Medicine 2011, Vol. 3, Issue 79, p. 79ps13.

A discussion of how adaptive clinical trial designs can accelerate vaccine development by rapidly screening out poor vaccines while extending the evaluation of efficacious ones, improving characterization of promising vaccine candidates and the identification of correlates of immune protection. <http://stm.sciencemag.org/content/3/79/79ps13.abstract>

If you are an author of or know of a recent publication relevant to the statistics of vaccines research, please email a summary (preferred to abstract) to newpublications@iscb-vaccines.info so it may be included in the newsletter and on the website.

Website

The sub-committee's website at www.iscb-vaccines.info contains archives of material from the newsletter.

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To contact us regarding the activities of the sub-committee, email the chair chair@iscb-vaccines.info, or visit our 'contact us' page at <http://www.iscb-vaccines.info/contactus.htm>.

The Vaccines Sub-Committee of the International Society for Clinical Biostatistics:

Jos Nauta (Abbott, Netherlands, chair), **Ivan Chan** (Merck, USA), **Yin Bun Cheung** (Singapore Clinical Research Institute), **Andrew Dunning** (Sanofi Pasteur, USA), **Allen Izu** (Novartis, USA), **Jingyee Kou** (FDA, USA, secretary), **Zoe Moodie** (Statistical Center for HIV/AIDS Research & Prevention, USA), **Larry Moulton** (Johns Hopkins Bloomberg School of Public Health, USA), **Jennifer Nelson** (Group Health Research Institute, USA), **Júlia Singer** (Baxter, Austria), **Fabian Tibaldi** (GSK, Belgium), **Koos Zwinderman** (Academic Medical Center Amsterdam, the Netherlands).

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