Vaccines: The Week in Review
10 January 2011
Center for Vaccine Ethics & Policy
http://centerforvaccineethicsandpolicy.wordpress.com/
A program of
- Center for Bioethics, University of Pennsylvania
http://www.bioethics.upenn.edu/
- The Wistar Institute Vaccine Center
http://www.wistar.org/vaccinecenter/default.html
- Children's Hospital of Philadelphia, Vaccine Education Center
http://www.chop.edu/consumer/jsp/microsite/microsite.jsp

This weekly summary targets news and events in global vaccines ethics and policy gathered from key governmental, NGO and industry sources, key journals and other sources. This summary supports ongoing initiatives of the Center for Vaccine Ethics & Policy, and is not intended to be exhaustive in its coverage. Vaccines: The Week in Review is now also posted in pdf form and as a set of blog posts at http://centerforvaccineethicsandpolicy.wordpress.com/. This blog allows full-texting searching of some 1,200 items.

Comments and suggestions should be directed to
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Editor's Note:
With this issue, we add two titles to our *Journal Watch* coverage: **Annals of Internal Medicine** and **Pharmacoeconomics.** These journals regularly carry articles, editorials and other content supportive of Center for Vaccine Ethics & Policy focus areas. Readers are encouraged to suggest other titles that might contribute to this weekly update.

The **WER for 7 January 2011**, vol. 86, 1/2 (pp 1–16) includes:
Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010 – summary, conclusions and recommendations.
WHO said the Strategic Advisory Group of Experts (SAGE) recommended at its November 2010 meeting that global measles mortality reduction and regional elimination efforts be carried out in the context of strengthening routine immunization programmes. SAGE "concluded that measles can and should be eradicated but proposed that demonstration of sufficient progress towards regional measles elimination targets be made a precursor to establishing a target date for global eradication. Recognizing the fragility of gains in measles mortality reduction, apparent through outbreaks affecting 28 countries in the African Region since 2009, the Group highlighted the growing risk that the contribution of the reduction in measles mortality to achieving Millennium Development Goal 4 will be lost because of declining political and financial commitment to measles control." Other topics discussed included: polio eradication; support to lower-middle-income countries; improving the accessibility of affordable vaccines; influenza and typhoid vaccination; optimization of immunization schedules; and epidemiology studies of unimmunized children and gender-related issues.

http://www.who.int/entity/wer/2011/wer8601_02.pdf

HHS said six experts from outside the federal government will join the National Biodefense Science Board (NBSB), a federal advisory committee which provides expert advice and guidance on preventing, preparing for, and responding to adverse health effects of public health emergencies to the Secretary of the U.S. Department of Health and Human Services and the HHS Assistant Secretary for Preparedness and Response (ASPR). The new members replace members whose 3-year terms expire Dec. 31. The ASPR serves as the Secretary's principal advisor on bioterrorism and other public health emergencies and coordinates the federal public health and medical response to disasters. The board was created under the Pandemic and All-Hazards Preparedness Act in 2006 and chartered in May 2007. Since then, the board has provided recommendations such issues as whether the federal government should encourage stockpiling antibiotics at home for use after a bioterrorism attack and how the department can help protect, preserve, and restore individual and community mental health after a disaster. In addition, the board has provided recommendations on ways to improve the management of the research and development of medicines, vaccines and equipment for pandemic diseases. By statute, the board has 13 voting members with a broad range of expertise in science, medicine, and public health. Additionally, there are non-voting members from federal and state government agencies as deemed appropriate by the Secretary.
http://www.phe.gov/preparedness/mcm/enterprisereview/Pages/default.aspx

[Editor's Note: We do not endorse or receive any support from any companies that produce market research analysis on the vaccine marketplace. But we are interested in the market growth of vaccines as a dimension of our focus on ethics and policy, so we will occasionally report scaling projections and other data from such reports.]

"The global vaccine market is expected to achieve $34 billion in sales by 2012. With an estimated annual growth rate of 14% during the next five years, vaccines will be the fastest-growing therapeutic area, even outpacing oncology," according to Research & Markets, a market research firm.
Observations made in the abstract for this report include:
- "... One of the most striking vaccine advances in recent years is active immunotherapies, including the April 2010 FDA approval of Dendreon's Provenge, a personalized vaccine targeting prostate cancer. Active immunotherapy stimulates the patient's immune system to fight cancer while sparing the patient most of the adverse side effects associated with chemotherapy, radiation, and other biologics that target antigens. The anti-cancer activity persists long after a course of treatment. These vaccines feature new modes of action and present opportunities for development of combination therapies to provide exceptional long-term tumor control. Therapeutic vaccines are also being researched for the treatment of HIV, hepatitis C, and more.
- "Novel delivery techniques will help improve access, compliance, and safety, particularly in developing nations. One such system, nanoemulsion, is an oil-based liquid placed in the nose. It has been shown to produce a strong immune response against

smallpox and HIV. Virtually any bacterial or viral disease that results in an immune response is a candidate for the development of a nanoemulsion-based vaccine.
- "Innovation among start-up companies is one of the main factors behind the renewed interest in vaccines. Top vaccine manufacturers seek collaboration with academia and small biotech firms in the early phases of development. As the industry continues to evolve, there will be many opportunities for collaboration and public-private partnerships, like the one GlaxoSmithKline established with Brazil's Oswaldo Cruz Foundation to develop and manufacture vaccines for urgent South American public health priorities. Moving forward, vaccine partners must continue to identify unmet public health needs and accelerate innovative vaccine R&D to create novel solutions.
- "While vaccines are less susceptible to erosion by generic competition because the cost of entry is extremely high, as vaccine formulations become more precise and defined, the vaccines sector will likely follow the lead of the biotech industry toward the production of biosimilar and biobetter vaccines. India and China are emerging as competitors in this area. Both countries have exhibited great skill in copying old vaccines and are becoming increasingly adept at copying new technology, with India having become the largest global producer of copied vaccines."
http://www.researchandmarkets.com/product/f29684/vaccines_review_and_outlook_2010

The MMWR for January 7, 2011 / 59(51);1687 includes:

Announcements: Clinical Vaccinology Course --- March 4--6, 2011

CDC and seven other national organizations are collaborating with the National Foundation for Infectious Diseases (NFID), the Emory University School of Medicine, and the Emory Vaccine Center to sponsor a Clinical Vaccinology Course to be held March 4--6, 2011, in Chicago, Illinois. Through lectures and interactive case presentations, the course will focus on new developments and concerns related to the use of vaccines in pediatric, adolescent, and adult populations. Leading infectious disease experts, including pediatricians, internists, and family physicians, will present the latest information on newly available vaccines and vaccines in development, as well as established vaccines whose continued administration is essential to disease prevention efforts.

This course is designed specifically for physicians, nurses, physician assistants, pharmacists, vaccine program administrators, and other health professionals involved with or interested in the clinical use of vaccines. It also will be of interest to health-care professionals involved in the prevention and control of infectious diseases, such as federal, state, and local public health officials. Course participants should have a knowledge of or interest in vaccines and vaccine-preventable diseases.

Continuing education credits will be offered. Information regarding the preliminary program, registration, and hotel accommodations is available at http://www.nfid.org, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5951a4.htm?s_cid=mm5951a4_w

Journal Watch

[Editor's Note]

Vaccines: The Week in Review continues its weekly scanning of key journals to identify and cite articles, commentary and editorials, books reviews and other content supporting our focus on vaccine ethics and policy. ***Journal Watch* is not intended to be exhaustive, but indicative of themes and issues the Center is actively tracking.** We selectively provide full text of some editorial and comment articles that are specifically relevant to our work. Successful access to some of the links provided may require subscription or other access arrangement unique to the publisher. Our initial scan list includes the journals below. If you would like to suggest other titles, please write to David Curry at david.r.curry@centerforvaccineethicsandpolicy.org

Annals of Internal Medicine
January 4, 2011; 154 (1)
http://www.annals.org/content/current
[No relevant content]

Clinical Infectious Diseases
Volume 52 Issue 3 February 1, 2011
http://www.journals.uchicago.edu/toc/cid/current

Jessica Leung, Rafael Harpaz, Noelle-Angelique Molinari, Aisha Jumaan, and Fangjun Zhou

Herpes Zoster Incidence Among Insured Persons in the United States, 1993–2006: Evaluation of Impact of Varicella Vaccination
Clin Infect Dis. (2011) 52(3): 332-340 doi:10.1093/cid/ciq077

Abstract

Background. Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus and is often associated with substantial pain and disability. Baseline incidence of HZ prior to introduction of HZ vaccine is not well described, and it is unclear whether introduction of the varicella vaccination program in 1995 has altered the epidemiology of HZ. We examined trends in the incidence of HZ and impact of varicella vaccination on HZ trends using a large medical claims database.

Methods. Medical claims data from the MarketScan® databases were obtained for 1993-2006. We calculated HZ incidence using all persons with a first outpatient service associated with a 053.xx code (HZ ICD-9 code) as the numerator, and total MarketScan enrollment as the denominator; HZ incidence was stratified by age and sex. We used statewide varicella vaccination coverage in children aged 19-35 months to explore the impact of varicella vaccination on HZ incidence.

Results. HZ incidence increased for the entire study period and for all age groups, with greater rates of increase 1993-1996 ($P < .001$). HZ rates were higher for females than males throughout the study period ($P < .001$) and for all age groups ($P < .001$). HZ incidence did not vary by state varicella vaccination coverage.

Conclusions. HZ incidence has been increasing from 1993-2006. We found no evidence to attribute the increase to the varicella vaccine program.

Emerging Infectious Diseases
Volume 17, Number 1–January 2011

http://www.cdc.gov/ncidod/EID/index.htm

Human Vaccines
Volume 7, Issue 1 January 2011
http://www.landesbioscience.com/journals/vaccines/toc/volume/6/issue/12/
[Reviewed last week]

JAMA
January 5, 2011, Vol 305, No. 1, pp 13-1042
http://jama.ama-assn.org/current.dtl
[No relevant content]

Journal of Infectious Diseases
Volume 203 Issue 3 February 1, 2011
http://www.journals.uchicago.edu/toc/jid/current
EDITORIAL COMMENTARIES
David W. Kimberlin
Control of Varicella Disease, Version 2.0
J Infect Dis. (2011) 203(3): 297-299 doi:10.1093/infdis/jiq053
In this issue of the Journal, Shapiro and colleagues present data from a case-controlled study of the effectiveness of 2 doses of varicella vaccine during the first several years after implementation of a routine 2-dose recommended schedule. At 98.3%, the effectiveness of the 2-dose schedule is welcome news indeed. These data validate the calculations of experts from the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID), made in 2006 when both groups approved a recommendation for routine use of 2 doses of varicella vaccine during childhood. Shapiro and colleagues are to be commended for their forethought in establishing a broad surveillance network in Connecticut in the years after licensure of the varicella vaccine in 1995 and for their careful scientific and statistical evaluation of data generated from this important resource.
In understanding the context within which these new data should be viewed, it is important to reflect on the overall development and implementation of varicella vaccine. The strain that ultimately became the varicella vaccine …
Stephen J. Thomas
The Necessity and Quandaries of Dengue Vaccine Development
J Infect Dis. (2011) 203(3): 299-303 doi:10.1093/infdis/jiq060
Dengue is an emerging and reemerging arboviral disease of great global public health importance. Increased transmission and disease outbreaks are being driven by population growth, urbanization, international travel, and unchecked vector populations [1]. Southeast Asia, Central and South America, and parts of the Caribbean experience endemic and hyperendemic dengue virus (DENV) transmission while indigenous transmission is being increasingly recognized in areas of Africa, the Middle East and South Asia [2– 5]. Reports indicate that southern US border-states and Hawaii can support episodic DENV transmission [6– 12]. Dengue poses a risk to traveler and

military populations, especially those originating from non-dengue endemic regions [13– 18].

Millions of DENV infections, hundreds of thousands of hospitalizations, and tens of thousands of deaths related to dengue occur annually [19]. There is no specific, licensed anti-DENV therapeutic or preventative vaccine. The financial, social and individual cost of dengue is significant, underestimated, and underappreciated [20– 25]. The strategic administration of a safe and efficacious dengue vaccine, in coordination with efforts to educate about personal protective measures and sustained vector control, is the best hope to reduce the global dengue burden.

There are numerous dengue vaccine candidates in clinical development. Early efforts to develop a dengue vaccine date back more than 70 years, with attempts to prevent virus transmission using infectious human plasma treated with ox bile or virus grown in live mosquitoes and inactivated with formalin [26]. Schelsinger and Sabin undertook the first attempts to immunize using mouse-passaged live-attenuated DENV-1 and -2 viruses [27– 29]. Halstead and colleagues discovered DENVs were attenuated following passage in primary dog kidney (PDK) cell culture [30]. …

MAJOR ARTICLES AND BRIEF REPORTS

VIRUSES

Eugene D. Shapiro, Marietta Vazquez, Daina Esposito, Nancy Holabird, Sharon P. Steinberg, James Dziura, Philip S. LaRussa, and Anne A. Gershon

Effectiveness of 2 Doses of Varicella Vaccine in Children

J Infect Dis. (2011) 203(3): 312-315 doi:10.1093/infdis/jiq052

Abstract

Background. Because of ongoing outbreaks of varicella, a second dose of varicella vaccine was added to the routine immunization schedule for children in June 2006 by the Centers for Disease Control and Prevention.

Methods. We assessed the effectiveness of 2 doses of varicella vaccine in a case-control study by identifying children ≥4 years of age with varicella confirmed by polymerase chain reaction assay and up to 2 controls matched by age and pediatric practice. Effectiveness was calculated using exact conditional logistic regression.

Results. From July 2006 to January 2010, of the 71 case subjects and 140 matched controls enrolled, no cases (0%) vs 22 controls (15.7%) had received 2 doses of varicella vaccine, 66 cases (93.0%) vs 117 controls (83.6%) had received 1 dose, and 5 cases (7.0%) vs 1 control (0.7%) did not receive varicella vaccine ($P < .001$). The effectiveness of 2 doses of the vaccine was 98.3% (95% confidence level [CI]: 83.5%–100%; $P < .001$). The matched odds ratio for 2 doses vs 1 dose of the vaccine was 0.053 (95% CI: 0.002–0.320; $P < .001$).

Conclusion. The effectiveness of 2 doses of varicella vaccine in the first 2.5 years after recommendation of a routine second dose of the vaccine for children is excellent. Odds of developing varicella were 95% lower for children who received 2 doses compared with 1 dose of varicella vaccine.

The Lancet

Jan 08, 2011 Volume 377 Number 9760 Pages 97 - 178

http://www.thelancet.com/journals/lancet/issue/current

Perspectives

When is research on children ethical?

Peter Singer
Preview
Is it ever ethical to do research on human subjects without their consent? The Nuremberg Code, written in the aftermath of the atrocities perpetrated by Nazi doctors, makes the voluntary consent of the human subject "absolutely essential". Understandable as the desire for so absolute a barrier may be, it comes at a high cost, for it blocks research with the potential to help many children. Hence in 1964 the World Medical Association, in the Declaration of Helsinki, took a different stance, allowing research on human beings without the capacity to consent, if consent can be obtained from a legally authorised representative.

The Lancet Infectious Disease
Jan 2011 Volume 11 Number 1 Pages 1 - 72
http://www.thelancet.com/journals/laninf/issue/current
[Reviewed last week]

Nature
Volume 469 Number 7328 pp5-126 6 January 2011
http://www.nature.com/nature/current_issue.html
[No relevant content]

Nature Medicine
January 2011, Volume 17 No 1
http://www.nature.com/nm/index.html
[No relevant content]

New England Journal of Medicine
January 6, 2011 Vol. 364 No. 1
http://content.nejm.org/current.shtml
Original Articles
The Origin of the Haitian Cholera Outbreak Strain
C.-S. Chin and Others
Abstract
Background
Although cholera has been present in Latin America since 1991, it had not been epidemic in Haiti for at least 100 years. Recently, however, there has been a severe outbreak of cholera in Haiti.
Methods
We used third-generation single-molecule real-time DNA sequencing to determine the genome sequences of 2 clinical Vibrio cholerae isolates from the current outbreak in Haiti, 1 strain that caused cholera in Latin America in 1991, and 2 strains isolated in South Asia in 2002 and 2008. Using primary sequence data, we compared the genomes of these 5 strains and a set of previously obtained partial genomic sequences of 23 diverse strains of V. cholerae to assess the likely origin of the cholera outbreak in Haiti.

Results
Both single-nucleotide variations and the presence and structure of hypervariable chromosomal elements indicate that there is a close relationship between the Haitian isolates and variant V. cholerae El Tor O1 strains isolated in Bangladesh in 2002 and 2008. In contrast, analysis of genomic variation of the Haitian isolates reveals a more distant relationship with circulating South American isolates.
Conclusions
The Haitian epidemic is probably the result of the introduction, through human activity, of a V. cholerae strain from a distant geographic source. (Funded by the National Institute of Allergy and Infectious Diseases and the Howard Hughes Medical Institute.)

The Pediatric Infectious Disease Journal
January 2011 - Volume 30 - Issue 1 pp: A9-A10,1-94,e1-e17
http://journals.lww.com/pidj/pa ges/currenttoc.aspx
[Reviewed last week]

Pediatrics
January 2011 / VOLUME 127 / ISSUE 1
http://pediatrics.aappublications.org/current.shtml
[Reviewed last week]

Pharmacoeconomics
January 1, 2011 - Volume 29 - Issue 1 pp: 1-86
http://adisonline.com/pharmacoeconomics/pages/currenttoc.aspx
Review Articles
Calibrating Models in Economic Evaluation: A Seven-Step Approach
Vanni, Tazio; Karnon, Jonathan; Madan, Jason; White, Richard G.; Edmunds, W. John; Foss, Anna M.; Legood, Rosa
Pharmacoeconomics. 29(1):35-49, January 1, 2011.
doi: 10.2165/11584600-000000000-00000
Abstract:
In economic evaluation, mathematical models have a central role as a way of integrating all the relevant information about a disease and health interventions, in order to estimate costs and consequences over an extended time horizon. Models are based on scientific knowledge of disease (which is likely to change over time), simplifying assumptions and input parameters with different levels of uncertainty; therefore, it is sensible to explore the consistency of model predictions with observational data. Calibration is a useful tool for estimating uncertain parameters, as well as more accurately defining model uncertainty (particularly with respect to the representation of correlations between parameters). Calibration involves the comparison of model outputs (e.g. disease prevalence rates) with empirical data, leading to the identification of model parameter values that achieve a good fit.

This article provides guidance on the theoretical underpinnings of different calibration methods. The calibration process is divided into seven steps and different potential methods at each step are discussed, focusing on the particular features of disease

models in economic evaluation. The seven steps are (i) Which parameters should be varied in the calibration process? (ii) Which calibration targets should be used? (iii) What measure of goodness of fit should be used? (iv) What parameter search strategy should be used? (v) What determines acceptable goodness-of-fit parameter sets (convergence criteria)? (vi) What determines the termination of the calibration process (stopping rule)? (vii) How should the model calibration results and economic parameters be integrated?

The lack of standards in calibrating disease models in economic evaluation can undermine the credibility of calibration methods. In order to avoid the scepticism regarding calibration, we ought to unify the way we approach the problems and report the methods used, and continue to investigate different methods.

Pharmacoeconomics & Outcomes News
January 8, 2011 - Volume - Issue 619 pp: 1-11
http://adisonline.com/pecnews/pages/currenttoc.aspx

Vaccine studies show advances in health economic research

PharmacoEconomics & Outcomes News. (619):5, January 8, 2011.

Abstract

Using steady-state population-based analyses has the "advantage of helping policy makers understand the impact of their policy decisions on a population level in the year that the decision has reached its full effect" says Dr Lieven Annemans, of the medical faculties at Ghent and Brussels Universities. Dr Annemans was commenting on two vaccine studies that used steady-state population model included in a supplement entitled "Progress in vaccines, progress in health economics" published in Vaccine. The supplement, sponsored by GlaxoSmithKline, included articles on the economic and health consequences of vaccinating against pneumococcal and haemophillus infections.

In the first study, the researchers used national estimates in order to determine the residual economic burden of pneumococcal and haemophilus infections following pneumococcal 7-valent CRM197 vaccine conjugate (PCV-7) vaccination in children under 10 years old in Canada, Germany, Mexico and Norway.2 They estimated direct and indirect costs (at 2008 values; converted to $US) and assumed full herd effect over 1 year.

The current annual national costs ranged from $2.59/capita in Mexico up to $7.89/capita in Canada. They found that because of the high incidence of otis media it accounted for up to 88% of national direct costs and up to 96% of caregiver costs for pneumococcal or haemophilus infections.

The researchers say that a strength of this study was that they included both direct medical and caregiver productivity loss costs for the diseases across each of the different countries, and that estimating these costs separately "gives decision makers a better understanding of how much of the cost burden is attributable" to these different factors.

The second study evaluated the cost effectiveness of haemophilus influenzae pneumococcal vaccine (PHiD-CV) compared with PCV-7 across the same four countries.3 This study used an adapted static population model in order to determine the costs and QALYs associated with each vaccine (2008 values were used in the local currency). The investigators also conducted a short-term analysis, with a separate module from the

underlying population, where vaccination of a single birth cohort each year for 10 years was simulated.

They found that, when price parity was assumed, "routine vaccination with PHiD-CV resulted in lower costs compared with PCV-7 in both the short term and the steady-state year". The cost savings were not so pronounced in the short-term analysis "but cost savings increased quickly after multiple birth cohorts were vaccinated".

Dr Annemans says that analyses like these "illustrate well what country-specific data really mean", highlighting that the differences observed between countries not only pertain to the epidemiology but the "management style, unit costs and quality-of-life impact".

PLoS Medicine
(Accessed 9 January 2011)
http://medicine.plosjournals.org/perlserv/?request=browse&issn=1549-1676&method=pubdate&search_fulltext=1&order=online_date&row_start=1&limit=10&document_count=1533&ct=1&SESSID=aac96924d41874935d8e1c2a2501181c#results
[No relevant content]

Science
7 January 2011 vol 331, issue 6013, pages 1-116
http://www.sciencemag.org/current.dtl
[No relevant content]

Science Translational Medicine
5 January 2011 vol 3, issue 64
http://stm.sciencemag.org/content/current
[No relevant content]

Vaccine
Volume 29, Issue 4 pp. 613-864 (17 January 2011)
http://www.sciencedirect.com/science/journal/0264410X
[Reviewed last week]