Vaccines: The Week in Review
5 May 2012
Center for Vaccine Ethics & Policy (CVEP)

This weekly summary targets news, announcements, articles 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 also posted in pdf form and as a set of blog posts at http://centerforvaccineethicsandpolicy.wordpress.com/. This blog allows full-text searching of some 2,500 entries..

Comments and suggestions should be directed to
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Editor's Note:
The first of two voluntarily-quarantined articles addressing potential H5N1 transmissibility in humans was published online in *Nature*. Please refer to the *Journal Watch* entry for *Nature* below.

Speech: *Keynote address at the International Conference on Oman Health Vision 2050: Quality Care, Sustained Health*
Dr Margaret Chan
Director-General of the World Health Organization
Muscat, Oman 30 April 2012
http://www.who.int/dg/speeches/2012/qualitycare_20120430/en/index.html

WHO Epidemiological Brief 23: European Region - Update on measles and rubella, regional and global polio outbreak status
Measles and rubella
Incomplete reporting makes it difficult to provide an accurate number of measles cases for 2012, thus far. The officially reported number of cases (4 463) is much lower than the actual number, with the Ukrainian Ministry of Health, for example, reporting nearly 8 000 cases on its web site. Romania continues to report the highest number of rubella cases in the Region, as it faces an ongoing outbreak.
Polio
The European Region has retained its polio-free status after a 2010 polio outbreak, but remains at risk of the poliovirus importation while polio is still endemic in countries like Afghanistan and Pakistan. A recent outbreak in China, which is no longer considered active, offers a sobering illustration of this risk. Consequently, it is critical to maintain high quality AFP, enterovirus and environmental surveillance in the Region to ensure early detection of wild poliovirus importation.
http://www.euro.who.int/__data/assets/pdf_file/0008/163970/EpiBrief-Issue-23.pdf

The TuBerculosis Vaccine Initiative (TBVI) and Aeras announced a new memorandum of understanding "to enhance and strengthen collaborative efforts to advance the world's most promising TB vaccine candidates." Aeras is "a nonprofit global TB vaccine biotech based in the US and South Africa" and TBVI is "a pan-European TB vaccine research foundation based in the Netherlands." The relationship "will address significant scientific opportunities and challenges described in *Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade"* – a unified global strategy published last month in the journal *Tuberculosis* which provides a comprehensive approach for developing and introducing safe and effective TB vaccines over the next decade." Jim Connolly, President and CEO of Aeras, said, "Without new TB vaccines, we cannot end this epidemic. TB vaccine development is particularly complex and costly, and to achieve our mission it is critical to bring together the best and brightest minds in the field. Aeras is looking forward to expanding our collaboration with TBVI, whose role has been pivotal in fueling the quality of research in Europe and the development of promising new vaccine candidates." Dr. Jelle Thole, Director of TBVI, said, "Aeras has deep experience with preclinical and clinical evaluation of TB vaccine candidates and expertise in identifying promising vaccines. This provides important added value to our know-how. Together we are able to develop vaccines as cost-effectively and efficiently as possible, moving seamlessly from early laboratory research through clinical development to licensure, to deliver vaccines to communities that need their protection."
http://www.aeras.org/newscenter/news-detail.php?id=1207

Event: *Annual Albert B. Sabin Gold Medal Award Ceremony*

The 19th annual Albert B. Sabin Gold Medal Award Ceremony will be held May 7, 2012 in Baltimore, Maryland. **This year the award ceremony will honor Dr. F. Marc LaForce** for his contributions to the development of a new vaccine for epidemic meningitis in Africa. The Gold Medal Award has been awarded annually since 1994 and is given to a distinguished member of the research community who has made extraordinary contributions in the field of vaccinology or a complementary field. Each recipient is a role model for young researchers, someone whose career has saved lives through the development and use of vaccines. The Medal is the highest scientific honor given by the Sabin Vaccine Institute and commemorates the legacy of the late Dr. Albert B. Sabin. This prestigious award is presented by the Sabin Vaccine Institute (Sabin) as part of the National Foundation for Infectious Diseases (NFID) annual conference in Baltimore, Maryland.
http://www.sabin.org/updates-events/events/gold-medal-awards

PATH and the World Health Organization (WHO) were named winners of the 2012 Vaccine Industry Excellence Award for best vaccine partnership in recognition of the **Meningitis Vaccine Project (MVP)** that led to the introduction of a new meningitis A vaccine. Created in 2001, MVP developed MenAfriVac™, "a

revolutionary vaccine that protects people against deadly meningitis A and could end a century of meningitis epidemics in sub-Saharan Africa. Since its introduction in 2010, more than 54 million Africans across six countries have received the vaccine. Not a single case of group A meningococcal meningitis has been reported among those vaccinated." MVP, a partnership between PATH and WHO, is funded by the Bill & Melinda Gates Foundation and involves dozens of partner organizations working together across four continents. MVP "marks the first time a philanthropic foundation has joined with public- and private-sector organizations as well as nongovernmental organizations to create a vaccine that would not otherwise have been developed by the private sector."

PATH's Malaria Vaccine Initiative received an honorable mention in the same category for its public-private partnership with GSK Biologicals. That collaboration is supporting the development of RTS,S, a malaria vaccine candidate that could add a powerful, complementary tool for the control of malaria in Africa. The Malaria Vaccine Initiative was established at PATH in 1999 with the mission to accelerate the development of malaria vaccines and ensure their availability and accessibility in the developing world. The collaboration with GSK Biologicals began in 2001.

The Vaccine Industry Excellence Awards "are organized by Terrapinn and sponsored by Novartis Vaccines to recognize outstanding achievements by organizations and individuals in the vaccine industry. Nominees are judged on their strategic potential to the industry and potential to address unmet needs, among other criteria." The awards were presented at the 12th World Vaccine Congress in Washington, DC, on April 11.
http://www.path.org/news/an120502-vie-award.php

The **Weekly Epidemiological Record (WER) for 4 May 2012,** vol. 87, 18 (pp 169–176) includes: Validation of maternal and neonatal tetanus elimination in Liberia, 2011.
http://www.who.int/entity/wer/2012/wer8718.pdf

The **MMWR Weekly for May 4, 2012** / Vol. 61 / No. 17 includes:
- Imported Human Rabies in a U.S. Army Soldier — New York, 2011
- Comparison of Meningococcal Disease Surveillance Systems — United States, 2005–2008
- **Notes from the Field: Identification of Vibrio cholerae Serogroup O1, Serotype Inaba, Biotype El Tor Strain — Haiti, March 2012**

Extract

On October 20, 2010, an outbreak of cholera was confirmed in Haiti for the first time in more than a century. As of April 10, 2012, a total of 534,647 cases, 287,656 hospitalizations, and 7,091 deaths have been reported in Haiti as a result of the outbreak (1). The Vibrio cholerae strain that caused the Haiti epidemic has been characterized as toxigenic V. cholerae, serogroup O1, serotype Ogawa, biotype El Tor (2).

Recently, two V. cholerae isolates collected on March 12 and 13, 2012, in Anse Rouge, Artibonite Department, were characterized at the National Public Health

Laboratory in Haiti as non-Ogawa serotypes. The isolates subsequently were confirmed by CDC to belong to the Inaba serotype. By molecular analyses (pulsed-field gel electrophoresis, multilocus variable number of tandem repeat analysis, and virulence gene sequencing [ctxB and tcpA]), these two isolates are indistinguishable from the currently circulating V. cholerae serotype Ogawa strain in Haiti. The molecular analyses conducted to date suggest that they arose from serotype switching, which is a commonly observed phenomenon in cholera epidemics, often driven by population immunity to the circulating serotype. Further characterization efforts are ongoing. Finding these two isolates does not change current clinical management guidelines (3)… …The two World Health Organization prequalified vaccines provide protection against the Ogawa and Inaba serotypes. In addition, the cholera rapid diagnostic tests detect all O1 serogroup infections, including Ogawa and Inaba serotypes.

This serotype conversion illustrates the increasing diversity of V. cholerae in Haiti (2) and emphasizes the importance of continued public health surveillance by the National Public Health Laboratory and CDC, which are partnering to establish a laboratory-enhanced sentinel surveillance system for a range of infectious diseases, including cholera and other diarrheal diseases. The system will provide data to determine the burden of diarrheal disease attributable to cholera and to help direct prevention efforts and programs to reduce morbidity and mortality from cholera in Haiti.

Twitter Watch *[accessed 5 May 2012 – 14:42]*

Items of interest from a variety of twitter feeds associated with immunization, vaccines and global public health. This capture is highly selective and is by no means intended to be exhaustive.

Shot@Life @ShotAtLife
What can you commit? We're kicking-off the campaign with a goal to vaccinate 1,000 children by Mother's Day. Will you help us? #vaccineswork
10:51 AM - 26 Apr 12

HarvardPublicHealth @HarvardHSPH
CDC reports cholera in Haiti has changed, a sign that it is becoming endemic http://ht.ly/aIECe #globalhealth
10:21 AM - 5 May 12

GAVI Alliance @GAVIAlliance
@MeaslesRubella provided indispensable funding 4 Nepal & Myanmar campaigns. But success also depends on vaccine heroes. http://ht.ly/aE0N0
3:35 AM - 5 May 12

Sandra Rotman Centre @srcglobal
"The challenge now is to stimulate public demand for vaccinations": http://bit.ly/IyhbCu
Southern Vaccine Advocacy Challenge
4:21 PM - 4 May 12

PAHO/WHO @pahowho

Top #PAHOWHO officials meet #Gates Foundation counterparts public health priorities http://bit.ly/IBtGw1
2:13 PM - 4 May 12

UofT Bioethics @utjcb
Anant Bhan, MHSc grad, has a new publication, "Clinical trial ethics in India: One step forward, two steps back". http://bit.ly/IGgPJK
Retweeted by Sandra Rotman Centre
12:39 PM - 2 May 12

ECDC Eurovaccine @Eurovaccine
Helpful reading: 7 key reasons to immunise from @WHO_Europe http://bit.ly/JgkyKx #EuropeDoctorsMeet #immuniseEurope
5:07 AM - 4 May 12

ECDC @ECDC_EU
Public health experts, doctors & patients discuss role of doctors in childhood #vaccination, 4May w/ @CPME_Europa.Follow #EuropeDoctorsMeet
3:39 AM - 3 May 12

Report/Research/Book Watch

Vaccines: The Week in Review is expanding its coverage of new reports, books, research and analysis published independent of the journal channel covered in *Journal Watch* below. Our interests span immunization and vaccines, as well as global public health, health governance, and associated themes. *If you would like to suggest content to be included in this service, please contact David Curry at:*
david.r.curry@centerforvaccineethicsandpolicy.org

Report: *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*

Institute of Medicine (IOM); 1 May 2012

Abstract

Prescription drugs are crucial for preventing and treating diseases and improving the public's health, but they can also have unintended harmful effects. Often, their benefits and risks cannot be fully identified until after a drug has been used by a large, diverse group of patients over time. The passage of the Food and Drug Administration Act in 2007 provides the Food and Drug Administration (FDA) with additional postmarketing regulatory tools to better protect the health of the public, including the authority to require manufacturers to continue studying drugs that are being marketed. The FDA asked the IOM to evaluate the scientific and ethical aspects of conducting safety studies for approved drugs. The IOM recommends implementing a life cycle approach to drug safety oversight that could allow the FDA to better anticipate post-approval research needs and improve drug safety for all Americans.

Read the Report >>

Journal Watch

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.

If you would like to suggest other journal titles to include in this service, please contact David Curry at: david.r.curry@centerforvaccineethicsandpolicy.org

Annals of Internal Medicine
May 1, 2012; 156 (9)
http://www.annals.org/content/current
[No relevant content]

British Medical Bulletin
Volume 101 Issue 1 March 2012
http://bmb.oxfordjournals.org/content/current
[Reviewed earlier]

British Medical Journal
05 May 2012 (Vol 344, Issue 7855)
http://www.bmj.com/content/344/7855
[No relevant content]

Bulletin of the World Health Organization
Volume 90, Number 5, May 2012, 321-400
http://www.who.int/bulletin/volumes/90/5/en/index.html
Special theme: e-health
EDITORIALS
Establishing an evidence base for e-health: the proof is in the pudding
Najeeb Al-Shorbaji & Antoine Geissbuhler
Bulletin of the World Health Organization 2012;90:322-322A. doi: 10.2471/BLT.12.106146

Seven years have passed since the World Health Assembly adopted resolution WHA58.28 urging the World Health Organization and its Member States1 to endorse e-health as a way to strengthen health systems. In defining e-health as "the cost-effective and secure use of information and communication technologies in support of health and health-related fields", the resolution offered a definition that was comprehensive and generic, yet specific enough for researchers wishing to evaluate the impact of e-health to know what to evaluate. Specifically, the resolution urged Member States to "mobilize multisectoral collaboration for determining evidence-based e-health standards and

norms, to evaluate e-health activities, and to share the knowledge of cost-effective models, thus ensuring quality, safety and ethical standards and respect for the principles of confidentiality of information, privacy, equity and equality".

This theme issue has three main objectives, as explained in a call for papers[2] published in June 2011:

- to provide an authoritative, critical and independent overview of current knowledge about appropriate, trans-disciplinary methods and applications in e-health;
- to include contributors from developing countries, who seldom have the opportunity to publish in international journals;
- to strengthen the commitment of high-level decision-makers to address e-health interoperability issues and seek to widened the application of e-health.

Researchers, academicians and practitioners from all over the world responded to the call for papers with more than 90 submissions, 14 of which are published here.

Van Gemert-Pijnen et al.'s editorial[3] makes a worthy point: e-health development must be holistic, evidence-based and people-centred; it must take into account how people live within their own environments and respond to stakeholders' needs. In the research section that follows, Wootton et al.[4] examine the characteristics of long-running telemedicine networks and conclude that "improved collaboration between networks could help attenuate the lack of resources [...] and improve sustainability". In a study of the health-related uses of information and communication technologies (ICT) in low- and middle-income countries, Lewis et al.[5] find three leading purposes: to extend geographic access to health care, to improve data management, and to facilitate communication between patients and physicians outside the physician's office. The authors highlight the need for more sustainable sources of funding, greater support for the adoption of new technologies, and better ways to evaluate impact. A review by Piette et al.[6] of the published literature on e-health systems of three types – systems facilitating clinical practice, institutional systems and systems facilitating care at a distance – shows that e-health can improve clinical care in low- and middle-income countries, but that more research is needed on its economic benefits and impact on patient health.

In a revealing Perspective, Thirumurthy & Lester[7] find evidence that mobile health (m-health) can enable behaviour change and improve health outcomes in resource-limited settings. Van Heerden et al.[8] argue, in the same section, that the real challenge for the deployment of e-health lies in establishing country-level best practices that are both cost-effective and supported by rigorous research and evaluation. Policy-makers and funders must promote, legislate and fund programmes and interventions that integrate and build upon a common m-health framework. Kwankam[9] identifies further challenges facing e-health: creating a platform for knowledge sharing; scaling up interventions; designing integrated e-health systems; conducting professional training on e-health; integrating e-health into the social and economic context, and building ICT into the health systems of the future.

Alkmim et al.,[10] in a Lesson from the field, describe a telehealth network in Brazil and how in just five years there was a notable increase in the number of professionals trained in telehealth and in the number of electrocardiograms and teleconsultations performed through the network. The authors caution, however, that to succeed, a telehealth service needs to be collaborative, to meet the real needs of local health professionals, to employ a simple technology and to have at least some face-to-face components. According to Braa et al.[11], data use workshops have strengthened the

health management information systems by improving the quality of public health data in Zanzibar, United Republic of Tanzania. In Madagascar,[12] Rajatonirina et al. found evidence of improved disease surveillance capacity despite resource constraints owing to an innovative sentinel system based on a short message service.

The factors promoting or inhibiting the implementation of e-health systems were the subject of a systematic review, by Mair et al.,[13] that shows a growing research emphasis on "workability", or the work that health professionals must undertake to make e-health systems function well in practice. The review also points to the need for more research on the impact of e-health services on everyday clinical practice.

This theme issue highlights what we have learnt from e-health projects throughout the world in terms of feasibility, acceptance and impact on processes. The recipe may seem familiar and replicable, but the proof is in the pudding, in the clear demonstration that e-health can result in economic benefits and improve health outcomes. Programme evaluators and implementers face the challenge of generating such evidence, a prerequisite for the widespread adoption of e-health.[14]

Cost Effectiveness and Resource Allocation
(Accessed 5 May 2012)
http://www.resource-allocation.com/
[No new relevant content]

Emerging Infectious Diseases
Volume 18, Number 5—May 201
http://www.cdc.gov/ncidod/EID/index.htm
[Reviewed earlier]

Foreign Affairs
May/June 2012 Volume 91, Number 3
http://www.foreignaffairs.com/
[Reviewed earlier]

Global Health
Winter 2012
http://www.globalhealthmagazine.com/in_this_issue/
[Reviewed earlier]

Globalization and Health
[Accessed 5 May 2012]
http://www.globalizationandhealth.com/
[No new relevant content]

Health Affairs

April 2012; Volume 31, Issue 4
http://content.healthaffairs.org/content/current
Theme: Issues In Cancer Care: Value, Quality & Costs
[Reviewed earlier]

Health and Human Rights
Vol 13, No 2 (2011) December
http://hhrjournal.org/index.php/hhr
[Reviewed earlier]
Papers in Press (Issue 14.1, June 2012)
Bridging international law and rights-based litigation: Mapping health-related rights through the development of the Global Health and Human Rights Database
Benjamin Mason Meier, Helena Nygren-Krug, Oscar A. Cabrera, Ana Ayala, Lawrence O. Gostin
Abstract
The O'Neill Institute for National and Global Health Law at Georgetown University, the World Health Organization, and the Lawyers Collective have come together to develop a searchable Global Health and Human Rights Database that maps the intersection of health and human rights in judgments, international and regional instruments, and national constitutions. Where states long remained unaccountable for violations of health-related human rights, litigation has arisen as a central mechanism in an expanding movement to create rights-based accountability. Facilitated by the incorporation of international human rights standards in national law, this judicial enforcement has supported the implementation of rights-based claims, giving meaning to states' longstanding obligations to realize the highest attainable standard of health. Yet despite these advancements, there has been insufficient awareness of the international and domestic legal instruments enshrining health-related rights and little understanding of the scope and content of litigation upholding these rights. As this accountability movement evolves, the Global Health and Human Rights Database seeks to chart this burgeoning landscape of international instruments, national constitutions, and judgments for health-related rights. Employing international legal research to document and catalogue these three interconnected aspects of human rights for the public's health, the Database's categorization by human rights, health topics, and regional scope provides a comprehensive means of understanding health and human rights law. Through these categorizations, the Global Health and Human Rights Database serves as a basis for analogous legal reasoning across states to serve as precedents for future cases, for comparative legal analysis of similar health claims in different country contexts, and for empirical research to clarify the impact of human rights judgments on public health outcomes.

Health Economics, Policy and Law
Volume 7 - Issue 02 - April 2012
http://journals.cambridge.org/action/displayIssue?jid=HEP&tab=currentissue
[Reviewed earlier]

Health Policy and Planning
Volume 27 Issue 3 May 2012
http://heapol.oxfordjournals.org/content/current
[Reviewed earlier]
Supplement: Policy making for new vaccines in low- and middle-income countries
Volume 27 suppl 2 May 2012
[Reviewed earlier]

Human Vaccines & Immunotherapeutics (formerly Human Vaccines)
Volume 8, Issue 5 May 2012
http://www.landesbioscience.com/journals/vaccines/toc/volume/8/issue/5/
REVIEW
Lessons learned and applied: What the 20th century vaccine experience can teach us about vaccines in the 21st century
Corey Joseph Hebert, Corey Hall and La' Nyia J. Odoms
Abstract *Open Access Article*
Most vaccines available in the United States have been incorporated into vaccination schedules for infants and young children, age groups particularly at risk of contracting infectious diseases. High universal vaccination coverage is responsible for substantially reducing or nearly eliminating many of the diseases that once killed thousands of children each year in the US…
Research Papers
The human potential of a recombinant pandemic influenza vaccine produced in tobacco plants
Asne Jul-Larsen, Abdullah Madhun, Karl Brokstad, Emanuele Montomoli, Vidadi Yusibov and Rebecca Cox
Abstract *Open Access Article*
Rapid production of influenza vaccine antigen is an important challenge when a new pandemic occurs. Production of recombinant antigens in plants is a quick, cost effective and up scalable new strategy for influenza vaccine production. In this study, we have characterized a recombinant influenza haemagglutinin antigen (HAC1) that was derived from the 2009 pandemic H1N1 virus and expressed in tobacco plants. Volunteers vaccinated with the 2009 pH1N1 oil-in-water adjuvanted vaccine provided serum and lymphocyte samples that were used to study the immunogenic properties of the HAC1 antigen in vitro. By 7 d post vaccination, the vaccine fulfilled the licensing criteria for antibody responses to the HA detected by haemagglutination inhibition and single radial hemolysis. By ELISA and ELISPOT analysis we showed that HAC1 was recognized by specific serum antibodies and antibody secreting cells, respectively. We conducted a kinetic analysis and found a peak of serum HAC1 spec antibody response between day 14 and 21 post vaccination by ELISA. We also detected elevated production of IL-2 and IFNγ and low frequencies of CD4+ T cells producing single or multiple Th1 cytokines after stimulating PBMCs (peripheral blood mononuclear cells) with the HAC1 antigen in vitro. This indicates that the antigen can interact with T cells, although confirming an effective adjuvant would be required to improve the T-cell stimulation of plant based

vaccines. We conclude that the tobacco derived recombinant HAC1 antigen is a promising vaccine candidate recognized by both B- and T cells.

RECENTLY ACCEPTED AND COMING SOON

Commentaries

Cholera vaccine: New preventive tool for endemic countries

Ramesh Verma, Pardeep Khanna and Suraj Chawla

Abstract

Cholera is a major global public health problem and remains an important threat in almost every developing country, especially in areas where population overcrowding and poor sanitation are common, such as slums and refugee camps. Cholera is one of the most dreaded diseases in the world, in some cases leading to death within 24 h if left untreated. Without treatment, severe infection has a mortality rate of 30–50%. In 2007, WHO recorded 177,963 cholera cases and 4,031 deaths worldwide. However, the estimated actual burden of cholera is in the vicinity of 3 to 5 million cases and 100 000 to 130 000 deaths per year. The disease is endemic to parts of Africa, Asia, the Middle East and South America.1 Large outbreaks are common after natural disasters or in populations displaced by war, where there is inadequate sewage disposal and contaminated water. In India, during the 10-y period (1997–2006) studied, the states having the highest number of reported outbreaks were West Bengal, Orissa, Maharashtra and Kerala, which together accounted for 60% of all reported outbreaks. A review of cholera cases in India reported to WHO from 2003–2007 showed that the numbers were in the few thousands with a case fatality rate of < 1%. However, it is believed that the number of cholera cases and deaths occurring annually in India is much greater than the number reported. A literature review covering a four-year period from 2003 to 2006 found reported cholera outbreaks in 18 of the 35 States and Union Territories of India. Of these, 11 had cholera outbreaks reported for multiple years. Vietnam has produced a cheaper variant of killed whole-cell vaccine devoid of the B subunit. This vaccine contains both Vibrio cholerae O1 and O139, and provides 50 per cent protection for at least three years after vaccination. For endemic cholera, population-level immunity is relatively high, making control possible with relatively low vaccine coverage levels. This vaccine should be used in areas where cholera is endemic, particularly in those at risk of outbreaks, in conjunction with other prevention and control strategies.

International Journal of Infectious Diseases

Volume 16, Issue 6 pp. e413-e468 (June 2012)

http://www.sciencedirect.com/science/journal/12019712

[Reviewed earlier]

JAMA

May 2, 2012, Vol 307, No. 17, pp 1775-1877

http://jama.ama-assn.org/current.dtl

Original Contributions

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, Deborah A. Zarin, Judith M. Kramer, Rachel E. Sherman, Laura H. Aberle, Asba Tasneem

JAMA. 2012;307(17):1838-1847.doi:10.1001/jama.2012.3424
Abstract

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was downloaded on September 27, 2010, and entered into a relational database to analyze aggregate data. Interventional trials were identified and analyses were focused on 3 clinical specialties—cardiovascular, mental health, and oncology—that together encompass the largest number of disability-adjusted life-years lost in the United States.

Main Outcome Measures Characteristics of registered clinical trials as reported data elements in the trial registry; how those characteristics have changed over time; differences in characteristics as a function of clinical specialty; and factors associated with use of randomization, blinding, and data monitoring committees (DMCs).

Results The number of registered interventional clinical trials increased from 28 881 (October 2004–September 2007) to 40 970 (October 2007–September 2010), and the number of missing data elements has generally declined. Most interventional trials registered between 2007 and 2010 were small, with 62% enrolling 100 or fewer participants. Many clinical trials were single-center (66%; 24 788/37 520) and funded by organizations other than industry or the National Institutes of Health (NIH) (47%; 17 592/37 520). Heterogeneity in the reported methods by clinical specialty; sponsor type; and the reported use of DMCs, randomization, and blinding was evident. For example, reported use of DMCs was less common in industry-sponsored vs NIH-sponsored trials (adjusted odds ratio [OR], 0.11; 95% CI, 0.09-0.14), earlier-phase vs phase 3 trials (adjusted OR, 0.83; 95% CI, 0.76-0.91), and mental health trials vs those in the other 2 specialties. In similar comparisons, randomization and blinding were less frequently reported in earlier-phase, oncology, and device trials.

Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.

Editorials

The Evolution of Trial Registries and Their Use to Assess the Clinical Trial Enterprise

Kay Dickersin, Drummond Rennie

JAMA. 2012;307(17):1861-1864.doi:10.1001/jama.2012.4230

Extract

The original purpose of registries of clinical trials was to reveal the existence of all trials, published or not, to investigators and systematic reviewers. Trials left unpublished because results were unfavorable to their sponsors, or simply because investigators never submitted them to journals for publication, could then be discovered, the trial investigators contacted, and the available trial evidence involving medical interventions could then be assessed. This would help eliminate publication bias, shown originally in the 1980s,1 demonstrated by Simes2 to affect the treatment of patients, and later revealed to be widespread by the expanding efforts of the Cochrane Collaboration. A seemingly arcane statistical point became a pressing clinical problem.

Although the 1997 US Food and Drug Administration Modernization Act (FDAMA)3 established a US-based trial registry, ClinicalTrials.gov, the mandated content was narrowly defined by law, and trial investigators, whether funded by commercial sponsors, government agencies, or academic institutions, …

Journal of Health Organization and Management
Volume 26 issue 3 - Current Issue
Published: 2012
http://www.emeraldinsight.com/journals.htm?issn=1477-7266&volume=26&issue=3
Theme: S*ocial Values and Health Policy*
[Reviewed earlier]

Journal of Infectious Diseases
Volume 205 Issue 10 May 15, 2012
http://www.journals.uchicago.edu/toc/jid/current
[Reviewed earlier]

The Lancet
May 05, 2012 Volume 379 Number 9827 p1677 – 1762 e49
http://www.thelancet.com/journals/lancet/issue/current
[No relevant content]

The Lancet Infectious Disease
May 2012 Volume 12 Number 5 p355 - 422
http://www.thelancet.com/journals/laninf/issue/current
[Reviewed earlier]

Medical Decision Making (MDM)
March–April 2012; 32 (2)
http://mdm.sagepub.com/content/current
[Reviewed earlier]

Nature
Volume 485 Number 7396 pp5-142 3 May 2012
http://www.nature.com/nature/current_issue.html
Advance Online Publication (AOP)
Letter
Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets
Masaki Imai, Tokiko Watanabe, Masato Hatta, Subash C. Das, Makoto Ozawa, Kyoko Shinya, Gongxun Zhong, Anthony Hanson, Hiroaki Katsura, Shinji Watanabe, Chengjun

Li, Eiryo Kawakami, Shinya Yamada, Maki Kiso, Yasuo Suzuki, Eileen A. Maher, Gabriele Neumann & Yoshihiro Kawaoka
Highly pathogenic avian H5N1 influenza A viruses occasionally infect humans, but currently do not transmit efficiently among humans. The viral haemagglutinin (HA) protein is a known host-range determinant as it mediates virus binding to host-specific cellular receptors1, 2, 3. Here we assess the molecular changes in HA that would allow a virus possessing subtype H5 HA to be transmissible among mammals. We identified a reassortant H5 HA/H1N1 virus—comprising H5 HA (from an H5N1 virus) with four mutations and the remaining seven gene segments from a 2009 pandemic H1N1 virus—that was capable of droplet transmission in a ferret model. The transmissible H5 reassortant virus preferentially recognized human-type receptors, replicated efficiently in ferrets, caused lung lesions and weight loss, but was not highly pathogenic and did not cause mortality. These results indicate that H5 HA can convert to an HA that supports efficient viral transmission in mammals; however, we do not know whether the four mutations in the H5 HA identified here would render a wholly avian H5N1 virus transmissible. The genetic origin of the remaining seven viral gene segments may also critically contribute to transmissibility in mammals. Nevertheless, as H5N1 viruses continue to evolve and infect humans, receptor-binding variants of H5N1 viruses with pandemic potential, including avian–human reassortant viruses as tested here, may emerge. Our findings emphasize the need to prepare for potential pandemics caused by influenza viruses possessing H5 HA, and will help individuals conducting surveillance in regions with circulating H5N1 viruses to recognize key residues that predict the pandemic potential of isolates, which will inform the development, production and distribution of effective countermeasures.
http://www.nature.com/nature/journal/vaop/ncurrent/full/nature10831.html

Nature Medicine
May 2012, Volume 18 No 5 pp631-834
http://www.nature.com/nm/journal/v18/n5/index.html
Opinion
The WHO must reform for its own health - p646
Tikki Pang & Laurie Garrett
doi:10.1038/nm0512-646
The World Health Organization (WHO) is facing an unprecedented crisis that threatens its position as the premier international health agency. To ensure its leading role, it must rethink its internal governance and revamp its financing mechanisms.
Published online
04 May 2012

Nature Reviews Immunology
May 2012 Vol 12 No 5
http://www.nature.com/nri/journal/v12/n5/index.html
[No relevant content]

New England Journal of Medicine

May 3, 2012 Vol. 366 No. 18
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[No relevant content]

OMICS: A Journal of Integrative Biology
May 2012, 16(5)
http://online.liebertpub.com/toc/omi/16/4
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The Pediatric Infectious Disease Journal
May 2012 - Volume 31 - Issue 5
pp: A7-A8,431-537,e73-e77
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[Reviewed earlier]

Pediatrics
May 2012, VOLUME 129 / ISSUE 5
http://pediatrics.aappublications.org/current.shtml
Pediatrics Perspective
Inside Millennium Development Goal 4
Jonathan M. Spector
Pediatrics 2012; 129:805-808
Context and Extract
This Pediatrics Perspectives column traces the origins of the promises and commitments made to decrease global under-5 mortality. The disparities that exist worldwide are extraordinarily large, although significant progress has been made since the establishment of the Millennium Development Goals (MDGs). Dr Spector traces the origins and challenges of Goal 4 (of 8) that relate specifically to this issue. Although overall survival rates are improving, outcome gaps in under-5 mortality have widened between rich and poor nations. Clearly, the MDGs must be looked at as a large package. There are specific measurements for each goal, but success in 1 area influences the outcomes in the others. Our advocacy efforts should focus on improving the lives of the world's poorest people broadly. World leaders have committed to achieving the MDGs by 2015. We all need to use our influence and personal resources to push the international community to succeed in eliminating extreme poverty and hunger everywhere, ultimately allowing for elimination of the growing health disparities among the affluent and poorest nations.
—Jay E. Berkelhamer, MD
Editor, Global Health Perspectives
The Millennium Development Goals (MDGs) have been dubbed the "world's biggest promise."1 At the turn of the 21st century, 189 (now 192) United Nations (UN) member states agreed to support the most comprehensive poverty reduction objectives ever established (Table 1).2,3 Child mortality is addressed through Goal 4: reduction of the global under-5 mortality rate (U5MR) by two-thirds between 1990 and 2015, equivalent to an annual drop rate of 4.3% (Table 2).4 In 1990, the U5MR was estimated at 84 of

1000 live births, and 11.9 million largely preventable child deaths took place. If MDG 4 could be achieved, 30 million children would be saved by 2015.2 Since their launch, the MDGs have been …

Articles

Measles-Containing Vaccines and Febrile Seizures in Children Age 4 to 6 Years

Nicola P. Klein, Edwin Lewis, Roger Baxter, Eric Weintraub, Jason Glanz, Allison Naleway, Lisa A. Jackson, James Nordin, Tracy Lieu, Edward A. Belongia, and Bruce Fireman

Pediatrics 2012; 129:809-814

Abstract

BACKGROUND: In the United States, children receive 2 doses of measles-mumps-rubella vaccine (MMR) and varicella vaccine (V), the first between ages 1 to 2 years and the second between ages 4 to 6 years. Among 1- to 2-year-olds, the risk of febrile seizures 7 to 10 days after MMRV is double that after separate MMR + V. Whether MMRV or MMR + V affects risk for febrile seizure risk among 4- to 6-year-olds has not been reported.

METHODS: Among 4- to 6-year-old Vaccine Safety Datalink members, we identified seizures in the emergency department and hospital from 2000 to 2008 and outpatient visits for fever from 2006 to 2008 during days 7 to 10 and 0 to 42 after MMRV and MMR + V. Incorporating medical record reviews, we assessed seizure risk after MMRV and MMR + V.

RESULTS: From 2006 through 2008, 86 750 children received MMRV; from 2000 through 2008, 67 438 received same-day MMR + V. Seizures were rare throughout days 0 to 42 without peaking during days 7 to 10. There was 1 febrile seizure 7 to 10 days after MMRV and 0 after MMR + V. Febrile seizure risk was 1 per 86 750 MMRV doses (95% confidence interval, 1 per 3 426 441, 1 per 15 570) and 0 per 67 438 MMR + V doses (1 per 18 282).

CONCLUSIONS: This study provides reassurance that MMRV and MMR + V were not associated with increased risk of febrile seizures among 4- to 6-year-olds. We can rule out with 95% confidence a risk greater than 1 febrile seizure per 15 500 MMRV doses and 1 per 18 000 MMR + V doses.

Commentaries

Why Do Pertussis Vaccines Fail?

James D. Cherry

Pediatrics 2012; 129:968-970

Extract

During the 2010 pertussis epidemic in California, there was considerable concern in the press and in public health communications about the possible contribution of vaccine failures to the problem.1,2.

…The first reason, and perhaps the most important one, is that our estimates of vaccine efficacy have been inflated because of case definition.3–11 At the time of the pediatric diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine efficacy trials in the early 1990s, it was hoped that a universal case definition could be developed so that the results of the various trials could be compared. To this end, the World Health Organization (WHO) case definition was developed.3 The primary case definition required laboratory confirmation and ≥21 days of paroxysmal cough. I was a member of the WHO committee and disagreed with the primary case definition because it was clear at that time that this definition would eliminate a substantial number of cases and

therefore inflate reported efficacy values.4–11 Nevertheless, the Center for Biologics Evaluation and Research of the Food and Drug Administration accepted this definition, and package inserts of the US-licensed DTaP vaccines reflect this. For example, Infanrix (containing 25 µg pertussis toxin [PT], 25 µg filamentous hemagglutinin [FHA], and 8 µg pertactin [PRN]) and Daptacel (containing 10 µg PT, 5 µg FHA, 5 µg fimbriae [FIM]-2/3, and 3 µg …

Pediatric Clinical Trial Registration and Trial Results: An Urgent Need for Improvement

Scott C. Denne

Pediatrics 2012; 129:e1320-e1321

Extract

Performing research studies in children to evaluate drugs and other therapies is critical to providing proper pediatric medical care. For too long, medication use in children has been limited to extrapolation from adult studies or off-label use for indications that have not been properly evaluated in children. It has been less than 20 years since practical measures have been put in place to ensure that the necessary research evaluating therapies is more consistently carried out in children. Prompted by the American Academy of Pediatrics and other pediatric organizations, the Food and Drug Administration (FDA) in 1997 and the National Institutes of Health (NIH) in 1998 initiated policies designed to increase the number of children in research studies, including drug trials.1,2 Along with subsequent legislation, including the Best Pharmaceuticals for Children Act (2002), and the Pediatric Research Equity Act (2007), the initiatives by the FDA and …

Pharmacoeconomics

May 1, 2012 - Volume 30 - Issue 5 pp: 355-445

http://adisonline.com/pharmacoeconomics/pages/currenttoc.aspx

[Reviewed earlier]

PLoS One

[Accessed 5 May 2012]

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PLoS Medicine

(Accessed 5 May 2012)

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[No new relevant content]

PLoS Neglected Tropical Diseases

April 2012

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[Reviewed earlier]

PNAS - Proceedings of the National Academy of Sciences of the United States of America
(Accessed 5 May 2012)
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[No new relevant content]

Public Health Ethics
Volume 5 Issue 1 April 2012
http://phe.oxfordjournals.org/content/current
[Reviewed earlier]

Science
4 May 2012 vol 336, issue 6081, pages 509-632
http://www.sciencemag.org/current.dtl
Policy Forum
Research Ethics
Rethinking Research Ethics: The Case of Postmarketing Trials
Alex John London, Jonathan Kimmelman, and Benjamin Carlisle
Science 4 May 2012: 544-545.
Human subjects research ethics needs to directly address threats to the evidence base of the medical information economy.
Summary
From the Nuremberg Code onward, the core mission of human subjects research ethics has been to protect study participants from infringements motivated by a zeal for medical progress. However, with individuals, clinicians, and policymakers increasingly dependent on scientific information for decision-making and with vast social resources invested in developing and utilizing the fruits of research, actors have powerful incentives to co-opt research for narrow ends. Contemplated revisions to human subjects research ethics policies in the United States (1) and existing policy in Canada (2) and the United Kingdom (3) fail to capture harms that, although they may not threaten participants, nonetheless undermine the social value of research. This is illustrated by postmarketing (phase IV) research. As a corrective, research ethics should focus on safeguarding the integrity of research as a critical component of an evidence-driven, health information economy.

Science Translational Medicine
2 May 2012 vol 4, issue 132
http://stm.sciencemag.org/content/current
Commentary
Policy
Learning from Hackers: Open-Source Clinical Trials
Adam G. Dunn, Richard O. Day, Kenneth D. Mandl, and Enrico Coiera
2 May 2012: 132cm5

Abstract
Open sharing of clinical trial data has been proposed as a way to address the gap between the production of clinical evidence and the decision-making of physicians. A similar gap was addressed in the software industry by their open-source software movement. Here, we examine how the social and technical principles of the movement can guide the growth of an open-source clinical trial community.

Tropical Medicine & International Health
May 2012 Volume 17, Issue 5 Pages 531–682
http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-3156/currentissue
[Reviewed earlier]

Vaccine
http://www.sciencedirect.com/science/journal/0264410X
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[Reviewed earlier]

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Vol 15 | No. 2 | March-April 2012 | Pages 215-400
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Volume 02, Number 01 (February 2012)
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