Vaccines: The Week in Review
20 June 2011
Center for Vaccine Ethics & Policy (CVEP)
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 1,600 items.

Comments and suggestions should be directed to
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The GAVI Alliance pledging conference – Saving children's lives – resulted in donors committing US$ 4.3 billion, exceeding an initial target of $3.7 billion, "enabling GAVI to reach more children faster than planned and to accelerate the introduction of new vaccines." A portion of the pledges are conditional upon GAVI raising additional funds from new donors in the future. Today's pledges bring GAVI's total available resources for the period 2011 to 2015 to $ 7.6 billion.
Download the press release and tables showing a breakdown of donor pledges from the conference, and a composition of pledges for 2011-2015 (PDF - 192K)
GAVI has provided a summary of publications and documents related to the pledging conference at:
http://www.gavialliance.org/media_centre/publications/pledging_conference.php

Speech: GAVI Replenishing Event
Anthony Lake, UNICEF Executive Director at London, 13 June 2011
http://www.unicef.org/media/media_58919.html

USAID announced the U.S. pledge to GAVI of US$450 million over the next 3 years, subject to congressional approval. Dr. Rajiv Shah, Administrator of the U.S. Agency for International Development (USAID), commented, "…At a time when budgets around the world are being scrutinized, this partnership with donor and host country

governments, civil society and private sector partners ensures our development dollars have the greatest impact. Not only is our commitment inspiring the generosity of other donors, it helps ensure the quantities of vaccine needed to obtain lower prices, allowing us to save even more lives." He also noted that "within the next year, the U.S. Government will host a high-level conference to assess progress against achieving impact based on the immunization pledges made here today."
http://www.prnewswire.com/news-releases/united-states-pledges-multi-year-contribution-to-reduce-immunization-cost-save-more-childrens-lives-123740664.html

The Special Programme for Research and Training in Tropical Diseases based at WHO and co-sponsored by UNICEF, UNDP, the World Bank and WHO – was awarded the 2011 Gates Award for Global Health. The "world's largest public health prize" was presented to TDR Director Dr Robert Ridley who commented, "This award represents the culmination of 36 years of history. Researchers from all over the world have worked with us to find improved health solutions for people in poor countries. The long-term commitments from our donors have led to major progress against many infectious diseases of poverty."
http://www.who.int/mediacentre/news/releases/2011/gatesaward_20110617/en/index.html

Speech: *Success, shocks, surprises, and moral vindication*
Dr Margaret Chan, Director-General of the World Health Organization
Address at the Chatham House event on the increasing importance of global health in international affairs, London, UK; 13 June 2011
http://www.who.int/dg/speeches/2011/globalhealth_20110613/en/index.html

HHS in the U.S., through the National Prevention, Health Promotion, and Public Health Council, announced the release of the **National Prevention Strategy**, described as a comprehensive plan that will help increase the number of Americans who are healthy at every stage of life. The National Prevention Strategy "recognizes that good health comes not just from receiving quality medical care, but also from clean air and water, safe outdoor spaces for physical activity, safe worksites, healthy foods, violence-free environments and healthy homes. Prevention should be woven into all aspects of our lives, including where and how we live, learn, work and play. Everyone—businesses, educators, health care institutions, government, communities and every single American—has a role in creating a healthier nation."
http://www.healthcare.gov/center/councils/nphpphc/strategy/index.html
The full report is available at:
http://www.healthcare.gov/center/councils/nphpphc/strategy/report.pdf
The report addresses vaccines in Strategic Directions No. 6 (p.20): Enhance coordination and integration of clinical, behavioral, and complementary health strategies:
Actions

The Federal Government will:
Develop new and improved vaccines, enhance understanding of the safety of vaccines and vaccination practices, support informed vaccine decision-making, and improve access to and better use of recommended vaccines.

The **MMWR Weekly for June 17, 2011** / Vol. 60 / No. 23, includes:
Place of Influenza Vaccination Among Adults --- United States, 2010--11 Influenza Season
http://www.cdc.gov/mmwr/pdf/wk/mm6023.pdf

WHO Europe: WHO Epidemiological Brief 15: Measles outbreaks and response to importation of wild poliovirus; Measles outbreaks continue

By the end of April 2011, the Region had reported more than 11 000 confirmed cases of measles. Over 75% of these cases are not immunized against measles. While western Europe is particularly affected by outbreaks, it is clear that the problem of measles outbreaks is not confined to any specific country or subregion.
Response to importation of wild poliovirus

Genetic analysis of the virus that caused the 2010 polio outbreak in Tajikistan and neighbouring countries has shed light on the possible origin and date of introduction, namely an importation of WPV1 of a South Asia (SOAS) genotype, which most likely occurred in late 2009 or early 2010. As part of the continued response to the outbreak, seven Member States have synchronized their supplementary immunization activities (SIAs). These campaigns have resulted in 15 rounds of polio immunization (mOPV and tOPV) and targeted more than 18 million children.
http://www.euro.who.int/__data/assets/pdf_file/0004/145291/WHO_EPI_Brief__Jun_2011e.pdf

The **Weekly Epidemiological Record (WER) for 17 June 2011**, vol. 86, 25 (pp 257–268) includes: Soil-transmitted helminthiases: estimates of the number of children needing preventive chemotherapy and number treated, 2009
267 Monthly report on dracunculiasis cases, January–April 2011
http://www.who.int/entity/wer/2011/wer8625.pdf

Twitter Watch
A selection of items of interest this week from a variety of twitter feeds. This capture is highly selective and by no means intended to be exhaustive.

whonews WHO News
by PeterASinger

Dramatic fall in cases of #meningitis A after new #vaccine introduction in Sub-Saharan #Africa j.mp/ipKeLH #globalhealth

PIH Partners In Health
World leaders launch plan to eliminate new #HIV infections among children by 2015 http://ow.ly/5kgCN via @unaids #AIDS

Eurovaccine ECDC Eurovaccine
Get vaccinated before attending mass gatherings http://bit.ly/jwG1Gz #measles @Madrid11_en #vaccine #WYD

GlobalHealth Global Health
@GAVIalliance provides a template to be adapted for #NCDs - Dr. Nabel at UN civil society hearing on #NCDs #globalhealth

USAID USAID
Reduced cost of key vaccines, exceeded pledge targets at #GAVI pledge conference. Special thanks to @onecampaign for highlighting the issue

rotary Rotary International
by EndPolioNow
We've raised about $174.7 million for Rotary's US$200 Million Challenge to eradicate polio. http://cot.ag/a5lkhN

unpublications UN Publications
Read the State of the World Population Report 2010 bit.ly/iykDH7 & go to new UN/DPI site on #decolonization bit.ly/iZIGlT. Also

Harvard_Health HarvardGlobalHealth
Epidemiologists are using social media to discover & track the spread of disease bitURL.net/bqtf #Facebook #Google #Twitter #Foursquare

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. 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

June 7, 2011; 154 (11)
http://www.annals.org/content/current
[Reviewed last week]

British Medical Bulletin
Volume 98 Issue 1 June 2011
http://bmb.oxfordjournals.org/content/current
[Reviewed earlier; No relevant content]

British Medical Journal
18 June 2011 Volume 342, Issue 7811
http://www.bmj.com/content/current
Editorials
H1N1 influenza in pregnant women
K S Joseph,
Robert M Liston
BMJ 2011;342:doi:10.1136/bmj.d3237 (Published 14 June 2011)
Vaccination is the key to mitigating the higher incidence of adverse outcomes
Although the 2009 H1N1 pandemic proved to be more benign than anticipated, it had a substantial effect on pregnant women. In the linked cohort study (doi: 10.1136/bmj.d3214), Pierce and colleagues report the perinatal outcomes of 256 pregnant women admitted to hospital with H1N1 influenza in the United Kingdom. 1 The study found that pregnant women admitted to hospital with H1N1 influenza had significantly higher rates of adverse pregnancy outcomes than uninfected pregnant women. These included three to four times higher rates of preterm birth, four to five times higher rates of stillbirth, and four to six times higher rates of neonatal death. 1 These high rates of adverse perinatal outcomes were consistent with those reported in a population based study from the United States, 2 which also found a high maternal death rate (five deaths in 489 pregnant women admitted to hospital). Presumably, details of specific maternal complications and causes of death will be forthcoming …
Analysis
Global health diplomacy: how foreign policy can influence health
Ilona Kickbusch
BMJ 2011;342:doi:10.1136/bmj.d3154 (Published 10 June 2011)
[No abstract]

Clinical Infectious Diseases
Volume 53 Issue 1 July 1, 2011
http://www.journals.uchicago.edu/toc/cid/current
[Reviewed last week]

Cost Effectiveness and Resource Allocation
(accessed 19 June 2011)
http://www.resource-allocation.com/

[No relevant content]

Emerging Infectious Diseases
Volume 17, Number 6–June 2011
http://www.cdc.gov/ncidod/EID/index.htm
[Reviewed earlier]

Health Affairs
June 2011; Volume 30, Issue 6
Strategies For The 'Decade Of Vaccines'
http://content.healthaffairs.org/content/current
Book Reviews
Vaccination: Facts Alone Do Not Policy Make
Deadly Choices: How The Anti-Vaccine Movement Threatens Us All by Paul A. Offit New York (NY): Basic Books, 2011 288 pp., $27.50
The Panic Virus: A True Story Of Medicine, Science, And Fear by Seth Mnookin New York (NY): Simon and Schuster, 2011 488 pp.; $26.99
Arthur Caplan
Extract
If biomedical scientists, physicians, or experts in health policy were asked what they base their clinical or policy recommendations on, one would probably hear references to facts, data, evidence, and confirmed findings. Little would be said about values—but they must be at the center of any discussion. These two books make this point clearly. Evidence-based medicine began as an effort to identify and examine regional variations in clinical practice with the goal of increasing safety and efficacy. The field has evolved into a full-fledged ideological movement that demands that clinical practice and policies rest on solid, objective evidence for their warrant and reimbursement. 1 Evidence surely is necessary and desirable in trying to decide what to do about health care at the bedside, in the legislature, or in the boardroom. But it is not sufficient. 2 Nowhere is this more in evidence than in the running battle about vaccination in the United States.
Two recent books lay out the facts about vaccine efficacy and safety. One, Deadly Choices: How the Anti-Vaccine Movement Threatens Us All, is by Paul A. Offit, a physician and infectious disease expert at the Children's Hospital of Philadelphia. The other, by writer and editor Seth Mnookin, is The Panic Virus: A True Story of Medicine, Science, and Fear.
Offit does yeoman's duty in showing that worries about vaccine safety rest firmly on a vast pile of nonsense, duplicity, hype, and deeply flawed science. He tracks the history of vaccine opposition from its start among the conscientious objectors to smallpox vaccine in Britain in the nineteenth century down to the gaggle of celebrities and media lights who lead the movement today. If you want a solid grasp of the worries, fears, misunderstandings, and ideology that have inspired a small minority of people to vocally oppose …

Health Economics, Policy and Law

Volume 6 - Issue 03 - 2011 http://journals.cambridge.org/action/displayIssue?jid=HEP&tab=currentissue

Should health authorities offer risk-sharing contracts to pharmaceutical firms? A theoretical approach

Fernando Antonanzas, Carmelo Juarez-Castello and Roberto Rodriguez-Ibeas

Abstract

In this paper, we characterise the risk-sharing contracts that health authorities can design when they face a regulatory decision on drug pricing and reimbursement in a context of uncertainty. We focus on two types of contracts. On the one hand, the health authority can reimburse the firm for each treated patient regardless of health outcomes (non risk-sharing). Alternatively, the health authority can pay for the drug only when the patient is cured (risk-sharing contract). The optimal contract depends on the trade-off between the monitoring costs, the marginal production cost and the utility derived from treatment. A non-risk-sharing agreement will be preferred by the health authority, if patients who should not be treated impose a relatively low cost to the health system. When this cost is high, the health authority would prefer a risk-sharing agreement for relatively low monitoring costs.

Human Vaccines

Volume 7, Issue 6 June 2011

http://www.landesbioscience.com/journals/vaccines/toc/volume/7/issue/6/

[Reviewed earlier]

JAMA

June 15, 2011, Vol 305, No. 23, pp 2379-2484

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

[No relevant content]

Journal of Infectious Diseases

Volume 204 Issue 2 July 15, 2011

http://www.journals.uchicago.edu/toc/jid/current

EDITORIAL COMMENTARIES

Frank Shann

Editor's Choice: The Nonspecific Effects of Vaccines and the Expanded Program on Immunization

J Infect Dis. (2011) 204(2): 182-184 doi:10.1093/infdis/jir244

(See the article by Aaby et al, on pages 245–52 .)

There is now clear evidence that the simplistic conventional model of immunization is invalid [1]. We can no longer assume that a vaccine acts independently of other vaccines, or that it influences only infections caused by the target disease. Strong evidence from randomized trials suggests that bacillus Calmette-Guérin vaccine (BCG) reduces mortality from infections other than tuberculosis and that measles vaccine reduces mortality from infections other than measles [1– 4]. However, there is worrying evidence that whole-cell diphtheria-tetanus-pertussis vaccine (DTP) may increase mortality from infections other than diphtheria, tetanus, or pertussis in high-mortality

areas [1, 3– 8]. These nonspecific effects of BCG, measles vaccine, and DTP are generally stronger in girls, appear to be maximal in the first 6 months after immunization, and are largely determined by the most recent vaccine administered [1].

Randomized trials show that measles vaccine has strong nonspecific effects. Providing it is not given after vitamin A or followed by DTP, measles vaccine reduces mortality from diseases other than measles by 45% (95% confidence interval [CI], 14%–65%) when given at 4.5 months of age [9], and by 47% (95% CI, 23%–63%) when given to girls at 9 to 10 months of age [1].

In this issue of the Journal, Aaby et al present further evidence, from Guinea-Bissau, that BCG has potent nonspecific effects on mortality [4]. Low-birth-weight neonates were randomized to receive BCG at birth or via the routine immunization program at an older age (median, 7.7 weeks). The biological effects of BCG are shown by the outcome during the first 4 weeks after randomization, before children in either group had been given DTP and when few …

[Free full text: http://jid.oxfordjournals.org/content/204/2/182.full]

The Lancet

Jun 18, 2011 Volume 377 Number 9783 Pages 2055 - 2150

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

[No relevant content]

The Lancet Infectious Disease

Jun 2011 Volume 11 Number 6 Pages 417 - 488

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

[Reviewed earlier]

Medical Decision Making (MDM)

May/June 2011; 31 (3)

http://mdm.sagepub.com/content/current

[Reviewed earlier]

Nature

Volume 474 Number 7351 pp251-412 16 June 2011

http://www.nature.com/nature/current_issue.html

[No relevant content]

Nature Medicine

June 2011, Volume 17 No 6

http://www.nature.com/nm/index.html

[Reviewed earlier]

New England Journal of Medicine

June 16, 2011 Vol. 364 No. 24
http://content.nejm.org/current.shtml
Perspective
The Polio Endgame
Bruce Aylward, M.D., and Tadataka Yamada, M.D.
N Engl J Med 2011; 364:2273-2275June 16, 2011
[Free full text]

Infection with poliovirus can have devastating consequences, including paralysis and death. In 1988, a year when an estimated 350,000 or more children were paralyzed by polio, the World Health Assembly initiated a global effort to eradicate the infection once and for all. It was an audacious undertaking, given that the virus circulates largely undetected, requires laborious cell-culture techniques to confirm infection, and is tackled with vaccines that provide imperfect protection in the gut.

Initially, the number of polio cases and countries with infections fell rapidly, particularly as financing and political support increased in the mid-1990s. The last case of paralytic poliomyelitis caused by the serotype 2 wild poliovirus was detected in 1999. The number of new polio cases caused by the two remaining wild serotypes had decreased by 99% between 1988 and 2005, but progress had stalled and there was a danger of failure when wild polio viruses were reintroduced into large areas of Africa and Asia. By the end of 2009, sustained investments in innovation had produced a new bivalent oral poliovirus vaccine (OPV)1 and novel tactics for reaching children who had been missed consistently by vaccination campaigns. A new independent monitoring process was established for overseeing the program and guiding course corrections. Since January 2010, new polio cases have decreased by 95% in the world's largest remaining reservoirs of indigenous virus in northern India and northern Nigeria; the number of cases caused by serotype 3 has fallen by 92% globally; and most countries where poliovirus had been reintroduced have again become polio-free (see map Cases of Poliomyelitis Caused by Wild Poliovirus Types 1 and 3, January 1–May 24, 2011. and interactive map).

Declines in the intensity of poliovirus transmission in India and Nigeria are key to interrupting wild poliovirus globally, since viruses originating in these countries have been responsible for all the recent importation-associated outbreaks in previously polio-free countries. Besides India and Nigeria, indigenous polioviruses now survive only in Pakistan and one part of Afghanistan, with just eight other countries currently responding to outbreaks caused by imported viruses. However, in three of these countries — Angola, Chad, and the Democratic Republic of Congo — transmission was reestablished (i.e., at least one imported virus continued to circulate for more than 12 months). All three countries then became secondary wild-poliovirus reservoirs, with onward spread to other previously polio-free countries. The logistic challenges of reaching more than 90% of young children in mass OPV immunization campaigns in countries with reestablished transmission are similar in scale to those faced in the remaining countries with endemic disease, where conflict, insecurity, and weak public services complicate eradication operations.

Although there is still much distance to cover to eradicate the remaining wild polioviruses, recent progress has generated new confidence in the eradication effort, and talk of the polio "endgame" has intensified. However, preventing new polio outbreaks in a "post-eradication era" will require more than biocontainment measures to prevent the reintroduction of wild virus from laboratory stocks or sites where inactivated

(Salk) polio vaccine (IPV) is produced. Achieving a polio-free world will eventually require stopping routine immunization with OPV and eliminating vaccine-derived polioviruses (VDPVs), particularly circulating VDPVs, which are Sabin-strain viruses that have acquired both neurovirulence and the capacity to circulate.[2]

Of the three risks associated with OPV, the most frequently realized one is vaccine-associated paralytic poliomyelitis (VAPP). This risk will disappear with the cessation of use of OPV. Outbreaks caused by circulating VDPVs are rarer than VAPP cases, but new diagnostic tests have confirmed their regular emergence, particularly that of serotype 2 circulating VDPVs, which were found in eight of the nine countries reporting VDPV outbreaks between 2008 and 2010. The persistence of such an outbreak for more than 4 years in Nigeria highlights the importance of reducing the risk of VDPV outbreaks when OPV use ceases and of actively managing any persisting outbreaks.

The rarest risk associated with OPV use is chronic VDPV excretion by people with severe primary B-cell immune disorders. All but one of these chronic immunodeficiency-associated VDPVs to date have occurred in industrialized countries that no longer use OPV. However, people with such infections may excrete virulent virus for years and are themselves at risk for fatal disease (see Brief Report by DeVries et al. in this issue of the Journal, pages 2316–2323). Although industrialized countries now use IPV and will therefore no longer generate new immunodeficiency-associated VDPVs, additional strategies and tools are required to mitigate the associated risk. Ongoing studies in nine low- and low-middle-income countries should help to inform more robust surveillance and, if necessary, case-management strategies for chronic immunodeficiency-associated VDPVs in such settings.

Stopping routine immunization with OPV globally after wild poliovirus is eradicated will eliminate VAPP immediately and halt the generation of new circulating and immunodeficiency-associated VDPVs. The challenge will be to synchronize global cessation of OPV immunization and then manage the transition, potentially lasting several years, to the point where residual VDPVs have been eliminated. Five years ago, the tools for executing this endgame didn't exist. Today, 12 monovalent OPVs, at least 1 for each serotype, are licensed, and a global stockpile is being built to facilitate a rapid response to any circulating VDPVs that persist after OPV immunization ceases.

It is important to decrease the risk of emergence and transmission of circulating VDPVs in low-income countries, as well as the transmission of any wild viruses introduced through breaks in laboratory containment. Low-cost solutions have been sought to facilitate routine immunization with IPV in such settings and thereby maintain some immunity to polio through at least the first 5 to 10 years after cessation of OPV administration, when risk would probably be highest. It now appears increasingly feasible to create an IPV administration schedule that costs no more than existing OPV schedules, through some combination of reducing the number of doses, delivering one fifth the amount of antigen per dose by intradermal administration, using adjuvants, and introducing seed strains (e.g., Sabin strains) that can be produced safely by low-cost manufacturers in developing countries.[3,4] To help address the problem of chronic shedding of immunodeficiency-associated VDPV and reduce the potential for emergence of resistance, there are at least two antiviral candidates in early stages of development. Given the potentially fatal outcome of chronic infection, the availability of such treatments should also facilitate screening of at-risk but asymptomatic people.

Of course, none of these tools is perfect. Using monovalent OPVs to combat residual circulating VDPVs incurs the small risk of generating a new circulating VDPV — a risk

that could increase with time after OPV use ceases. Since IPV does not induce the same level of intestinal mucosal immunity as OPV, we don't yet know how effective IPV would be in terminating transmission of a circulating VDPV in tropical settings. Even if an antiviral drug is successfully developed, viral resistance may be encountered in the treatment of chronic shedders of immunodeficiency-associated VDPVs. Further research is providing additional tools and strategies that may be necessary for managing the risks in the posteradication era. Already the availability of these new tools has allowed serious discussions to begin regarding replacing trivalent OPV with bivalent OPV in routine vaccination programs, to take advantage of the apparent eradication of wild poliovirus type 2 and eliminate the VDPV risks associated with continued routine use of live vaccines with a type 2 component.

Uncertainties about the risks associated with cessation of OPV use have contributed to arguments that continued OPV immunization might be a more prudent approach to the polio endgame. However, there is accumulating evidence that intelligent application of innovative tools and strategies has shifted the balance of risk so that sustaining routine OPV immunization after the eradication of wild-type virus would present a greater risk to society and cost much more[5] than eventual cessation of OPV immunization as a critical step in eradicating all polio disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Source Information

From the World Health Organization, Geneva (B.A.); and the Bill and Melinda Gates Foundation, Seattle (T.Y.).

Original Article

Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil

Manish M. Patel, Vesta Richardson López-Collada, Marília Mattos Bulhões, Lucia Helena De Oliveira, Aurora Bautista Márquez, Brendan Flannery, Marcelino Esparza-Aguilar, Ernesto Isaac Montenegro Renoiner, María Edilia Luna-Cruz, Helena Keico Sato, Luz del Carmen Hernández-Hernández, Gerardo Toledo-Cortina, Magdalena Cerón-Rodríguez, Neydi Osnaya-Romero, Mario Martínez-Alcazar, Rocío Gabriela Aguinaga-Villasenor, Arturo Plascencia-Hernández, Francisco Fojaco-González, Guillermo Hernández-Peredo Rezk, Sixto Fortino Gutierrez-Ramírez, Roberto Dorame-Castillo, Rogelio Tinajero-Pizano, Bernice Mercado-Villegas, Marilia Reichelt Barbosa, Eliane Mara Cesário Maluf, Lucimar Bozza Ferreira, Francisca Maria de Carvalho, Ana Rosa dos Santos, Eduardo Dolabella Cesar, Maria Elisa Paula de Oliveira, Carmem Lúcia Osterno Silva, Maria de los Angeles Cortes, Cuauhtemoc Ruiz Matus, Jacqueline Tate, Paul Gargiullo, and Umesh D. Parashar

N Engl J Med 2011; 364:2283-2292June 16, 2011

Background

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

Full Text of Background...

Methods

We used case-series and case–control methods to assess the association between RV1 and intussusception. Infants with intussusception were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants

from the same neighborhood were enrolled as controls. Vaccination dates were verified by a review of vaccination cards or clinic records.
Full Text of Methods...
Results
We enrolled 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1 to 7 days after the first dose of RV1 was identified among infants in Mexico with the use of both the case-series method (incidence ratio, 5.3; 95% confidence interval [CI], 3.0 to 9.3) and the case–control method (odds ratio, 5.8; 95% CI, 2.6 to 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk, albeit smaller than that seen after the first dose in Mexico — an increase by a factor of 1.9 to 2.6 — was seen 1 to 7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51,000 infants) and in Brazil (approximately 1 per 68,000 infants) and of 5 deaths due to intussusception was attributable to RV1. However, RV1 prevented approximately 80,000 hospitalizations and 1300 deaths from diarrhea each year in these two countries.
Full Text of Results...
Conclusions
RV1 was associated with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants. The absolute number of deaths and hospitalizations averted because of vaccination far exceeded the number of intussusception cases that may have been associated with vaccination. (Funded in part by the GAVI Alliance and the U.S. Department of Health and Human Services.)
Full Text of Discussion...

Original Article

Immunogenicity and Safety of a Meningococcal A Conjugate Vaccine in Africans

Samba O. Sow, M.D., Brown J. Okoko, M.D., M.P.H., Aldiouma Diallo, M.D., M.P.H., Simonetta Viviani, M.D., Ray Borrow, Ph.D., George Carlone, Ph.D., Milagritos Tapia, M.D., Adebayo K. Akinsola, M.D., Pascal Arduin, M.Sc., Helen Findlow, Ph.D., Cheryl Elie, M.Sc., Fadima Cheick Haidara, M.D., Richard A. Adegbola, Ph.D., F.R.C.Path., Doudou Diop, M.D., Varsha Parulekar, M.Sc., Julie Chaumont, M.Sc., Lionel Martellet, M.A., Fatoumata Diallo, M.D., Olubukola T. Idoko, M.D., Yuxiao Tang, Ph.D., Brian D. Plikaytis, M.Sc., Prasad S. Kulkarni, M.D., Elisa Marchetti, Ph.D., F. Marc LaForce, M.D., and Marie-Pierre Preziosi, M.D., Ph.D.

N Engl J Med 2011; 364:2293-2304June 16, 2011

Original Article

Vaccine-Derived Poliomyelitis 12 Years after Infection in Minnesota

Aaron S. DeVries, M.D., M.P.H., Jane Harper, M.S., Andrew Murray, M.P.H., Catherine Lexau, Ph.D., M.P.H., Lynn Bahta, B.S.N., Jaime Christensen, B.S., Elizabeth Cebelinski, B.S., Susan Fuller, M.B.S., Susan Kline, M.D., M.P.H., Gregory S. Wallace, M.D., M.P.H., Jing H. Shaw, M.D., Cara C. Burns, Ph.D., and Ruth Lynfield, M.D.

N Engl J Med 2011; 364:2316-2323June 16, 2011

A 44-year-old woman with long-standing common variable immunodeficiency who was receiving intravenous immune globulin suddenly had paralysis of all four limbs and the respiratory muscles, resulting in death. Type 2 vaccine-derived poliovirus was isolated from stool. The viral capsid protein VP1 region had diverged from the vaccine strain at 12.3% of nucleotide positions, and the two attenuating substitutions had reverted to the

wild-type sequence. Infection probably occurred 11.9 years earlier (95% confidence interval [CI], 10.9 to 13.2), when her child received the oral poliovirus vaccine. No secondary cases were identified among close contacts or 2038 screened health care workers. Patients with common variable immunodeficiency can be chronically infected with poliovirus, and poliomyelitis can develop despite treatment with intravenous immune globulin.

Editorial

Rotavirus Vaccination and Intussusception — Act Two

Harry B. Greenberg, M.D.

N Engl J Med 2011; 364:2354-2355June 16, 2011

[Free full text]

The development of vaccines has been a triumph of modern medicine.1 In addition to the eradication of smallpox and the near-eradication of polio, the past 30 years has seen an impressive decline in many vaccine-preventable diseases, including measles, hepatitis B virus, serious pneumococcal infection, hemophilus influenza, and, recently, rotavirus. Vaccination has been an enormously powerful force for health improvement because of the large societal benefits provided with remarkably small risks. However, some have expressed worry that current vaccines are dangerous and represent a considerable threat to the health of the recipients.2 These concerns often do not include an analysis of the benefits as well as the risks of a given vaccine.

Rotavirus infection is the most important cause of severe diarrheal disease in young children. In less-developed countries, rotavirus accounts for more than 500,000 childhood deaths annually; in developed countries, rotavirus is an infrequent cause of death but a common cause of hospitalizations and outpatient visits. RotaShield, a rotavirus vaccine composed of four human×simian reassortants (RV4), was recommended for universal pediatric use in the United States in 1998. Within a year, after the vaccine had been given to more than 500,000 children, it was found to cause a transient increased risk of intussusception (estimated to occur in 1 child in 10,000) in the first 10 days after the initial vaccination. It was rapidly withdrawn from the market before there was an opportunity for a detailed public discussion of the risks and benefits surrounding its use.3

Two second-generation rotavirus vaccine candidates (one composed of five human×animal reassortants [RV5] and the other a monovalent attenuated human rotavirus vaccine [RV1]) were in development in 1999 and, after 7 additional years of study, were licensed in the United States and other countries. Both second-generation vaccines are efficacious, and both underwent extensive safety trials (together involving more than 130,000 subjects); no association with intussusception was detected in these trials.4 In the 4 years since RV1 and RV5 were licensed, we have witnessed a substantial reduction in the rates of hospitalization and death from rotavirus in both developed and less-developed countries.5 As part of the postlicensure safety follow-up, the possible effect of the widespread use of RV1 and RV5 on intussusception rates has been monitored in the United States and abroad. In this issue of the Journal, Patel et al.6 report the results of safety assessments of RV1 in Mexico and Brazil.

RV1 was found to be associated with a small excess risk of intussusception (approximately 1 in 51,000 vaccinated children) in Mexico in the first week after the initial vaccination. The timing of the excess risk is similar to that originally seen with RV4 and corresponds to the peak timing of vaccine replication. A smaller excess risk was observed after the second RV1 dose, but this occurred during the second and third week

after vaccination and its significance is unclear. Interestingly, in Brazilian children receiving RV1, a smaller excess risk of intussusception was observed (approximately 1 in 68,000 vaccinated children) and then only in the first week after the second dose. The reasons for these differences in timing and rate are not clear but might include the fact that in Brazil, but not in Mexico, the first dose of RV1 was administered with the oral poliovirus vaccine, which suppresses rotavirus vaccine replication. Recent preliminary studies from Australia also suggest a link between RV5 and intussusception.[7] Hence, we can infer from these studies that any orally administered live rotavirus vaccines will probably carry some detectable risk of intussusception, that the risks associated with RV4 were not unique, and that the risk of intussusception seems to be small. Since RV1 was originally derived from a virulent human rotavirus, it is likely that natural, wild-type rotavirus infection is also associated with intussusception at a very low frequency.

A likely reason that the very large prelicensure safety trials of RV1 and RV5 did not detect an intussusception signal is that they were simply underpowered to pick up rare events occurring at rates below 1 in 50,000. The study by Patel et al. was insufficiently powered to determine whether the risk of intussusception associated with RV1 in infants receiving their first vaccination after 15 weeks of age was increased, as has been suggested previously in the case of recipients of RV4. Whether the various licensed or candidate live, attenuated rotavirus vaccines — or natural rotavirus infection, for that matter — actually carry different intrinsic risks of intussusception cannot be determined with the current data, but given the ability of viral strains to have distinct pathogenic phenotypes, this possibility is plausible. We do not know whether the temporally associated increase in the rate of intussusception in the first week after vaccination actually translates into an increase in the overall attributable risk of intussusception from rotavirus vaccine or whether there might be a compensatory decrease in the rates of intussusception at later times after vaccination, as was hinted in the original data from the RV1 safety trials, which showed a significant decrease in intussusceptions among children who received the vaccine as compared with those who received placebo during the year-long follow-up.[8] Since RV1 and RV5 both efficiently prevent natural rotavirus infection, it is plausible that vaccination might reduce the overall intussusception burden if wild-type infection was also responsible for some sporadic cases.

The study by Patel et al. contextualizes the risks associated with RV1 vaccination and its increasingly well-documented and substantial benefits. It is crucial that the medical community in general, and the vaccine establishment in particular, work to better educate the public to the fact that virtually all beneficial interventions, including vaccination, come with some risk and that the key issue is to ensure that the ratio of benefit to risk is most favorable. As Patel and colleagues point out, in Mexico alone, RV1 vaccination would be expected to prevent 663 childhood deaths and 11,551 hospitalizations, while causing 41 excess hospitalizations and 2 additional deaths due to intussusception. Similar favorable ratios of benefit to risk would be expected to be found in virtually all less-developed countries, in which diarrheal disease remains a leading cause of death. A favorable ratio would probably also be present with RV4. Rotavirus infection is now a rare cause of death in the United States but remains a very common cause of hospitalization and physician visits.[9] Intussusception is also a rare cause of death in the United States and other developed countries. Given the low rates of intussusception associated with rotavirus vaccine that were observed in Mexico and Brazil, as well as the possibility that rotavirus vaccination might actually reduce the absolute rate of intussusception, it seems both appropriate and advisable to continue to

recommend the rotavirus vaccine for children in both the developed and the developing world, on the basis of the increasingly well documented and substantial benefits.[10]
Disclosure forms provided by the author are available with the full text of this article at NEJM.org.
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Leading Article
Presenting Evidence and Summary Measures to Best Inform Societal Decisions When Comparing Multiple Strategies
Eckermann, Simon; Willan, Andrew R.
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Global Protection and the Health Impact of Migration Interception
Zachary Steel, Belinda J. Liddell, Catherine R. Bateman-Steel, Anthony B. Zwi Policy Forum, published 14 Jun 2011
doi:10.1371/journal.pmed.1001038
Summary Points
The volume of international travel and irregular migration places pressure on states to maintain orderly migration programs. Interception strategies are increasingly used by states to halt the movement of irregular migrants, including asylum seekers.
Some strategies, such as immigration detention, pose a serious threat to health and mental health. Others, such as the use of visa restrictions or other pre-emptive interception measures, have a potentially large impact on migrants' health and welfare by forcing people to remain in settings where they face the chance of persecution.

Interception can also promote humanitarian outcomes. Refugee camps, for example, address immediate protection, safety, and service needs of forcibly displaced persons, but they have limits as long-term solutions.
Migration interception practices are a major global determinant of health and mental health. Health professionals must remain engaged in discussions about migration and humanitarian protection to ensure a broader consideration of the health impact of these practices.

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Policy Forum - Infectious Disease
Solving the Sisyphean Problem of Malaria in Zanzibar
David L. Smith, Justin M. Cohen, Bruno Moonen, Andrew J. Tatem, Oliver J. Sabot, Abdullah Ali, and Sultan M. Mugheiry
Science 17 June 2011: 1384-1385.

The Global Malaria Action Plan (GMAP), a consensus framework for coordinated action, aims to end malaria deaths by 2015 and eventually to eradicate malaria (1). The plan calls for universal access to effective antimalarial drugs and universal coverage with appropriate vector interventions. Strategic planning for how best to reach these goals has been left to individual countries, some of which have already made plans to eliminate malaria, i.e., to rid their countries of malaria parasites and to suppress transmission from imported malaria (travelers carrying malaria infections from one region into another) so that locally acquired cases are rare (2). Critics have argued that plans for national elimination distract attention and resources from the priority of reducing malaria's heavy burden in sub-Saharan Africa (3) and that a better strategy would be "control," i.e., reducing malaria to a minor public health problem. These sides reflect the bipolar history of antimalaria efforts. When funding collapsed for a previous attempt to eradicate malaria, control defined the malaria agenda through decades of neglect. Control and elimination are often presented as opposite sides of a debate over how to allocate billions of dollars allocated globally for malaria aid. But a recent study in Zanzibar (4) concluded the dichotomy was false. A more urgent problem is continuity. How can enthusiasm for funding malaria be sustained?

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http://onlinelibrary.wiley.com/doi/10.1111/tmi.2011.16.issue-6/issuetoc
Achieving STOP TB Partnership goals: perspectives on development of new diagnostics, drugs and vaccines for tuberculosis (pages 819–827)

Peter Mwaba, Ruth McNerney, Martin Peter Grobusch, Justin O'Grady, Matthew Bates, Nathan Kapata, Markus Maeurer and Alimuddin Zumla
Article first published online: 13 APR 2011 | DOI: 10.1111/j.1365-3156.2011.02777.x
Summary
Global eradication of tuberculosis (TB) depends on identification and treatment of all active TB cases and of the two billion people who are estimated to be latently infected with Mycobacterium tuberculosis. The past decade has seen a renaissance of scientific activities and funder investment into development of new TB drugs, diagnostics, biomarkers and vaccines. This viewpoint critically summarises the promising portfolio of more accurate TB diagnostics, new TB drugs and vaccines that have been endorsed by the STOP TB Partnership. Increasing numbers of Phase 2 and 3 drug, vaccine and diagnostic clinical trials in high-TB endemic areas reflect substantial progress towards attaining Global STOP-TB Partnership targets. Achievement of STOP-TB Partnership goals will crucially depend on political will and serious investment by funders and developing country governments into improving delivery of better health services and living conditions for their people. Long-term sustainability of any newer tools implemented at point of care is essential.

Methodology

Clustered lot quality assurance sampling: a pragmatic tool for timely assessment of vaccination coverage (pages 863–868)

K. Greenland, M. Rondy, A. Chevez, N. Sadozai, A. Gasasira, E. A. Abanida, M. A. Pate, O. Ronveaux, H. Okayasu, B. Pedalino and L. Pezzoli
Article first published online: 11 APR 2011 | DOI: 10.1111/j.1365-3156.2011.02770.x
Summary
Objectives To evaluate oral poliovirus vaccine (OPV) coverage of the November 2009 round in five Northern Nigeria states with ongoing wild poliovirus transmission using clustered lot quality assurance sampling (CLQAS).
Methods We selected four local government areas in each pre-selected state and sampled six clusters of 10 children in each Local Government Area, defined as the lot area. We used three decision thresholds to classify OPV coverage: 75–90%, 55–70% and 35–50%. A full lot was completed, but we also assessed in retrospect the potential time-saving benefits of stopping sampling when a lot had been classified.
Results We accepted two local government areas (LGAs) with vaccination coverage above 75%. Of the remaining 18 rejected LGAs, 11 also failed to reach 70% coverage, of which four also failed to reach 50%. The average time taken to complete a lot was 10 h. By stopping sampling when a decision was reached, we could have classified lots in 5.3, 7.7 and 7.3 h on average at the 90%, 70% and 50% coverage targets, respectively.
Conclusions Clustered lot quality assurance sampling was feasible and useful to estimate OPV coverage in Northern Nigeria. The multi-threshold approach provided useful information on the variation of IPD vaccination coverage. CLQAS is a very timely tool, allowing corrective actions to be directly taken in insufficiently covered areas.

Vaccine

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Cost-Effectiveness of a Recommendation of Universal Mass Vaccination for Seasonal Influenza in the United States

Karen M. Clements, ScD; Jeremy Chancellor, MSc; Kristin Nichol, MD, MPH, MBA; Kelly DeLong; David Thompson, PhD
published online 06 June 2011.
Abstract
Objectives
We evaluated the cost-effectiveness of universal mass vaccination (UMV) against influenza compared with a targeted vaccine program (TVP) for selected age and risk groups in the United States.
Methods
We modeled costs and outcomes of seasonal influenza with UMV and TVP, taking a societal perspective. The US population was stratified to model age-specific (< 5, 5–17, 18–49, 50–64, and 65+ years) vaccine coverage and efficacy. Probability of influenza-related illness (ILI) and complications, health-care utilization, costs, and survival were estimated. For a season's intervention, ILI cases in that year, lifetime costs (2008 US$), and quality-adjusted life years (QALYs) lost (both discounted at 3% per annum) were calculated for each policy and used to derive incremental cost-effectiveness ratios. A range of sensitivity and alternative-scenario analyses were conducted.
Results
In base-case analyses, TVP resulted in 63 million ILI cases, 859,000 QALYs lost, and $114.5 billion in direct and indirect costs; corresponding estimates for UMV were 61 million cases, 825,000 QALYs lost, and $111.4 billion. UMV was therefore estimated to dominate TVP, saving $3.1 billion and 34,000 QALYs. In probabilistic sensitivity analyses, UMV was dominant in 82% and dominated in 0% of iterations. In alternative-scenario analyses, UMV dominated TVP when lower estimates of vaccine coverage were used. Lower estimates of ILI risk among unvaccinated, vaccine effectiveness, and risk of complications resulted in ICERs of $2800, $8100, and $15,900 per QALY gained, respectively, for UMV compared with TVP.
Conclusions
UMV against seasonal influenza is cost saving in the United States under reasonable assumptions for coverage, cost, and efficacy.

Scientific Report

Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force

This report presents a checklist for good research practices of conjoint analysis in health care applications.

Abstract
Background
The application of conjoint analysis (including discrete-choice experiments and other multiattribute stated-preference methods) in health has increased rapidly over the past decade. A wider acceptance of these methods is limited by an absence of consensus-based methodological standards.

Objective
The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices for Conjoint Analysis Task Force was established to identify good research practices for conjoint-analysis applications in health.
Methods
The task force met regularly to identify the important steps in a conjoint analysis, to discuss good research practices for conjoint analysis, and to develop and refine the key criteria for identifying good research practices. ISPOR members contributed to this process through an extensive consultation process. A final consensus meeting was held to revise the article using these comments, and those of a number of international reviewers.
Results
Task force findings are presented as a 10-item checklist covering: 1) research question; 2) attributes and levels; 3) construction of tasks; 4) experimental design; 5) preference elicitation; 6) instrument design; 7) data-collection plan; 8) statistical analyses; 9) results and conclusions; and 10) study presentation. A primary question relating to each of the 10 items is posed, and three sub-questions examine finer issues within items.
Conclusions
Although the checklist should not be interpreted as endorsing any specific methodological approach to conjoint analysis, it can facilitate future training activities and discussions of good research practices for the application of conjoint-analysis methods in health care studies.

Health Policy Analysis

Pharmaceutical Priority Setting and the Use of Health Economic Evaluations: A Systematic Literature Review

Factors that seem to support the increased use of health economic evaluations are well-developed frameworks for evaluations, the presence of health economic skills, and an explicit priority setting process.

Abstract

Objectives
To investigate which factors and criteria are used in priority setting of pharmaceuticals, in what contexts health economic evaluations are used, and barriers to the use of health economic evaluations at micro, meso, and macro health-care levels.
Methods
The search for empirical articles was based on the MeSH index (Medical Substance Heading), including the search terms "economic evaluation," "cost-effectiveness analysis," "cost-utility analysis," "cost-benefit analysis," "pharmacoeconomic," AND "drug cost(s)," AND "eligibility determination," AND "decision-making," AND "rationing," AND formulary. The following databases were searched: PubMed, EconLit, Cochrane, Web of Science, CINAHL, and PsycINFO. More than 3100 studies were identified, 31 of which were included in this review.
Results
The use of health economic evaluations at all three health-care levels was investigated in three countries (United States [US], United Kingdom [UK], and Sweden). Postal and telephone survey methods dominated (n = 17) followed by interviews (n = 13), document analysis (n = 10), and observations of group deliberations (n = 9). The cost-effectiveness criterion was most important at the macro level. A number of contextual uses of health economic evaluations were identified, including importantly the

legitimizing of decisions, structuring the priority-setting process, and requesting additional budgets to finance expensive pharmaceuticals.

Conclusion

Factors that seem to support the increased use of health economic evaluations are well-developed frameworks for evaluations, the presence of health economic skills, and an explicit priority-setting process. Differences in how economic evaluations are used at macro, meso, and micro levels are attributed to differences in the preconditions at each level.