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

This weekly summary targets news, announcements 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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A pdf of this issue is available here: http://centerforvaccineethicsandpolicy.wordpress.com/

GAVI CEO Seth Berkley, MD, speaking in Hyderabad, India, praised India's emergence as both a global vaccine supplier and a leader in vaccine science. He noted, "India is a prime example of how the vaccine landscape has changed over the past 20 years. Indian manufacturers can produce vaccines that meet high quality standards, are appropriate to specific country settings, and are offered at lower and sustainable prices through a reliable supply over time. (They) also have the capacity to engage in applied vaccine development." Dr. Berkley's comments came as he accepted the "Genome Valley Excellence Award," described as a special award from the Federation of the Asian Biotech Association (FABA). The GAVI announcement noted that Dr. Berkley paid tribute to the contribution of India's biotech sector to the explosion in vaccine research and development and the number of new vaccines currently in the pipeline for a variety of diseases. He continued, "Never before have we seen such a concentration of scientific innovations for vaccines in such a short period of time…These vaccines are set to contribute to big declines in child mortality and morbidity to allow healthy children to meet their full potential which is what it is all about. We hope to see in the coming years a vaccine against malaria and hopefully not too far in the distant future against HIV, TB and, Dengue."
http://www.gavialliance.org/library/news/gavi-features/2012/seth-berkley-india-award/

Meeting: Progress Toward Rubella Elimination and CRS Prevention in Europe
When: February 8-10 Where: Rome, Italy
The Sabin Vaccine Institute, together with the March of Dimes Foundation, the World Health Organization Regional Office for Europe (EURO), the International Pediatric Association and its regional affiliate, the European Pediatric Association and the United States Centers for Disease Control and Prevention (CDC) brought together experts from around the world to discuss the continued outbreaks of measles and rubella in the European region. The meeting also focused on the impact of associated congenital rubella syndrome (CRS) and the pressing need to increase regional measles and rubella vaccine coverage to ensure immunity among susceptible populations. Dr. Ciro de Quadros, Executive Vice President of the Sabin Vaccine Institute, said, "We have made

great strides in eliminating these diseases in the Americas and we must work together to discover why we are seeing these cases re-emerge in Europe and what can be done to stop the outbreaks."
http://www.sabin.org/news-resources/in-news/2012/02/08/european-outbreaks-take-spotlight-conference-dedicated-measles-and

Meeting: Extraordinary Strategic Advisory Group of Experts (SAGE) Meeting to Review the Global Vaccine Action Plan for the Decade of Vaccines (DoV)
When: 16-17 February 2012 Where: Geneva, Switzerland
Purpose: "Present SAGE with the Global Vaccine Action Plan (GVAP) revised as a result of the consultative process and ask for SAGE's endorsement of this action plan and/or necessary modification prior to the document being submitted to the WHA."
Draft Agenda:
http://www.who.int/entity/immunization/sage/Agenda_DOV_Feb_2012_Feb_8.pdf

[Editor's Note: Please see Journal Watch below for entries from the current issues of Nature and Science for continuing commentary and analysis on the overall H5N1 research issue]
Meeting: Preliminary Consultation on H5N1 Research Issues (WHO)
When: 16–17 February 2012 Where: Geneva, Switzerland
Purpose:
Recently, two unpublished research studies on the transmissibility of influenza A H5N1 viruses have raised urgent questions related to the two studies, as well as broader concerns related to the balance between scientific research and public concerns about safety.
Given the global relevance of these issues, WHO has been asked to facilitate a process to address the issues. WHO will hold a first technical meeting on 16 - 17 February to clarify key facts about the two research studies and the most urgent related issues. Invited participants in this meeting will be people who have direct involvement or knowledge about these two studies, their review or oversight, or potential dissemination of results. Participants will discuss the specific circumstances and results of the two studies and will try to reach a consensus about ad hoc, practical actions to resolve the most urgent issues, particularly related to access to and dissemination of the results of this research.
Because many broader concerns that have been raised will not be addressed at this meeting, further consultation with wider input is anticipated at a later date to be determined. More details will be provided as they become available.
WHO statement on new H5N1 influenza research [30 December 2011]

UNICEF reported that Liberian President Ellen Johnson Sirleaf officially launched the Children's Law of Liberia "to protect children and their right to participate meaningfully in their development." The law is described as one of the most comprehensive pieces of children's rights legislation on the continent and is largely based on the UN Convention on the Rights of the Child (UNCRC) and the African

Charter on the Rights and Welfare of the Child, ratified by Liberia in 1993 and 1992 respectively. This new law "reflects the government's commitment to support the progressive realization of all rights for all children: including their right to health: education; freedom from violence, abuse, and exploitation; and their right participate meaningfully in their own development." The UNICEF announcement said the law "is the result of more than two years of advocacy by the government of Liberia, domestic and international non-governmental organizations, the Liberia Children's Parliament and UNICEF, all working together through the Child Protection Network."
http://www.unicef.org/media/media_61579.html

Report: The Private-Sector Role in Public Health – Reflections on the New Global Architecture in Health
CSIS - by Jeffrey L. Sturchio and Akash Goel
Jan 31, 2012
Abstract [full text]

In recent decades, there has been a decided evolution in perspectives on the roles and responsibilities of business in society. The classic position was Milton Friedman's 1970 pronouncement that the only responsibility a business has is to return a profit to its shareholders. That view has largely been replaced by a more nuanced understanding of the ways in which businesses can enhance their competitiveness and economic returns by addressing the needs and challenges of the communities in which they operate. Corporate responsibility is no longer an oxymoron, as skeptics claim, but rather an emerging approach designed to create shared value for businesses and their shareholders—having positive social impact while also generating the return on investment expected by shareholders. There is still wide variation in corporate responsibility practices, from firms that see such activities as little more than a public relations strategy to improve their brand image to others that find meaningful opportunities to drive social change through their core businesses. At the same time, there has been growing interest and acceptance of the private sector in the broader global development agenda. Private-sector engagement was among the main issues addressed at the recent 4th High Level Forum for Aid Effectiveness in Busan, Korea; as Lars Thunell, executive vice president and CEO of the International Finance Corporation (IFC), observed, "This could be the turning point where we recognize the mutually supportive roles of the private and public sectors in promoting development."
http://csis.org/files/publication/120131_Sturchio_PrivateSectorRole_Web.pdf

Working Paper: An Index of the Quality of Official Development Assistance in Health
Denizhan Duran and Amanda Glassman
02/07/2012
http://www.cgdev.org/files/1425926_file_Duran_Glassman_QuODAH_FINAL.pdf
Overview:

Health is one of the largest and most complex aid sectors: 16 percent of all aid went to the health sector in 2009. While many stress the importance of aid effectiveness,

there are limited quantitative analyses of the quality of health aid, and various studies point out to the failure of health aid to increase health outcomes.

In this study, Denizhan Duran and Amanda Glassman apply Nancy Birdsall and Homi Kharas's Quality of Official Development Assistance (QuODA) methodology to rank 30 donors across 23 indicators of aid effectiveness in health. Their indicators rely on the premise that health aid effectiveness would increase through increased donor efficiency, reduced burden on recipients, support to local institutions, and transparent reporting practices.

By ranking donors across these indicators, the authors seek to point out best practices in health aid and hold donors accountable for their performance. Some donors perform better on health than they do in other sectors. This paper tracks donors' progress from 2008 to 2009, compares health to overall aid, and calls on donors to make available transparent and relevant aid data in the sector level and to focus on impact and results.

Data disclosure: The data and Stata code underlying this analysis are available as a data set.

The **MMWR Weekly for February 10, 2012** / Vol. 61 / No. 5 includes: Recommended Immunization Schedules for Persons Aged 0 Through 18 Years — United States, 2012

The **Weekly Epidemiological Record (WER) for 10 February 2012**, vol. 87, 6 (pp 53–60) includes: Global Advisory Committee on Vaccine Safety, December 2011; Monthly report on dracunculiasis cases, January–November 2011
http://www.who.int/entity/wer/2012/wer8706.pdf

Twitter Watch *[accessed 12 February 18:35]*
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.

UNICEF UNICEF
"Never before have we been better placed to achieve an AIDS free generation." UNICEF Chief of HIV & AIDS bit.ly/zZ9lJo
11 Feb

TheLancet The Lancet
Most read this week: Global malaria mortality between 1980 and 2010 bit.ly/xSW45U
10 Feb

GAVIAlliance GAVI Alliance
Help increase access to life-saving vaccines: GAVI is recruiting new members for its Independent Review Committees: ht.ly/8ZKyH
10 Feb

GAVISeth Seth Berkley
Indian vaccine industry promoting innovation, quality and a stronger regulatory system at power breakfast with Indian Vax CEOs in Hyderabad
10 Feb

AIDSvaccine IAVI
Exciting new efforts on accelerating #globalhealth R&D through science, tech & #innovation announced @WhiteHouse: 1.usa.gov/yO3Tyo
9 Feb

MalariaVaccine PATH MVI
Adjuvant, antigens, gametocytes… Curious about malaria vaccine terminology? There's a glossary for that: bit.ly/MVIglossary
9 Feb

sabinvaccine Sabin Vaccine Inst.
"Only 2 WHO Regions (@pahowho & @who_europe) have 100% of their countries using #Rubella Containing Vaccines" ~ Susan Reef @cdcgov
9 Feb

sabinvaccine Sabin Vaccine Inst.
Over 100 people from 47 countries at Progress Toward #Rubella meeting in Rome. bit.ly/w4T812 twitpic.com/8hk90t
9 Feb

historyvaccines History of Vaccines
Vaccine developer Stanley Plotkin discusses early #rubella vaccines, their differences/shortcomings bit.ly/wWZhaG #CRS
8 Feb

glassmanamanda Amanda Glassman
An Index of the Quality of Official Development Assistance in Health - cgdev.org/content/public… via @CGDev
7 Feb

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
February 7, 2012; 156 (3)
http://www.annals.org/content/current

Original Research

Effects of School Closure on Incidence of Pandemic Influenza in Alberta, Canada

David J.D. Earn, Daihai He, Mark B. Loeb, Kevin Fonseca, Bonita E. Lee, and Jonathan Dushoff

Ann Intern Med February 7, 2012 156:173-181;

Controversy exists as to whether schools should close during influenza epidemics. Researchers developed a mathematical model of H1N1 influenza transmission in Alberta, Canada, by using virologic data, census data, climate records, and school calendars. The model suggests that school closure reduced influenza transmission among schoolchildren by more than 50%, attenuating the first peak of the H1N1 influenza epidemic. Reopening of schools initiated the second peak. Closing schools may be an effective strategy to slow the spread of influenza during epidemics.

Editorials

Getting Schooled: School Closure, Age Distribution, and Pandemic Mitigation

David N. Fisman

Ann Intern Med February 7, 2012 156:238-240;

Excerpt

Despite the gains in antimicrobial therapy and vaccines that have come in the past 100 years (1), epidemics and pandemics (synchronized, global epidemics) remain an important source of morbidity, mortality, and costs in high-, middle-, and low-income countries. Epidemics can be thought of as self-perpetuating, exponential growth processes; because infections are communicable, the more cases you have, the more cases you will get, as long as the population contains susceptible persons to infect.

Epidemiologists refer to the key index of this type of growth as the reproductive number of an infectious disease—the number of new (incident) cases created by each old (prevalent) case before the prevalent case recovers (2). Reproductive numbers are the product of 3 core components: how infectious a person is, the duration of infectiousness of a person, and how many contacts that person has. Epidemic mitigation strategies that seek to reduce the latter component of the reproductive number (contact between infectious and susceptible persons) are often referred to as social-distancing measures.

Social-distancing measures may include closing schools, suspending religious services, and canceling large public gatherings. A famous study in contrasts with respect to the implementation of social distancing for influenza pandemic control occurred in St. Louis and Philadelphia during the severe influenza A(H1N1) pandemic in 1918 to 1919 (3). Authorities in Philadelphia declined to impose social-distancing measures (including, famously, not canceling a parade through the center of the city that drew large crowds) until the epidemic was severe. In contrast, St. Louis proactively and aggressively restricted religious and social gatherings and closed schools early in its epidemic, and the effect of influenza seems to have been greatly mitigated (3). Whether the divergent courses of St. Louis and Philadelphia were attributable to social-distancing measures or whether the willingness to implement such measures reflected …

British Medical Bulletin
Volume 100 Issue 1 December 2011
http://bmb.oxfordjournals.org/content/current
[Reviewed earlier; No relevant content]

British Medical Journal
11 February 2012 (Vol 344, Issue 7843)
http://www.bmj.com/content/current
[No relevant content]

Cost Effectiveness and Resource Allocation
(Accessed 12 February 2012)
http://www.resource-allocation.com/
[No new relevant content]

Emerging Infectious Diseases
Volume 18, Number 2—February 2012
http://www.cdc.gov/ncidod/EID/index.htm
[Reviewed earlier]

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

Globalization and Health
[Accessed 12 February 2012]
http://www.globalizationandhealth.com/
[No new relevant content]

Health Affairs
February 2012; Volume 31, Issue 2
http://content.healthaffairs.org/content/current
Theme: The Future of The Small Business Insurance Exchange
[No relevant content]

Health and Human Rights
Vol 13, No 2 (2011)
http://hhrjournal.org/index.php/hhr
[Reviewed earlier]

Health Economics, Policy and Law
Volume 7 - Special Issue 01 - January 2012
http://journals.cambridge.org/action/displayIssue?jid=HEP&tab=currentissue
[Reviewed earlier]

Health Policy and Planning
Volume 27 Issue 1 January 2012
http://heapol.oxfordjournals.org/content/current
[Reviewed earlier]

Human Vaccines & Immunotherapeutics (formerly Human Vaccines)
Volume 8, Issue 2 February 2012
http://www.landesbioscience.com/journals/vaccines/toc/volume/8/issue/2/
[Reviewed last week]

International Journal of Infectious Diseases
Volume 16, Issue 2 pp. e75-e150 (February 2012)
http://www.sciencedirect.com/science/journal/12019712
[Reviewed earlier]

JAMA
February 8, 2012, Vol 307, No. 6, pp 539-628
http://jama.ama-assn.org/current.dtl
Original Contributions
Immunogenicity and Tolerability of Recombinant Serogroup B Meningococcal Vaccine Administered With or Without Routine Infant Vaccinations According to Different Immunization Schedules: A Randomized Controlled Trial
Nicoletta Gossger, Matthew D. Snape, Ly-Mee Yu, Adam Finn, Gianni Bona, Susanna Esposito, Nicola Principi, Javier Diez-Domingo, Etienne Sokal, Birgitta Becker, Dorothee Kieninger, Roman Prymula, Peter Dull, Ellen Ypma, Daniela Toneatto, Alan Kimura, Andrew J. Pollard, for the European MenB Vaccine Study Group
JAMA. 2012;307(6):573-582.doi:10.1001/jama.2012.85
Abstract
Context
In the absence of an effective vaccine, serogroup B Neisseria meningitidis (MenB) remains a major cause of invasive disease in early childhood in developed countries.
Objective
To determine the immunogenicity and reactogenicity of a multicomponent MenB vaccine (4CMenB) and routine infant vaccines when given either concomitantly or separately.
Design, Setting, and Participants Phase 2b, multicenter, open-label, parallel-group, randomized controlled study of 1885 infants enrolled at age 2 months from August 2008 to July 2010 in Europe.

Intervention
Participants were randomized 2:2:1:1 to receive (1) 4CMenB at 2, 4, and 6 months with routine vaccines (7-valent pneumococcal and combined diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, Haemophilus influenzae type b vaccines); (2) 4CMenB at 2, 4, and 6 months and routine vaccines at 3, 5, and 7 months; (3) 4CMenB with routine vaccines at 2, 3, and 4 months; or (4) routine vaccines alone at 2, 3, and 4 months.
Main Outcome
Measures Percentage of participants with human complement serum bactericidal activity (hSBA) titer of 1:5 or greater against 3 MenB strains specific for vaccine antigens (NZ98/254, 44/76-SL, and 5/99).
Results
After three 4CMenB vaccinations, 99% or more of infants developed hSBA titers of 1:5 or greater against strains 44/76-SL and 5/99. For NZ98/254, this proportion was 79% (95% CI, 75.2%-82.4%) for vaccination at 2, 4, and 6 months with routine vaccines, 86.1% (95% CI, 82.9%-89.0%) for vaccination at 2, 4, and 6 months without routine vaccines, and 81.7% (95% CI, 76.6%-86.2%) for vaccination at 2, 3, and 4 months with routine vaccines. Responses to routine vaccines given with 4CMenB were noninferior to routine vaccines alone for all antigens, except for the responses to pertactin and serotype 6B pneumococcal polysaccharide. Fever was seen following 26% (158/602) to 41% (247/607) of 4CMenB doses when administered alone, compared with 23% (69/304) to 36% (109/306) after routine vaccines given alone and 51% (306/605) to 61% (380/624) after 4CMenB and routine vaccines administered together.
Conclusion
A 4CMenB vaccine is immunogenic against reference strains when administered with routine vaccines at 2, 4, and 6 or at 2, 3, and 4 months of age, producing minimal interference with the response to routine infant vaccinations.
Trial Registration clinicaltrials.gov Identifier: NCT00721396

Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants

Irene M. Shui, James Baggs, Manish Patel, Umesh D. Parashar, Melisa Rett, Edward A. Belongia, Simon J. Hambidge, Jason M. Glanz, Nicola P. Klein, Eric Weintraub
JAMA. 2012;307(6):598-604.doi:10.1001/jama.2012.97
Author Video/Audio Interview
JAMA Report Video
Abstract
Context
Current rotavirus vaccines were not associated with intussusception in large prelicensure trials. However, recent postlicensure data from international settings suggest the possibility of a low-level elevated risk, primarily in the first week after the first vaccine dose.
Objective
To examine the risk of intussusception following pentavalent rotavirus vaccine (RV5) in US infants.
Design, Setting, and Patients
This cohort study included infants 4 to 34 weeks of age, enrolled in the Vaccine Safety Datalink (VSD) who received RV5 from May 2006-February 2010. We calculated standardized incidence ratios (SIRs), relative risks (RRs), and 95% confidence intervals

for the association between intussusception and RV5 by comparing the rates of intussusception in infants who had received RV5 with the rates of intussusception in infants who received other recommended vaccines without concomitant RV5 during the concurrent period and with the expected number of intussusception visits based on background rates assessed prior to US licensure of the RV5 (2001-2005).
Main Outcome
Measure Intussusception occurring in the 1- to 7-day and 1- to 30-day risk windows following RV5 vaccination.
Results
During the study period, 786 725 total RV5 doses, which included 309 844 first doses, were administered. We did not observe a statistically significant increased risk of intussusception with RV5 for either comparison group following any dose in either the 1- to 7-day or 1- to 30-day risk window. For the 1- to 30-day window following all RV5 doses, we observed 21 cases of intussusception compared with 20.9 expected cases (SIR, 1.01; 95% CI, 0.62-1.54); following dose 1, we observed 7 cases compared with 5.7 expected cases (SIR, 1.23; 95% CI, 0.5-2.54). For the 1- to 7-day window following all RV5 doses, we observed 4 cases compared with 4.3 expected cases (SIR, 0.92; 95% CI, 0.25-2.36); for dose 1, we observed 1 case compared with 0.8 expected case (SIR, 1.21; 95% CI, 0.03-6.75). The upper 95% CI limit of the SIR (6.75) from the historical comparison translates to an upper limit for the attributable risk of 1 intussusception case per 65 287 RV5 dose-1 recipients.
Conclusion
Among US infants aged 4 to 34 weeks who received RV5, the risk of intussusception was not increased compared with infants who did not receive the rotavirus vaccine.

Editorials

Inching Toward a Serogroup B Meningococcal Vaccine for Infants

Amanda C. Cohn, Nancy E. Messonnier
JAMA. 2012;307(6):614-615.doi:10.1001/jama.2012.118
Excerpt
In the past decade, the introduction of meningococcal conjugate vaccines has led to substantial reductions in meningococcal disease. Monovalent serogroup C vaccines have virtually eliminated serogroup C disease from the United Kingdom and other countries, and serogroup A, C, W, and Y vaccines have reduced disease among adolescents in the United States.1,2 In 2010 and 2011, Burkina Faso, Mali, Niger, and part of Nigeria introduced serogroup A conjugate vaccine, which may eliminate epidemic meningitis from the meningitis belt of Africa. These accomplishments have been dampened by the lack of effective serogroup B meningococcal vaccines. Serogroup B meningococcal disease causes substantial morbidity and mortality globally, especially in young infants.3,4,5 Serogroup B disease can be devastating; 5% to 10% of children with the disease do not survive and another 10% to 20% experience long-term sequelae such as hearing loss, limb loss, and neurologic deficits. …

Journal of Infectious Diseases

Volume 205 Issue 5 March 1, 2012
http://www.journals.uchicago.edu/toc/jid/current

EDITORIAL COMMENTARIES

Kathleen M. Neuzil

Influenza Vaccines: More Options and More Opportunities

J Infect Dis. (2012) 205(5): 700-701 doi:10.1093/infdis/jir646

(See the article by Ferguson et al, on pages 733–44.)

Extract

Influenza, whether seasonal or pandemic, causes substantial morbidity and mortality. Today, vaccines are the foundation of influenza prevention. Globally, influenza vaccine manufacturing capacity is at an all-time high [1], as are the number and types of influenza vaccines available on the market and in development. In the United States, in addition to the live attenuated and inactivated subunit and split influenza vaccines, a high-dose inactivated vaccine for persons aged ≥65 years, and an intradermally administered inactivated vaccine for persons aged 18–64 years have been recently licensed for seasonal use. This is remarkable progress, considering that as recently as the 2004–2005 influenza season, only one inactivated vaccine was available on the US market [2]. In the United States, all of these vaccines are produced in eggs, although cell-based inactivated and recombinant vaccines are in the late stages of development. Outside the United States, additional inactivated vaccines are licensed for seasonal use, including those manufactured in cell culture, subvirion vaccines combined with the oil-in-water adjuvant MF59 for persons aged ≥65 years, and whole virus and virosomal vaccines. During the 2009 H1N1 pandemic, many countries, not including the United States, also licensed and used monovalent inactivated vaccines adjuvanted with an oil-in-water adjuvant, either AS03 or MF59.

When compared with other vaccines, the range of influenza vaccines that are licensed or in development is unprecedented. The robust market and development pipeline are …

VIRUSES

Murdo Ferguson, George Risi, Matthew Davis, Eric Sheldon, Mira Baron, Ping Li, Miguel Madariaga, Louis Fries, Olivier Godeaux, and David Vaughn

Safety and Long-term Humoral Immune Response in Adults After Vaccination With an H1N1 2009 Pandemic Influenza Vaccine With or Without AS03 Adjuvant

J Infect Dis. (2012) 205(5): 733-744 doi:10.1093/infdis/jir641

Abstract

EDITORIAL COMMENTARIES

Kathleen B. Schwarz

More Lessons From the Taiwanese Hepatitis B Virus Vaccine Program

J Infect Dis. (2012) 205(5): 702 doi:10.1093/infdis/jir854

(See the article by Su et al, on pages 757–762.)

Extract

In this issue of The Journal of Infectious Diseases, the Taiwan National Children's Hospital group, under the capable leadership of Dr Mei-Hwei Chang, has once again used carefully constructed national surveillance data to teach us something about hepatitis B virus (HBV) infection in young subjects who received neonatal HBV vaccine. As one would predict, the highest rates for acute HBV infection were in unvaccinated individuals. Also, as expected, rates of acute HBV infection were lower in vaccinated birth cohorts aged 15–24 years than in unvaccinated birth cohorts, demonstrating once again the efficacy of the universal newborn vaccination program. The biggest disappointment was that, due to …

Viruses

Wei-Ju Su, Cheng-Chung Liu, Ding-Ping Liu, Shu-Fong Chen, Ji-Jia Huang, Ta-Chien Chan, and Mei-Hwei Chang

Effect of Age on the Incidence of Acute Hepatitis B After 25 Years of a Universal Newborn Hepatitis B Immunization Program in Taiwan

J Infect Dis. (2012) 205(5): 757-762 doi:10.1093/infdis/jir852

Abstract

The Lancet

Feb 11, 2012 Volume 379 Number 9815 p493 - 588
http://www.thelancet.com/journals/lancet/issue/current

Editorials

The Bangkok Statement on universal health coverage

The Lancet

Preview

The theme of the Prince Mahidol Award Conference in Bangkok, Thailand on Jan 24–28, 2012, was Moving towards universal health coverage: health financing matters. At the close of the meeting, a 10-point declaration recognised universal health coverage (UHC) as fundamental to the right to health, and marked the commitment by more than 800 delegates to translate the rhetoric of UHC into better, more equitable health outcomes. Similar endorsements of UHC have been made before, including at the World Health Assembly in 2011.

Correspondence

Vaccine-associated paralytic poliomyelitis in Japan

Miwako Hosoda, Hajime Inoue, Yasuo Miyazawa, Eiji Kusumi, Kenji Shibuya

Preview

Despite WHO's recommendation to switch the poliomyelitis vaccine from oral polio vaccine (OPV) to inactivated polio vaccine (IPV) in countries where polio elimination has been achieved, Japan has continued to use OPV. In Japan, OPV is given twice to children aged from 3 to 18 months.1 More than 10 years after the elimination of wild polio virus, tragic cases of vaccine-associated paralytic poliomyelitis (VAPP) continue to be reported every year—most recently in May, 2011. The Ministry of Health, Labour and Welfare claims that IPV is still being developed by Japanese vaccine companies and that it will not be available until the end of 2012 at the earliest.

Articles

Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis

Karen M Edmond, Christina Kortsalioudaki, Susana Scott, Stephanie J Schrag, Anita KM Zaidi, Simon Cousens, Paul T Heath

Preview

More high-quality studies are needed to accurately estimate the global burden of group B streptococcus, especially in low-income countries. A conjugate vaccine incorporating five serotypes (Ia, Ib, II, III, V) could prevent most global group B streptococcal disease.

The Lancet Infectious Disease

Feb 2012 Volume 12 Number 2 p89 - 166

http://www.thelancet.com/journals/laninf/issue/current
[Reviewed earlier]

Medical Decision Making (MDM)
January–February 2012; 32 (1)
http://mdm.sagepub.com/content/current
[Reviewed last week]

Nature
Volume 482 Number 7384 pp131-268 9 February 2012
http://www.nature.com/nature/current_issue.html
Nature | Editorial
Facing up to flu
Nature 482, 131 (09 February 2012)
doi:10.1038/482131a
Published online 08 February 2012
[Free full text]

The potential for mutant-flu research to improve public health any time soon has been exaggerated. Timely production of sufficient vaccine remains the biggest challenge.

Amid the scientific controversy over lab-created strains of the H5N1 avian influenza virus that can skip between mammals, it is easy to lose sight of an important public-health question: what will help the wider world to prepare for a flu pandemic? The question is crucial, because when it comes to setting priorities, the fuss over how to regulate the controversial research must not be allowed to distract from a much bigger concern. The world is ill-prepared for a severe flu pandemic of any type. In particular, it cannot yet produce enough vaccine to protect more than just a small proportion of people.

The problem was demonstrated by the 2009 pandemic of H1N1 flu. Vaccines only became available months after the outbreak began, and after the first wave had peaked in many countries. Health systems were stretched despite the relative mildness of the pandemic. The mutant-flu research does nothing to prevent a repeat of this situation.

Research to create mammalian-transmissible strains is vital basic science that could deepen our understanding of flu viruses, and of what allows a virus to jump from other species and spread easily in humans. These insights may one day produce better ways to tackle a pandemic, including ones we cannot picture today. But scientists need to be more modest and realistic with their claims about the short-term public-health benefits of such research, and provide better explanations that include the caveats.

For example, many commentators say that the biggest public-health benefit promised by the research is in the field of disease surveillance. The experiments reveal one combination of mutations that allowed the H5N1 virus to jump between species and then spread; in theory, animal-health experts can now watch out for these mutations in affected animals such as pigs and birds.

In practice, the immediate benefits are minimal. Surveillance of influenza in animals is slow and patchy at best, and follow-up sequencing of samples more so. And the mutations that we know about are likely to be outnumbered by those about which we are still ignorant.

Consider H5N1 in pigs. There is almost no systematic flu surveillance in the animals (see Nature 459, 894–895; 2009). Infections are infrequent, symptoms are mild and the pig industry is concerned that talk of swine flu could unfairly taint the image of pork. As a result, the world's one billion or so pigs have yielded partial DNA sequences of just 24 H5N1 isolates, meaning that were a pandemic H5N1 virus to emerge from pigs, just as H1N1 did in 2009, there would be little or no possibility of detecting it in advance.

That does not mean that the idea of using the mutant-flu research to improve surveillance is without merit; far from it. Further work could yield a more comprehensive bank of mutations, and greater investment could create specialized centres to screen more samples in affected countries, in real time. Improving flu-virus surveillance should be a public-health priority, but international groups and governments have, in the past, been reluctant to fund it adequately. If the world is serious about preparing for a pandemic, this must change. Done properly, surveillance could one day give early warning of an approaching pandemic. What then?

At present, such advance knowledge would make little difference to the world's limited abilities to manufacture and distribute vaccines. Current techniques can produce vaccine only six months after a pandemic emerges. Doing so faster and in much larger quantities is the most urgent public-health priority when it comes to planning for the next pandemic.

The mutant-flu studies contribute little to this goal. They offer no serious immediate application in vaccine research (see page 142). Any benefits to drug development — which are important, but less so than churning out vaccine for a pandemic — are more likely to flow from longer-term basic research. The mutant-flu work could certainly help this research. Yet the work itself carries a risk. An accidental, or intentional, release of the mutant viruses from a lab could spark an H5N1 pandemic that we are currently in no position to mitigate.

The fact that the risks seem to far outweigh the public-health benefits of the research, at least in the short term, means that there is no need to rush headlong into an expansion of the work. Rather, regulators and flu researchers must take whatever time they need to decide the best way for such work to proceed safely.

Comment

Policy: Adaptations of avian flu virus are a cause for concern

Members of the US National Science Advisory Board for Biosecurity explain its recommendations on the communication of experimental work on H5N1 influenza.

H5N1: Flu transmission work is urgent

Yoshihiro Kawaoka explains that research on transmissible avian flu viruses needs to continue if pandemics are to be prevented.

Q&A: Reasons for proposed redaction of flu paper

US National Science Advisory Board for Biosecurity explains recommendation to publish H5N1 work in a form that withholds essential data.

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Integrated HIV Testing, Malaria, and Diarrhea Prevention Campaign in Kenya: Modeled Health Impact and Cost-Effectiveness
James G. Kahn, Nicholas Muraguri, Brian Harris, Eric Lugada, Thomas Clasen, Mark Grabowsky, Jonathan Mermin, Shahnaaz Shariff
PLoS ONE: Research Article, published 08 Feb 2012 10.1371/journal.pone.0031316
Abstract
Background

Efficiently delivered interventions to reduce HIV, malaria, and diarrhea are essential to accelerating global health efforts. A 2008 community integrated prevention campaign in Western Province, Kenya, reached 47,000 individuals over 7 days, providing HIV testing and counseling, water filters, insecticide-treated bed nets, condoms, and for HIV-infected individuals cotrimoxazole prophylaxis and referral for ongoing care. We modeled the potential cost-effectiveness of a scaled-up integrated prevention campaign.
Methods
We estimated averted deaths and disability-adjusted life years (DALYs) based on published data on baseline mortality and morbidity and on the protective effect of interventions, including antiretroviral therapy. We incorporate a previously estimated scaled-up campaign cost. We used published costs of medical care to estimate savings from averted illness (for all three diseases) and the added costs of initiating treatment earlier in the course of HIV disease.
Results
Per 1000 participants, projected reductions in cases of diarrhea, malaria, and HIV infection avert an estimated 16.3 deaths, 359 DALYs and $85,113 in medical care costs. Earlier care for HIV-infected persons adds an estimated 82 DALYs averted (to a total of 442), at a cost of $37,097 (reducing total averted costs to $48,015). Accounting for the estimated campaign cost of $32,000, the campaign saves an estimated $16,015 per 1000 participants. In multivariate sensitivity analyses, 83% of simulations result in net savings, and 93% in a cost per DALY averted of less than $20.
Discussion
A mass, rapidly implemented campaign for HIV testing, safe water, and malaria control appears economically attractive.

Trends in Population-Based Studies of Human Genetics in Infectious Diseases

Jessica L. Rowell, Nicole F. Dowling, Wei Yu, Ajay Yesupriya, Lyna Zhang, Marta Gwinn
PLoS ONE: Research Article, published 07 Feb 2012 10.1371/journal.pone.0025431
Abstract
Pathogen genetics is already a mainstay of public health investigation and control efforts; now advances in technology make it possible to investigate the role of human genetic variation in the epidemiology of infectious diseases. To describe trends in this field, we analyzed articles that were published from 2001 through 2010 and indexed by the HuGE Navigator, a curated online database of PubMed abstracts in human genome epidemiology. We extracted the principal findings from all meta-analyses and genome-wide association studies (GWAS) with an infectious disease-related outcome. Finally, we compared the representation of diseases in HuGE Navigator with their contributions to morbidity worldwide. We identified 3,730 articles on infectious diseases, including 27 meta-analyses and 23 GWAS. The number published each year increased from 148 in 2001 to 543 in 2010 but remained a small fraction (about 7%) of all studies in human genome epidemiology. Most articles were by authors from developed countries, but the percentage by authors from resource-limited countries increased from 9% to 25% during the period studied. The most commonly studied diseases were HIV/AIDS, tuberculosis, hepatitis B infection, hepatitis C infection, sepsis, and malaria. As genomic research methods become more affordable and accessible, population-based research on infectious diseases will be able to examine the role of variation in human as well as pathogen genomes. This approach offers new opportunities for understanding infectious disease susceptibility, severity, treatment, control, and prevention.

Fighting Misconceptions to Improve Compliance with Influenza Vaccination among Health Care Workers: An Educational Project

Carla R. Couto, Cláudio S. Pannuti, José P. Paz, Maria C. D. Fink, Alessandra A. Machado, Michela de Marchi, Clarisse M. Machado

PLoS ONE: Research Article, published 06 Feb 2012 10.1371/journal.pone.0030670

Abstract

The compliance with influenza vaccination is poor among health care workers (HCWs) due to misconceptions about safety and effectiveness of influenza vaccine. We proposed an educational prospective study to demonstrate to HCWs that influenza vaccine is safe and that other respiratory viruses (RV) are the cause of respiratory symptoms in the months following influenza vaccination. 398 HCWs were surveyed for adverse events (AE) occurring within 48 h of vaccination. AE were reported by 30% of the HCWs. No severe AE was observed. A subset of 337 HCWs was followed up during four months, twice a week, for the detection of respiratory symptoms. RV was diagnosed by direct immunofluorescent assay (DFA) and real time PCR in symptomatic HCWs. Influenza A was detected in five episodes of respiratory symptoms (5.3%) and other RV in 26 (27.9%) episodes. The incidence density of influenza and other RV was 4.3 and 10.8 episodes per 100 HCW-month, respectively. The educational nature of the present study may persuade HCWs to develop a more positive attitude to influenza vaccination.

PLoS Medicine

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10 February 2012 vol 335, issue 6069, pages 625-764

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Policy Forum

Public Health and Biosecurity

Adaptations of Avian Flu Virus Are a Cause for Concern

Kenneth I. Berns1,*, Arturo Casadevall2, Murray L. Cohen3, Susan A. Ehrlich4, Lynn W. Enquist5, J. Patrick Fitch6, David R. Franz7, Claire M. Fraser-Liggett8, Christine M. Grant9, Michael J. Imperiale10, Joseph Kanabrocki11, Paul S. Keim12,†, Stanley M. Lemon13, Stuart B. Levy14, John R. Lumpkin15, Jeffery F. Miller16, Randall Murch17, Mark E. Nance18, Michael T. Osterholm19, David A. Relman20, James A. Roth21, Anne K. Vidaver22

We are in the midst of a revolutionary period in the life sciences. Technological capabilities have dramatically expanded, we have a much improved understanding of the complex biology of selected microorganisms, and we have a much improved ability to manipulate microbial genomes. With this has come unprecedented potential for better control of infectious diseases and significant societal benefit. However, there is also a growing risk that the same science will be deliberately misused and that the consequences could be catastrophic. Efforts to describe or define life-sciences research of particular concern have focused on the possibility that knowledge or products derived from such research, or new technologies, could be directly misapplied with a sufficiently broad scope to affect national or global security. Research that might greatly enhance the harm caused by microbial pathogens has been of special concern (1–3). Until now, these efforts have suffered from a lack of specificity and a paucity of concrete examples of "dual use research of concern" (3). Dual use is defined as research that could be used for good or bad purposes. We are now confronted by a potent, real-world example.

Highly pathogenic avian influenza A/H5N1 infection of humans has been a serious public health concern since its identification in 1997 in Asia. This virus rarely infects humans, but when it does, it causes severe disease with case fatality rates of 59% (4). To date, the transmission of influenza A/H5N1 virus from human to human has been rare, and no human pandemic has occurred. If influenza A/H5N1 virus acquired the capacity for human-to-human spread and retained its current virulence, we could face an epidemic of substantial proportions. Historically, epidemics or pandemics with high mortalities have been documented when humans interact with new agents for which they have no immunity, such as with Yersinia pestis (plague) in the Middle Ages and the introduction of smallpox and measles into the Americas after the arrival of Europeans.

Recently, several scientific research teams have achieved some success in isolating influenza A/H5N1 viruses that are transmitted efficiently between mammals, in one instance with maintenance of high pathogenicity. This information is very important because, before these experiments were done, it was uncertain whether avian influenza A/H5N1 could ever acquire the capacity for mammal-to-mammal transmission. Now that this information is known, society can take steps globally to prepare for when nature might generate such a virus spontaneously. At the same time, these scientific results also represent a grave concern for global biosecurity, biosafety, and public health. Could this knowledge, in the hands of malevolent individuals, organizations, or governments, allow construction of a genetically altered influenza virus capable of causing a pandemic with mortality exceeding that of the "Spanish flu" epidemic of 1918? The research teams that performed this work did so in a well-intended effort to discover evolutionary routes by which avian influenza A/H5N1 viruses might adapt to humans. Such knowledge may be valuable for improving the public health response to a looming natural threat. And, to their credit and that of the peer reviewers selected by the journals Science and Nature, the journals themselves, as well as the U.S. government, it was recognized before their publication that these experiments had dual use of concern potential.

The U.S. government asked the National Science Advisory Board for Biosecurity (NSABB) (5), to assess the dual-use research implications of two as-yet-unpublished manuscripts on the avian influenza A/H5N1 virus, to consider the risks and benefits of communicating the research results, and to provide findings and recommendations regarding the responsible communication of this research.

Risk assessment of public harm is challenging because it necessitates consideration of the intent and capability of those who wish to do harm, as well as the vulnerability of

the public and the status of public health preparedness for both deliberate and accidental events. We found the potential risk of public harm to be of unusually high magnitude. In formulating our recommendations to the government, scientific journals, and the broader scientific community, we tried to balance the great risks against the benefits that could come from making the details of this research known. Because the NSABB found that there was significant potential for harm in fully publishing these results and that the harm exceeded the benefits of publication, we therefore recommended that the work not be fully communicated in an open forum. The NSABB was unanimous that communication of the results in the two manuscripts it reviewed should be greatly limited in terms of the experimental details and results.

This is an unprecedented recommendation for work in the life sciences, and our analysis was conducted with careful consideration both of the potential benefits of publication and of the potential harm that could occur from such a precedent. Our concern is that publishing these experiments in detail would provide information to some person, organization, or government that would help them to develop similar mammal-adapted influenza A/H5N1 viruses for harmful purposes. We believe that as scientists and as members of the general public, we have a primary responsibility "to do no harm" as well as to act prudently and with some humility as we consider the immense power of the life sciences to create microbes with novel and unusually consequential properties. At the same time, we acknowledge that there are clear benefits to be realized for the public good in alerting humanity of this potential threat and in pursuing those aspects of this work that will allow greater preparedness and the potential development of novel strategies leading to future disease control. By recommending that the basic result be communicated without methods or details, we believe that the benefits to society are maximized and the risks minimized. Although scientists pride themselves on the creation of scientific literature that defines careful methodology that would allow other scientists to replicate experiments, we do not believe that widespread dissemination of the methodology in this case is a responsible action.

The life sciences have reached a crossroads. The direction we choose and the process by which we arrive at this decision must be undertaken as a community and not relegated to small segments of government, the scientific community, or society. Physicists faced a similar situation in the 1940s with nuclear weapons research, and it is inevitable that other scientific disciplines will also do so.

Along with our recommendation to restrict communication of these particular scientific results, we discussed the need for a rapid and broad international discussion of dual-use research policy concerning influenza A/H5N1 virus with the goal of developing a consensus on the path forward. There is no doubt that this is a complex endeavor that will require diligent and nuanced consideration. There are many important stakeholders whose opinions need to be heard at this juncture. This must be done quickly and with the full participation of multiple societal components.

We are aware that the continuing circulation of the highly pathogenic avian influenza A/H5N1 virus in Eurasia—where it is constantly found to cause disease in animals of particular regions—constitutes a continuing threat to humankind. A pandemic, or the deliberate release of a transmissible highly pathogenic influenza A/H5N1 virus, would be an unimaginable catastrophe for which the world is currently inadequately prepared. It is urgent to establish how best to facilitate the much-needed research, as well as minimize potential dual use.

To facilitate and motivate this process, we also discussed the possibility of the scientific community participating in a self-imposed moratorium on the broad communication of the results of experiments that show greatly enhanced virulence or transmissibility of such potentially dangerous microbes as the influenza A/H5N1 virus, until consensus is reached on the balance that must be struck between academic freedom and protecting the greater good of humankind from potential danger. With proper diligence and rapid achievement of a consensus on a proper path forward, this could have little detrimental effect on scientific progress but significant effect on diminishing risk.

There are many parallels with the situation in the 1970s and recombinant DNA technologies (6–8). The Asilomar Conference in California in 1975 was a landmark meeting important to the identification, evaluation, and mitigation of risks posed by recombinant DNA technologies. In that case, the research community voluntarily imposed a temporary moratorium on the conduct of recombinant DNA research until they could develop guidance for the safe and responsible conduct of such research. We believe that this is another Asilomar-type moment for public health and infectious-disease research that urgently needs our attention.

Appendix

Published online 31 January 2012

* The authors are members of the U.S. National Science Advisory Board for Biosecurity.

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R. G. Webster (St. Jude Children's Research Hospital, Memphis, TN) and J. W. Curran (Emory University, Atlanta GA) contributed substantially to the content of this Policy Forum.

Policy Forum
Public Health and BIosecurity

Restricted Data on Influenza H5N1 Virus Transmission

Ron A. M. Fouchier*, Sander Herfst, Albert D. M. E. Osterhaus

Since its first detection in 1997, highly pathogenic avian influenza (HPAI) H5N1 virus has devastated the poultry industry of numerous countries of the Eastern Hemisphere. As of January 2012, HPAI H5N1 virus caused 577 laboratory-confirmed human cases of infection, of which 340 were fatal. Sustained human-to-human transmission has not been reported. Whether this virus may acquire the ability to be transmitted via aerosols and cause a future pandemic has been a matter of intense debate in the influenza field and in public health research communities.

Scientific advice about the risk of HPAI H5N1 virus to cause a future pandemic is largely based on expert opinion rather than facts. Some experts have judged this risk to be low on the basis of the following assumptions stemming from historical data: (i) only virus subtypes H1, H2, and H3 cause pandemics; (ii) influenza viruses do not cause pandemics without reassortment ("genetic mixing") of human and animal viruses; and (iii) pigs are required as an intermediate host to yield pandemic viruses (1). Partly as a consequence of inconsistent scientific advice, H5N1 virus outbreaks in poultry are not always stamped out with a sense of urgency for human health (2).

Estimates of the impact—including the death toll—of a possible future H5N1 virus pandemic for use in (inter)national pandemic preparedness plans do not generally exceed those of the H1N1 Spanish influenza pandemic of 1918 (3). Although it is recognized that the case-fatality rate of current H5N1 infections is much higher than that of the Spanish influenza pandemic, experts have argued that an aerosol-transmissible H5N1 virus would probably be less virulent than the currently circulating HPAI H5N1 viruses. However, there is no scientific evidence to support this assumption.

Our research program on H5N1 virus transmission, which led to submission of one of the papers that has stirred up so much recent controversy, aimed to investigate whether and how HPAI H5N1 virus can acquire the ability to be transmitted via aerosols among mammals and whether it would retain its virulence. If H5N1 virus can acquire the ability of aerosol transmission with few mutations without significantly losing virulence, existing assumptions should no longer be used as the basis for scientific advice. Furthermore, pandemic preparedness plans would need to be revised globally to account for much higher numbers of hospitalized cases and deaths. These are important issues in risk communication and in preventing a future pandemic or handling it as well as possible if prevention fails.

In addition, our research project has direct practical implications. Currently, our knowledge of determinants of airborne transmission of influenza virus is virtually nonexistent. If we knew which mutations and biological traits can change the zoonotic H5N1 virus into a virus with major public health impact, detection of specific mutations in circulating avian viruses should trigger more aggressive control programs than those employed currently. Moreover, if a HPAI H5N1 virus has the potential to cause a future pandemic, our last resort would consist of implementing societal measures (such as quarantine and travel restrictions), surveillance, vaccination, and the use of antiviral drugs. Diagnostic tests, antiviral drugs, and prepandemic H5N1 vaccines are currently evaluated using HPAI H5N1 strains with biological properties that are similar (but may not be identical) to the strain that would cause the pandemic. Because surveillance and effectiveness of vaccination and antiviral drugs may depend on virus lineage and specific

mutations, these measures need to be evaluated in the context of viruses with the most relevant genetic and biologic properties.

Oversight, Biosafety, and Biosecurity

Our work on aerosol transmission of HPAI H5N1 virus was done completely openly, and the decision to perform the work was reached upon serious local, national, and international consultation. The work has been discussed among staff members of the Department of Virology at Erasmus Medical Center (MC) since 1997, followed by consultation with local biosafety officers and facility managers. Over several years, numerous international influenza specialists and other virologists operating in class-3 and-4 facilities were consulted, and a plan was drawn to obtain adequate research facilities in Rotterdam.

After a Broad Agency Announcement of the National Institute of Allergy and Infectious Diseases and National Institutes of Health (BAA NIH-NIAID-DMID-07-20) in 2005, the Department of Virology, along with U.S. partners, drafted a research proposal to become an NIAID NIH Center of Excellence for Influenza Research and Surveillance (CEIRS) to support the research agenda of the U.S. Department of Health and Human Services (DHHS) Pandemic Influenza Plan. The proposal was reviewed favorably with the help of external reviewers, and the research contract was awarded.

An explicit permit to work with aerosol-transmissible H5N1 virus was obtained from the Dutch Ministry for Infrastructure and the Environment (I&M) in 2007. To this end, I&M was advised by the Commission on Genetic Modification (COGEM), an independent scientific advisory committee for the Dutch government. I&M and COGEM concluded that the proposed work could be performed with negligible risk to humans and the environment under the conditions outlined in the application.

The facility designed for the research consists of a negative-pressurized laboratory in which all work is carried out in class-3 isolators or class-3 biosafety cabinets, which are also negative pressurized. Only authorized personnel who have received appropriate training can access the facility, which has state-of-the art security systems. All facilities, personnel, procedures, and records are subject to inspection and oversight by institutional biosafety officers of Erasmus MC in close consultation with the facility management. In agreement with the U.S. select agent regulations for oversees laboratories, the facilities, personnel, procedures, and records are further inspected by the U.S. Centers for Disease Control and Prevention every 3 years. The most recent inspection took place in February 2011, at which time no shortcomings in biosafety and biosecurity measures were identified.

Other research institutes—following similar but independent routes in the United States and elsewhere—have also come to the conclusion that this type of research is important, is of major interest to public health, and can be performed safely (4–8).

Dissemination of Results

After the decision was made that the research project was important and could be performed safely, the next question to address was whether the methods and results should be published in detail. We decided to describe our data, although not in complete detail, during a keynote lecture at the influenza conference organized by the European Scientific Working Group on Influenza (ESWI) in Malta in September 2011 to inform the influenza field, as well as policy-makers, of our results. About the same time, a manuscript was submitted for publication. We consulted with NIAID NIH staff, collaborators within our CEIRS center, and organizers of the ESWI meeting about the decision to make our results available to the public.

In agreement with the Dutch Code of Conduct for Biosecurity and the U.S. regulations on "dual use research of concern," Science first conducted its own biosecurity review and the manuscript was independently sent to the National Science Advisory Board for Biosecurity (NSABB) for advice. The NSABB drafted recommendations for the U.S. government suggesting that the conclusions of the manuscript could be published, but without experimental details and mutation data that would enable replication of the experiments. It was recognized by NSABB that detailed information about the results (specific mutations) should be shared under confidentiality with parties that "need to know."

Important questions that stem from the draft NSABB recommendations are who will identify the parties that need to know, how, and what mechanism can be used to share classified information? In our opinion, identification of relevant parties should be done liberally and should include the public health services of countries where H5N1 virus has infected humans, poultry, and other animals in recent history. According to the databases of the World Health Organization (WHO) and Food and Agriculture Organization (FAO), these countries span Bangladesh, Cambodia, China, Egypt, Hong Kong SARPRC, India, Indonesia, Iran, Israel, Japan, Korea, Mongolia, Myanmar, Nepal, Palestinian Autonomous Territories, and Vietnam (9, 10). WHO and FAO reference laboratories around the world and other expert laboratories affiliated to affected countries need to know. Affected countries and affiliated laboratories require detailed knowledge of our results to ensure implementation of the most up-to-date molecular diagnostics and virus genome sequence interpretation. Companies and research organizations with research and development programs aiming at the development of diagnostic tests, vaccines, and antiviral drugs for H5N1 virus need to know if the effectiveness of such tools depends on the virus lineage or specific mutations. Finally, research laboratories that study H5N1 virus host adaptation, H5N1 virus in mammalian model systems, or use the virus lineage that was the subject of our studies have a need to know because they may unknowingly develop high-risk variants. The latter group is not hypothetical, as we have identified, from published literature, laboratories working with H5N1 viruses that may only require one to three mutations before the viruses used may become transmissible via aerosols.

The WHO-coordinated Pandemic Influenza Preparedness (PIP) Framework went into effect at the World Health Assembly in May 2011 after 4 years of intense international negotiations. The PIP was implemented to promote sharing of influenza viruses and to provide the member states access to vaccines and other benefits. With-holding information from countries that share influenza viruses and their sequence data would be a major step backward in the field of global infectious disease surveillance and research.

Biosecurity experts have argued that the methods we have used represent a recipe to create biological weapons and that information about the specific mutations that determine transmission of H5N1 virus could also be misused for this purpose. However, it is important to emphasize that we did not develop novel methods and that we only used information and methods that are available freely from the scientific literature. The logic in this work is sufficiently obvious that virologists could perform experiments similar to ours even if our method is not published.

Perspective on Dual-Use Research

The recent recommendation of the NSABB to restrict publication of research results is unprecedented and is a major deviation from common practice in the life sciences.

Among thousands of manuscripts that describe potential dual-use research according to the NSABB guidelines (11), only a handful has raised questions (7, 8, 12) and none has triggered similar advice. In dual-use research, weighing risks and benefits of the research is the crux. Biosecurity experts are more likely to lean toward zero or near-zero tolerance with respect to risk, whereas for infectious disease specialists, incremental risks may be waived in light of potentially important public health benefits. Reaching consensus among scientific disciplines, let alone among the public at large, is virtually impossible.

We do not agree with the NSABB recommendations. Nevertheless, we have respected their advice. Together with the NSABB, NIAID NIH, and Science, and in close consultation with key parties in the public health field, we hope to find a solution for disseminating key information to those who need to know while shielding this information from potential misuse. However, we cannot rule out the possibility that new scientific research, outbreak events, political sensitivities, or other circumstances may call for deviation from this route.

As we compare the current threat posed by bioterrorism and our past experience with the threat of influenza, we would argue that nature itself should be considered the prime bioterrorist. Viruses emerging from animal reservoirs have killed many millions of people around the globe without the help of direct human interference, and we need to be prepared for other naturally occurring events similar to those caused by influenza A virus, HIV, SARS-coronavirus, West Nile virus, filoviruses, and henipaviruses. Infectious disease specialists have a moral obligation to perform dual-use research in the interest of public health and to communicate the results of their work responsibly.

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Roman Chlibek, Ioana Anca, Francis André, Milan Čižman, Inga Ivaskeviciene, Atanas Mangarov, Zsófia Mészner, Penka Perenovska, Marko Pokorn, Roman Prymula, Darko Richter, Nuran Salman, Pavol Šimurka, Eda Tamm, Goran Tešović, Ingrid Urbancikova, Dace Zavadska, Vytautas Usonis
Abstract
As Europe's population ages, disease morbidity and treatment costs in the adult population are likely to rise substantially, making this a pertinent time to review and revise preventive strategies such as vaccination. Vaccine uptake remains a problem for adults and there is a lack of coordinated programmes for vaccination of adults. Countries in Western Europe have begun to identify the need to increase adult vaccination, but the situation in Central European countries remains poorly identified and inadequately described. This paper summarises the evidence to support the development of an adult vaccination calendar in the Central European Vaccination Awareness Group (CEVAG) member countries (Bulgaria, Croatia, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Romania, Slovakia, Slovenia and Turkey). CEVAG recommends the introduction of an adult vaccination calendar, which should include vaccination against diseases that represent a large burden in adults in terms of mortality and morbidity. This calendar could be modified to meet the priorities of individual countries.
Measles control in Sub-Saharan Africa: South Africa as a case study
Original Research Article Pages 1594-1600
Stéphane Verguet, Waasila Jassat, Calle Hedberg, Stephen Tollman, Dean T. Jamison, Karen J. Hofman

Abstract
Background
Due to intensified measles immunization efforts, measles mortality has decreased substantially worldwide, particularly in Sub-Saharan Africa (SSA). The World Health Organization (WHO) estimated a 92% decrease in measles-related deaths in the WHO AFRO region for the period 2000–2008. Recently, the AFRO region established a measles pre-elimination goal and experts have suggested engaging in a measles eradication campaign at the global level. However, recent large-scale outbreaks in many Sub-Saharan African countries present a challenge to measles control efforts. This paper examines measles immunization and the impact of measles supplemental immunization activities (SIAs) on routine immunization coverage in South Africa (SA).
Methods
We reported on immunization coverage trends in SA for the period 2001–2010 at the province and district levels. The data included routine immunization for 1st and 2nd doses of measles vaccine (MCV1, MCV2), SIAs, 1st dose of Bacille Calmette-Guérin vaccine, 1st and 3rd doses of oral polio vaccine (OPV1, OPV3), 3rd dose of Diphtheria–Tetanus–Pertussis–Haemophilus-influenzae-B vaccine (DTP-Hib3), and the number of under-one-year-olds having completed a primary course of immunization (Imm1). A regression model looked at the SIA impact on routine coverage.
Results
Over the past decade, MCV1 and MCV2 coverage have increased nationally from 68% and 57% in 2001 to 95% and 83% in 2010, respectively. SIA coverage has remained at high levels, around 90%, over the same period. Substantial heterogeneity in MCV1 and MCV2 coverage is present across SA districts, with differences in coverage of 56% (MCV1) and 51% (MCV2) in 2010. In any given year, occurrence of SIAs was associated with a decrease in routine immunization coverage of MCV1, MCV2, OPV1, OPV3, DTP-Hib3, and Imm1, at the district level.
Conclusions
The heterogeneity in measles vaccination coverage across SA districts challenges the goal of measles elimination in SA and SSA. The reduction in routine immunization coverage associated with the occurrence of SIAs raises the legitimate concern that SIAs may negatively impact health systems' functioning.

Medicaid reimbursement and the uptake of adolescent vaccines

Original Research Article Pages 1682-1689

Charitha Gowda, Amanda F. Dempsey

Abstract
Background
In light of low adolescent vaccination rates, state-level policies that could improve vaccine coverage should be evaluated. Approximately 1/3 of adolescents are eligible, primarily through Medicaid enrollment, to receive vaccines from state-administered Vaccines for Children (VFC) programs. We investigated whether Medicaid reimbursement, the scope of implementation of VFC programs (i.e. limited or universal purchase), and/or presence of school-based vaccine mandates were associated with adolescent vaccination levels.
Methods
We performed a cross-sectional analysis of state-level associations between these policies and 2009 National Immunization Survey-TEEN vaccination rates for tetanus-

containing, meningococcal conjugate (MCV4), and among females only, human papillomavirus (HPV) vaccines.
Results
Medicaid reimbursement was not associated with vaccine coverage rates after adjusting for presence of vaccine-related school mandates, type of VFC program, proportion of adolescents attending preventive care visits, and state-specific distribution of insurance coverage. Participation in a more expansive VFC program (universal or universal-select) was significantly associated with HPV vaccine coverage, but not tetanus-containing vaccine or MCV4, among states that had mandates for any vaccines.
Conclusions
Our results suggest that, contrary to what has been shown for childhood vaccines, raising Medicaid reimbursement rates may not improve adolescent vaccine utilization. Instead, other policy changes may be more effective, such as expansion of VFC programs into universal purchase programs, further implementation of school-based vaccine mandates and efforts to raise preventive care visits among adolescents.

Vaccination Coverage in Haiti: Results from the 2009 National Survey

Original Research Article Pages 1746-1751

Jeanette J. Rainey, François Lacapère, M. Carolina Danovaro-Holliday, Kam Mung, Roc Magloire, Gregoire Kananda, Jean Ronald Cadet, Carla E. Lee, Henriette Chamouillet, Elizabeth T. Luman

Abstract
Introduction
Since 1977, vaccinations to protect against tuberculosis, diphtheria, tetanus, pertussis, polio, and measles (and rubella since 2009) have been offered to children in Haiti through the routine immunization program. From April to July 2009, a national vaccination coverage survey was conducted to assess the success of the routine immunization program at reaching children in Haiti.
Methods
A multi-stage cluster survey was conducted using a modified WHO method for household sampling. A standardized questionnaire was administered to collect vaccination histories, demographic information, and reasons for under-vaccination of children aged 12–23 months. A child who received the eight recommended routine vaccinations was considered fully vaccinated. The routine vaccination schedule was used to define valid doses and estimate the percentage of children vaccinated on time.
Results
Among 1345 children surveyed, 40.4% (95% CI: 36.6–44.2) of the 840 children with vaccination cards had received all eight recommended vaccinations. Coverage was highest for the Bacille Calmette–Guérin vaccine (87.3%), the first doses of the diphtheria–tetanus–pertussis vaccine (92.0%), and oral poliovirus vaccine (93.4%) and lowest for measles vaccine (46.9%). Timely vaccination rates were lower. Assuming similar coverage for the 505 children without cards, coverage with the complete vaccination series among all surveyed children 31.9%. Reasons for under-vaccination included not having enough time to reach the vaccination location (24.8%), having a child who was ill (13.8%), and not knowing when, or forgetting, to go for vaccination (12.8%).
Conclusions and recommendations
Coverage for early-infant vaccines was high; however, most children did not complete the full vaccination series, and many children received vaccinations later than

recommended. Efforts to improve the immunization program should include increasing the frequency of outreach services, training for vaccination staff to minimize missed opportunities, and better communicating the timing of vaccinations to encourage caregivers to bring their children for vaccinations at the recommended age. Efforts to promote the benefits of vaccination and card retention are also needed.

Value in Health
January 2012, Vol. 15, No. 1
http://www.valueinhealthjournal.com/home
[Reviewed earlier]

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Vaccines: The Week in Review *is a service of the Center for Vaccines Ethics and Policy (CVEP) which is solely responsible for its content. Support for this service is provided by CVEP co-founders – - Penn Center for Bioethics, The Wistar Institute Vaccine Center and Children's Hospital of Philadelphia Vaccine Education Center. Additional support is provided by PATH Vaccine Development Program and the International Vaccine Institute (IVI), and by vaccine industry leaders including GSK and Pfizer (list in formation), as well as the Developing Countries Vaccine Manufacturers Network (DCVMN). Support is also provided by a growing list of individuals who use this service to support their roles in public health, clinical practice, government, IGOs/NGOs, research, industry and academia.*