DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 22-23, 2016
Atlanta, Georgia

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Final - June 15, 2016

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30329
June 22-23, 2016

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, June 22			
8:00	**Welcome & Introductions**		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:30	**Agency Updates**		
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); CDC and Ex *Officio M* embers
8:45	**Cholera Vaccine**		
	Introduction	Information & Discussion	Dr. Art Reingold (ACIP, WG Chair)
	Cholera vaccine updates		Dr. Karen Wong (CDC/NCEZID)
	Proposed recommendations		Dr. Karen Wong (CDC/NCEZID)
	Public Comment		
	Recommendation Vote	**Vote**	Dr. Karen Wong (CDC/NCEZID)
10:00	***Break***		
10:30	**Meningococcal Vaccines**		
	Introduction		Dr. Lorry Rubin (ACIP, WG Chair)
	Update: Trumenba Label		Dr. Laura York (Pfizer)
	Summary of WG Discussions: Trumenba Label	Information & Discussion	Ms. Jessica MacNeil (CDC/NCIRD)
	Cost-effectiveness of MenACWY in HIV-Infected Persons		Dr. Ismael Ortega-Sanchez (CDC/NCIRD)
	GRADE for MenACWY in HIV-Infected Persons		Dr. Monica Patton (CDC/ NCIRD)
	Considerations for Use of MenACWY in HIV-Infected Persons		Ms. Jessica MacNeil (CDC/NCIRD)
	Proposed recommendations		Ms. Jessica MacNeil (CDC/NCIRD)
	Public Comment		
	Recommendation Vote	**Vote**	Ms. Jessica MacNeil (CDC/NCIRD)
	VFC Vote	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
12:40	***Lunch***		
2:00	**Evidence-Based Recommendations Work Group Update**	Information	Dr. Art Reingold (ACIP, WG Chair) Dr. Wendy Carr (CDC/NCIRD)
2:05	**Hepatitis Vaccines Update**	Information	Dr. Art Reingold (ACIP, WG Chair) Dr. Noele Nelson (CDC/NCHHSTP)
2:10	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
2:20	**Influenza**		
	Introduction		Dr. Ruth Karron (ACIP, WG Chair)
	Flulaval quadrivalent	Information & Discussion	Dr. Bruce Innis (GSK)
	Flucelvax Quadrivalent		Dr. James Mansi (Seqirus)
	Vaccine safety update		Dr. Tom Shimabukuro (CDC/NCEZID)
3:10	***Break***		
3:30	Vaccine effectiveness update		Dr. Brendan Flannery (CDC/NCIRD) Dr. Chris Ambrose (MedImmune)
	Proposed recommendations summary		Dr. Lisa Grohskopf (CDC/NCIRD)
	Public Comment		
	Recommendation Vote	**Vote**	Dr. Lisa Grohskopf (CDC/NCIRD)
	VFC Vote	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
5:00	**Public Comment**		
5:15	**Adjourn**		

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Thursday, June 23

8:00	**Unfinished business**		
8:30	**Respiratory Syncytial Virus (RSV) Vaccine – Older Adults**		
	Introduction	Information & Discussion	Dr. Ruth Karron (ACIP, WG Chair)
	Overview of RSV Vaccines		Dr. Lindsay Kim (CDC/NCIRD)
9:00	**Safety of Maternal Tetanus, Diphtheria, Acellular Pertussis (Tdap) Immunization**		
	Introduction and enhanced surveillance of Tdap vaccine safety in pregnancy in VAERS		Dr. Pedro Moro (CDC/NCEZID)
	Maternal pertussis vaccination and structural birth defects in offspring	Information & Discussion	Dr. Lakshmi Sukumaran (CDC/NCEZID)
	Reactogenicity and immunogencity of Tdap vaccine in pregnant women		Dr. Kathryn M. Edwards (Vanderbilt University School of Medicine)
	Pertussis Vaccines Work Group Update		Dr. Art Reingold (ACIP, WG Chair)
9:55	***Break***		
10:25	**Laboratory Containment of Poliovirus Type 2**	Information & Discussion	Dr. Olen Kew, National Poliovirus Containment Coordinator
10:40	**Human Papillomavirus (HPV) Vaccines**		
	Introduction		Dr. Allison Kempe (ACIP, WG Chair)
	HPV vaccine duration of protection		TBD
	Modeling and cost effectiveness of 2-dose vaccination schedules	Information & Discussion	Dr. Marc Brisson (Laval University)
	HPV vaccine effectiveness studies		Dr. Sara Oliver (CDC/NCIRD)
	GRADE for 2-dose schedules		Dr. Elissa Meites (CDC/NCIRD)
	Recommendation options		Dr. Lauri Markowitz (CDC/NCIRD)
12:45	**Public Comment**		
1:00	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
Tdap	Tetanus, Diphtheria, Acellular Pertussis Vaccine
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
LAIV	Live Attenuated Influenza Vaccine
MSM	Men who have sex with men
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
VFC	Vaccines for Children
WG	Work Group

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Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
AE	Adverse Events
AIN	Anal Intraepithelial Neoplasia
ARI	Acute Respiratory Infections
BLA	Biologics License Application
ccIIV4	Flucelvax Quadrivalent®
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
CFRs	Case Fatality Ratios
CHIP	Children's Health Insurance Program
CICP	Countermeasures Injury Compensation Program
CIN	Cervical Intraepithelial Neoplasia
CISA Project	Clinical Immunization Safety Assessment Project
cLIA	Competitive Luminex Immunoassay
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest
COID	Committee on Infectious Disease, AAP
COPD	Chronic Obstructive Pulmonary Disease
DD	Deputy Director
DFO	Designated Federal Official
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DtaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
HER	Electronic Health Record
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FHA	Filamentous Hemagglutinin
FIM	Fimbria
FLU VE	Influenza Vaccine Effectiveness Network
GAP	Global Action Plan
GBS	Guillain-Barré Syndrome
GCC	Global Certification Commission
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSA	Gerontological Society of America
GSK	Glaxo Smith Kline
HAIs	Hospital-Associated Infections
HCP	Healthcare Personnel
HHS	(Department of) Health and Human Services
HI	Hemagglutination Inhibition
HIV	Human Iimmunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration

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HRT	Hormone Replacement Therapy
hSBA	Human Complement Serum Bactericidal Antibody
ICD	International Classification of Diseases
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
HIS	Indian Health Service
IIV	Inactivated Influenza Vaccine
INDs	Investigational New Drugs
ISO	Immunization Safety Office
JEV	Japanese Encephalitis Vaccine
LAIV	Live Attenuated Influenza Vaccine
LLOQ	Lower Limit of Quantitation
LRTI	Lower Respiratory Tract Illness
MCC	Meningococcal C Conjugate
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MenB	Serogroup B Meningococcal Disease
mAb	Monoclonal Antibody
MMWR	*Morbidity and Mortality Weekly Report*
MPL	3-O-desacyl-4'-monophosphoryl lipid A
MRC	(British) Medical Research Council
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NCC	National Certification Committee
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccine
NPCC	(Office of) National Poliovirus Containment Coordinator
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
OASH	Office of Assistant Secretary of Health
OPV	Oral Polio Vaccine
PACCARB	President’s Advisory Council on Combating Antibiotic-Resistant Bacteria
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV13	Pneumococcal Conjugate Vaccine
PhRMA	Pharmaceutical Research and Manufacturers of America
PIV	Purified Inactivated Virus
PPE	Personal Protective Equipment
PRN	Pertactin
PT	Pertussis Toxin
QALYs	Quality Adjusted Life Years
RCC	Regional Certification Commission
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction

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SAEs	Serious Adverse Events
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate
SCRI	Self-Controlled Risk Interval
SES	Socioeconomic Status
SGA	Small for Gestational Age
SME	Subject Matter Experts
STI	Sexually Transmitted Infection
TB	Tuberculosis
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
THB	Travelers' Health Branch
TIV	Trivalent Influenza Vaccine
TORCH Infections	Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes Simplex
TVC	Total Vaccinated Cohort
UCF	University of Central Florida
UK	United Kingdom
US	United States
V. cholera	*Vibrio cholerae*
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VistA	Veterans Information Systems and Technology Architecture
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization
WPV	Wild Poliovirus
WRAIR	Walter Reed Army Institute of Research
YF	Yellow Fever
ZIP	Zika in Infants and Pregnancy

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Call To Order & Welcome, Dr. Frieden's Opening Remarks, Meeting Overview, Announcements, & Introductions

Call To Order & Welcome

Nancy Bennett, MD, MS
ACIP Chair

Dr. Bennett called the June 2016 Advisory Committee on Immunization Practices (ACIP) meeting to order and welcomed those present. She said that they were very honored to have Dr. Frieden in attendance to deliver the keynote address, and invited him to give the opening remarks.

Opening Remarks

Thomas Frieden, MD, MPH
Director, Centers for Disease Control and Prevention

Dr. Frieden welcomed the ACIP and thanked them for their attendance, attention, focus, and commitment to continuing to openly debate, discuss, and move forward immunization policy for the United States (US). He said that he often points to the ACIP as one of the truly great examples of the way this country sets health policy in a manner that combines science with an understanding of its impact on people. ACIP is, indeed, a model for the world and he expressed his appreciation for the members' contributions and commitment.

Recognizing that the ACIP had a full agenda and would be discussing a series of very important issues over the next two days, he pointed out that they also would have to address a particularly unusual and challenging situation with regard to influenza. Though he did not plan to discuss the details of what the ACIP would deliberate later in the day, he said he did want to take a step back to think more about actionable data. In public health, action often must be taken based on what is currently known. He emphasized the importance of keeping in mind that a non-decision is also a decision. While he was aware that ACIP had carefully assessed this for many years and that there are varying perspectives on it across the world, he said he wanted to challenge them with some of his perspectives on the issue.

He first reiterated the principles of Centers for Disease Control and Prevention's (CDC's) pledge to the American people. Dr. Walter Dowdle outlined this years ago. Dr. Frieden first saw it 20 years ago when he was required to take ethics training with CDC. He was sitting in his home office in India working for CDC and the World Health Organization (WHO). He was so struck with the following five points that he has kept them on his desk ever since:

- ❑ Be a diligent steward of the funds entrusted to our agency
- ❑ Provide an environment for intellectual and personal growth and integrity
- ❑ Base all public health decisions on the highest quality scientific data that is derived openly and objectively
- ❑ Place the benefits to society above the benefits to our institution
- ❑ Treat all persons with dignity, honesty, and respect

Focusing on the principle to “base all public health decisions on the highest quality scientific data that is derived openly and objectively,” Dr. Frieden stressed that there was a lot packed into that single bullet point. He pointed out that the words “randomized controlled trial (RCT)” is not included in that bullet. Randomized, double-blind, placebo-controlled trials are, in fact, one of the great accomplishments of the 20th Century.

Given that his background is as a Tuberculosis (TB) Control Specialist, Dr. Frieden said that he must wave the flag for tuberculosis control work. In 1946, the British Medical Research Council (MRC) conducted the first RCT that showed unequivocally that streptomycin was effective for TB. In fact, streptomycin is not that good because as a single drug, one rapidly develops resistance. What followed from the British MRC was a remarkable, several decades long, multi-country collaboration of RCTs that optimized treatment of TB. These were truly matters of decades long commitment and brilliance, because the trials had recruited over a couple of years and followed everyone for five years. They systematically figured out how to reduce treatment from 12 months, to 9 months, to 6 months; how long each medication must be given; the different doses; and which medications were equivalent. With those treatment regimens developed over decades, 50 million patients have been treated over recent years as this has been expanded around the world.

That notwithstanding, Dr. Frieden emphasized that RCTs are a fantastic tool. However, there are some challenges. With regard to influenza, there is a striking disconnect between what the RCTs found and what other trials with other information sources found about efficacy. The influenza program is unique. No other vaccine is given every year. No other vaccine is evaluated for efficacy every year. This helps to measure the impact of public health interventions and determine what difference is being made in order to report, based on reliable model information, how many cases, hospitalizations, and deaths are prevented each year. Influenza is a serious and formidable challenge. Even in a “good” year, it causes millions of illnesses, hundreds of thousands of hospitalizations, and thousands to tens of thousands of deaths. The only thing that can be predicted definitely about influenza is that is unpredictable.

Dr. Frieden said that he wanted to leave the issue of influenza, which ACIP would be discussing in the afternoon, to speak further about RCTs. He quoted Angus Deaton, Nobel Laureate in Economics who said that “Randomized controlled trials cannot automatically trump other evidence, they do not occupy any special place in some hierarchy of evidence, nor does it make sense to refer to them as ‘hard’ while other methods are ‘soft.’ These rhetorical devices are just that; metaphor is not argument, nor does endless repetition make it so” [Deaton A. J Econ Literature 2010;48:424-455]. While this quote refers to the use of RCTs in development policies, it is equally relevant to use in medicine and science. There are definitely limitations of RCTs. That is not to say that RCTs are not important, not wonderful, not potentially pivotal. However, it is important to put them within the landscape of evidence and data used for decision-making.

Dr. Frieden said he thought it was worth outlining some of the limitations of RCTs. Some of these are in the implementation phase, so an RCT might be done incorrectly. However, some of them are inherent to the practice of RCTs. One limitation is external validity, so it may be that what is correct today is not correct tomorrow. It may be that there is a temporal component, or that what is relevant in one place is not in another. It may be that the changing epidemiology of disease changes the outcome, or that the program impact changes. Even if the RCT is meticulously done, it may lack external validity and not be generalizable to other settings. Dr. Frieden said he would never forget an offhand comment in an article that George Comstock

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wrote on TB that someone really should study the prognosis of a positive tuberculin test. Dr. Frieden was really confused by that remark, but was too shy to ask him for years. He finally asked him 20 years later, “Dr. Comstock, you did that in Alaska. In fact, it is always your studies that we point to when we say that there is a 5% to 10% lifetime risk of progressing from TB infection to TB disease. Why do you say that someone should study the prognosis of a positive tuberculin test?” Dr. Comstock said, “Well, because that’s what it was then. But, we don’t know what it is now. Maybe the force of infection was greater. Maybe there were differences in the genetic make-up or environmental components of the individual.” It was a remarkably perceptive statement from someone who had done the definitive studies and knew that they were not definitive.

There also are temporal changes. Treatments, exposures, and populations change. This is commonly observed in modern medicine where someone conducts an RCT of Intervention X and finds that it is no better than Intervention Y that costs a tenth as much and is much older. By the time it comes out they say, “Ah yes, but now we have Intervention X^2 so we’re going to use that.” There is often a situation of not having information that is relevant to the decisions people are making, or at least that do not appear to be relevant. In addition, there are many rare diseases that added up affect many people. However, there will never be enough participants to accrue an RCT of sufficient size.

Efficiency is another issue. RCTs take time and money and there are often quicker, more efficient ways to get an answer. There also are design and implementation limitations. These may be inherent or not. For example, treatment may not be standardized in the case of surgery or psychotherapy. Placebo effects are an interesting topic. With certain mental health conditions, people have such confidence in the treatment that the placebo has quite a good impact. That has changed dramatically over the last few decades. Randomization may be challenging, and controls / confounding may be issues.

RCTs generally cannot evaluate population-level interventions and impacts. In the field of TB, one might conduct a trial of one modality of treatment, but that may not indicate whether multi-drug resistance is being risked in society as a whole. Or in the case of vaccine, there may be a major impact on health population or herd immunity that would not be captured in an RCT. Finally, there is what Dr. Frieden refers to as the “dark matter of clinical medicine.” The fact is, when this is considered objectively, an enormous proportion of what is done in modern medicine today is not based on data, and there is no realistic possibility or probability that there will be an RCT to evaluate it soon.

It can be said that either RCTs are the “only game in town” or that RCTs and other sources can be used as well when possible. A few other data sources include observational, program implementation and evaluation, epidemiological analyses, aggregated clinical information (potentially as a prelude to an RCT), and others. Program implementation and evaluation is like a treatment trial. A public health program can be implemented and it can be determined whether there is an impact. There are situations in which the aggregate information may be more accurate than the individual information. Aggregate information has been used to deal with nutritional issues, public programming issues, et cetera. In terms of aggregated clinical information, some of the older case series provided granular information on individual patients and are much more informative than some of the more recent journal articles that give aggregated information. With a rare condition, a case series can help to understand what happened and see how that might reflect on individual treatment / prognosis. Interestingly in terms of electronic health records (IHRs), patient registries, patient willingness to participate and

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share their information, there is a possibility of developing granular information across programs.

An example that is always raised in relation to observational or non-randomized information is the fiasco with the recommendation of hormone replacement therapy (HRT). There is a pretty strong argument that the data itself, had it been analyzed correctly, would not have led to the recommendation for HRT. The people who conducted that study are excellent epidemiologists. Everyone makes mistakes and hindsight is always 20/20. With any form of data, whether it be RCTs (for which limitations must be recognized) or other data sources, it is important to have humility because action is always being taken on imperfect data.

On Dr. Frieden's first day of medical school, the Dean told them, "Half of what we teach you is wrong, but we don't know what half it is so you will be tested on all of it." It is important to take a holistic approach to health data. That begins with having clarity about the health outcome being sought. Knowledge is not being sought for the purposes of seeking knowledge. Instead, knowledge is being sought for the purpose of improving health and addressing a specific health outcome. Therefore, data sources are needed that are fit to the purpose of achieving that health outcome. Also needed is rigor in evaluating all data sources for their strengths and limitations. There must be humility about conclusions regardless of the data sources, with an understanding that conclusions may change over time as Professor Comstock knew they might, or that there may be problems with the analyses, changes in modalities, and/or that viruses and bacteria may be evolving. The focus must be on when the data are sufficient for action. There always will be an argument for more research. There always will be an argument for more perfect data. Nevertheless, it is always important to understand that even a non-decision is a decision. Failure to act is a decision. The goal is to seek actionable data—data that are sufficient in an open, objectively derived, transparent fashion to make a recommendation and substantiate why.

Dr. Bennett thanked Dr. Frieden for the very inspiring and motivating presentation, which certainly would be taken up by ACIP's Evidence-Based Recommendations Work Group (WG). She then introduced Dr. Cohn for the meeting overview, roll call, and introductions.

Overview

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Cohn welcomed everyone to the June 2016 ACIP meeting. She indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. She then recognized several others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Stephanie Thomas, Natalie Greene, and Chris Caraway. She noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes after being made visually accessible to all viewers, including the visually disabled. The live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within approximately 90 days following this meeting. Members of the press interested in conducting interviews with ACIP members were instructed to contact Ian Branam, located at the press table, for assistance in arranging interviews.

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The next ACIP meeting will be convened at CDC on Wednesday and Thursday, October 19-20, 2016. Registration for all meeting attendees is required. The registration deadline for Non-US citizens is September 28, 2016 and for US citizens registration closes October 10, 2016. Registration is not required for webcast viewing. As a reminder for non-US citizens attending ACIP meetings, completion of several forms is required for each meeting at the time of registration. It is important that these forms are submitted within the required time frame. Stephanie Thomas, the ACIP Committee Management Specialist, will be able to help with any questions about the process.

Dr. Cohn then made the following announcements pertaining to *Ex Officio* and Liaison Representatives:

Ex Officio Members

- Dr. Jennifer Gordon is representing the National Vaccine Program Office (NVPO)

Liaison Representatives

- Dr. Corey Robertson is representing Pharmaceutical Research and Manufacturers of America (PhRMA)
- Dr. Kimberly Thompson, Professor of Preventive Medicine and Global Health, University of Central Florida (UCF) College of Medicine is representing National Vaccine Advisory Committee (NVAC) as the Chair, replacing Dr. Walt Orenstein

Regarding public comments, Dr. Cohn indicated that topics presented during ACIP meetings include open discussion with time reserved for public comment. She explained that time for public comment pertaining to topics on the agenda was scheduled following the end of the day's sessions, and that time for public comments also would be prior to each vote by ACIP to enable these comments to be considered before a vote. Registration for public comments is solicited in advance of meetings. People who planned to make public comments were instructed to visit the registration table at the rear of the auditorium where Ms. Stephanie Thomas would record their name and provide information on the process. People making public comments were instructed to provide 3 pieces of information: name, organization if applicable, and any conflicts of interest (COI). Registration for public comment also was solicited in advance of this meeting through the *Federal Register*. Given time constraints, each comment was limited to 3 minutes. Participants unable to present comments during this meeting were invited to submit their comments in writing for inclusion in the meeting minutes.

Recommendations and immunization schedules can be downloaded from the ACIP website. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, revised, or retired. During every meeting, an update is provided on the status of ACIP recommendations. There was one ACIP publication since February 2016 meeting, which is reflected in the following table:

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ACIP Recommendations Published Since February 2016

Title	Publication Date	MMWR Reference
• Use of Vaccinia Virus Smallpox Vaccine in Laboratory and Health-care Personnel at Risk for Occupational Exposure to Orthopoxviruses	March 18, 2016	65(10);257–262

http://www.cdc.gov/vaccines/HCP/acip-recs/recs-by-date.html 7

Applications for ACIP membership are due no later than June 30, 2016 for the 4-year term beginning July 1, 2018. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site:

E-mail: acip@cdc.gov Web homepage: www.cdc.gov/vaccines/acip/index.html

Nominations: www.cdc.gov/vaccines/acip/committee/req-nominate.html

A current CV, at least one recommendation letter from a non-federal government employee, and complete contact information are required. These may be submitted as e-mail attachments to Dr. Jean Clare Smith at jsmith2@cdc.gov

To summarize COI provisions applicable to the ACIP, as noted in the ACIP Policies and Procedures manual, members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited COI waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but these members are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions, with the proviso that he/she abstains on all votes related to the vaccines of that company. It is important to note that at the beginning of each meeting, ACIP members state any COIs.

Announcements: Welcomes & Goodbyes

Nancy Bennett, MD, MS
ACIP Chair

Dr. Bennett shared the following announcements, welcoming individuals new to ACIP and wishing farewell to those who were moving on, emphasizing how sad it was to be losing several members. She presented Certificates of Appreciation to each departing member.

Dr. Nancy Messonnier

Dr. Messonnier was named Director of the National Center for Immunization and Respiratory Diseases (NCIRD) in March 2016. Dr. Messonnier received her BA from the University of Pennsylvania and MD from the University of Chicago School of Medicine, and completed internal medicine residency training at the University of Pennsylvania. She joined CDC in 1995 as an Epidemic Intelligence Service (EIS) officer in the Childhood and Respiratory Diseases Branch, and she served as Branch Chief of the Meningitis and Vaccine-Preventable Disease Branch in NCIRD from the Center's formation in 2006 through 2012. Since 2012, Dr. Messonnier has held several additional leadership positions across CDC, and most recently served as Deputy Director of NCIRD.

Dr. Kathy Harriman

Dr. Harriman is Chief of the Vaccine Preventable Disease Epidemiology Section, Immunization Branch of the California Department of Public Health (CDPH) in Richmond, California. Dr. Harriman has done an outstanding job of representing public health on ACIP, for which ACIP is extremely grateful. Dr. Harriman believed that going to Africa to work on Ebola was not a good enough excuse to miss a meeting, so she decided to break her leg as well. She has served on the following ACIP WGs: Adult Immunization (Chair), General Recommendations (Chair), Meningococcal Vaccines (Member), Pertussis-Containing Vaccines (Member), and Hepatitis Vaccines (Member). She has helped to keep ACIP on track with her great public health expertise and vision.

Dr. Lee Harrison

Dr. Harrison is Professor of Medicine and Epidemiology in the Infectious Diseases Epidemiology Research Unit at the University of Pittsburgh in Pittsburgh, Pennsylvania (PA). Dr. Harrison was so deeply engaged in the Zoster WG that he actually got Zoster. He has always been an incredible voice for everyone with inquisitive questions, calm reason, and delightful nature. He has served on the following ACIP Work Groups: Smallpox Vaccine (Chair), Meningococcal Vaccines (Member), Herpes Zoster (Member), Influenza (Member), and Meningococcal Disease Outbreaks (Member).

Dr. Ruth Karron

Dr. Karron is a Professor and Director of the Center for Immunization Research in the Department of International Health at Johns Hopkins Bloomberg School of Public Health Baltimore, Maryland. Clearly, Dr. Karron has magical powers. She has managed to Chair the Influenza WG and to convince Dr. Walter to take it over from her. Given the breadth and depth of the issues through which Dr. Karron has led the ACIP, this is truly striking. She has had the shortest tenure of any WG member on the respiratory syncytial virus (RSV) WG. Since new ACIP members have not yet been named, it is possible that Dr. Karron will continue to Chair that WG. She always asks critical questions and exhibits incredible persistence in seeking to acquire the most important information to help ACIP make decisions.

Dr. Lorry Rubin

Dr. Rubin is the Director of Pediatric Infectious Diseases at the Steven and Alexandra Cohen Children's Medical Center of New York of the North Shore-Long Island Jewish Health System in New Hyde Park, New York. He is also Professor of Pediatrics at Hofstra-North Shore LIJ School of Medicine in Hempstead, New York. When Dr. Rubin took over as the Chair of the Meningococcal WG, he was promised that it was soon to go on hiatus. It is still almost going on hiatus. Dr. Rubin has made incredible contributions across the board for ACIP. Though Dr.

Bennett was his mentor when he joined ACIP, she said she learned everything she knows from him. Dr. Rubin has always been completely on point, is entirely unflappable, and his wisdom has helped ACIP in many ways. He has served on the following ACIP WGs: Meningococcal Vaccines (Chair), Yellow Fever/Japanese Encephalitis Vaccines (Chair), and Pneumococcal Vaccines (Member).

Dr. Bennett thanked departing members for their service, emphasizing what a pleasure and honor it had been to work with them, and what sadness there was in seeing them go.

Before officially beginning the meeting, Dr. Bennett called the roll to determine whether any ACIP members had COIs. The following COIs were declared:

- Dr. Belongia has a conflict for influenza and RSV due to receiving research support from Medimmune and Novovax.
- Dr. Romero has a conflict for RSV for funding non-related to vaccine trials and therapeutics.
- The remainder of the ACIP members declared no conflicts.

Dr. Bennett then requested that the liaison and *ex officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaisons are included in the appendixes at this end of this document.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier thanked everyone for the warm welcome and said that she was looking forward to this new role. She reported that in the June 6, 2016 *Morbidity and Mortality Weekly Report* (*MMWR*), CDC released a *Vital*signs™ on Legionnaires' disease titled, *Legionnaires' Disease: Use water management programs in buildings to help prevent outbreaks.* This is a new look for CDC at Legionnaires' disease and the launch of a new initiative to try to be more proactive about the role of Legionnaires' disease. The 2016 National Immunization Conference (NIC) will be convened on September 13-15, 2016 at the Hilton Hotel in downtown Atlanta. The NIC is one of the largest public health events sponsored by CDC, with approximately 1500 participants (physicians, nurses, scientists, program managers) representing all 50 states and US territories. It is a 3-day conference with 3 plenary sessions, 12 breakout sessions, multiple workshops, immunization question and answer (Q & A) sessions, exhibits, posters, and the Hilleman Lecture. The agenda for the event is still under development. Registration is open through August 22, 2016. Space is limited, so Dr. Messonnier encouraged everyone to sign up early.

Centers for Medicare and Medicaid Services (CMS)

Dr. Cohn delivered the report for CMS on behalf of Dr. Hence, who was unable to attend but was watching the webcast: CMS recently released the *2015 Annual Report on the Quality of Care for Children in Medicaid and CHIP* (Children's Health Insurance Program), and the same report for adults. This year for the first time, CMS developed a number of domain-specific reports. One of the domain-specific reports is *Primary Care Access and Preventive Care in Medicaid and CHIP* that includes information on a number of immunization quality measures. These reports can be found in the "Quality of Care" section of www.medicaid.gov

Department of Defense (DoD)

Dr. Sergienko reported that the Walter Reid Army Institute of Research (WRAIR) is working in conjunction with the Beth Israel Deaconess Medical Center at Harvard on two Zika vaccine candidates. They have been tested as single doses in mice and have been shown to be protective. WRAIR is moving forward with the purified inactivated virus vaccine called Zika purified inactivated virus (PIV) and expects to move that into human trials before the end of 2016. Other immunization-related news is that the Accession Screening and Immunization Screening Program within the Defense Health Agency (DHA) Immunization Healthcare Branch is continuing forward. This is a program to ensure that military recruits receive the appropriate immunizations in adherence to accepted medical standards, and to gain clinical and economic advantages by delivering only the vaccines that are needed. This has been done through a combination of screening and serological testing, and shows that the requirements for immunization have been reduced for incoming recruits. There is a continuous quality immunization improvement process ongoing within the DHA that dispatches immunization healthcare specialists out to DoD facilities and immunization clinics throughout the world, ensuring that those installations adhere to the standards for military immunizations. The DoD educational training activity for the next fiscal year is ongoing, ensuring that the members of all of those facilities providing immunizations complete 8 hours of immunization training annually. For further information on all of these programs, the DHA Immunization Healthcare Branch has migrated from a prior website to a new website, which is www.health.mil/vaccines. This has an expanded portfolio on all immunization-related programs.

Department of Veterans Affairs (DVA)

Dr. Kim reported that DVA continues to collaborate with 5 states on the Veterans Information Systems and Technology Architecture (VistA) to have privately provided immunizations autonomously written to VA records. The plan is to add a minimum of 10 more states each fiscal year for the next two years. This project is also developing the capacity for inbound communications from the DoD for read / write to a veteran's electronic medical record (EMR) of their immunizations received during military service. DVA completed a successful partnership with Walgreen's for the 2015-2016 influenza season. Through this program, no cost influenza vaccinations for veterans were provided if they were enrolled in VA healthcare. This was a national program available at approximately 8000 Walgreen's locations. Automated data population into the VA health record was provided through this program, as well as an update of the VA clinician prompts for influenza. Through this program, approximately 50,000 vaccines were administered to veterans at Walgreen's, with almost all being influenza vaccines. VA clinical reminders, which are electronic decision support tools, were released for tetanus and herpes zoster immunizations for use in the VA healthcare system in May 2016.

Food and Drug Administration (FDA)

Dr. Sun reported that since the February 2016 ACIP meeting, FDA approved Flucelvax® trivalent influenza vaccine for those 4 through 18 years of age that was previously approved for 18 years of age and above. Flucelvax Quadrivalent® was approved for all individuals 4 years of age and older. Trumemba® 2-dose was approved for an alternative regimen consisting of a 0- and 6-month schedule. Previously, Trumenba® was approved only for a 0-, 2-, and 6-month schedule. On March 21, 2016, the first Fluzone® Southern Hemisphere formulation was approved for the US. For this year, this is based on WHO recommendations. In future years, it will be based on the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

that will probably be held twice a year now. A cholera vaccine was recently approved for travelers for individuals 18 through 64 years of age. In addition to these approvals, it has been almost a year since the Pregnancy and Lactation Labeling Rule has been in place. This is applicable to all drug prescribing information, and will start appearing in all vaccine labels. This is a way in which the FDA has tried to improve communication of safety data related to use of drugs and vaccines in pregnant women and women who are breastfeeding. The old pregnancy classification had been set aside.

Health Resources and Services Administration (HRSA)

Dr. Nair reported that the national Vaccine Immunization Compensation Program (VICP) has had a busy year processing claims. As of early May 2016, 637 claims have been filed for the current fiscal year. Thus far, 303 of these claims have been adjudicated. To date in 2016, $125 million in awards have been paid to petitioners, and $11 million have been paid to attorneys for fees and costs for compensated and dismissed claims. More data about the program can be obtained on the HRSA website. HRSA completed development of proposed regulations to update the Vaccine Injury Table. The Notice for Proposed Rulemaking was issued in July 2015 and was available for comment for 180 days, which concluded in January 2016. A hearing to obtain comments from the public on the proposed changes took place on January 14, 2016. Comments received from the public are still being reviewed in order to finalize that rule. To date in this fiscal year, the Countermeasures Injury Compensation Program (CICP) has compensated 27 claims totaling $4.5 million.

Indian Health Services (IHS)

No report.

National Institutes of Health (NIH)

Dr. Gorman reported that NIH is working with four vaccine manufacturers and producers to enable them to develop Zika virus vaccine through Investigational New Drugs (INDs) and clinical trials. There is a deoxyribonucleic acid (DNA)-based vaccine, a live-attenuated vaccine, a genetically engineered Zika virus vaccine, and the vaccine being developed by WRAIR. On June 21, 2016, NIH announced that the Zika in Infants and Pregnancy (ZIP) trial would be ongoing. ZIP is a collaborative effort between the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), and National Institute of Environmental Health Sciences (NIEHS). The plan is to enroll 10,000 pregnancies and follow the infants for infections and environmental status. An experimental malaria vaccine, developed by Sanaria, has been shown to provide protection for one year against malaria. Those who are vaccinated are followed for one year and then re-challenged in a challenge model. All vaccinees were protected for one year in duration. The NIAID awarded a large contract for the study of adjuvants, matching adjuvants with antigens and providing multiple adjuvants to a single adjuvant to determine whether better immune responses can be evoked. NIH and NIAID have a longstanding policy of not releasing promissory notes. However, for this particularly report, they were allowed to release a promissory note. A large-scale HIV vaccine trial is being planned in South Africa. Based on the results of a previous trial in Southeast Asia where there seemed to be some evidence of protection, those vaccines have been improved or ways to increase their immune response have been changed. The trial is anticipated to start in November 2016 in South Africa pending the multiple regulatory approvals

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required between now and then. A paper was published recently pertaining to the promises and challenges of vaccines for hospital-associated infections (HAIs).

National Vaccine Program Office (NVPO) / NVAC

Dr. Gordon indicated that she was reporting on behalf of Dr. Gellin, who also is the Designated Federal Official (DFO) for the President's Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) that was meeting at the same time as ACIP. Dr. Gelling asked Dr. Gordon to convey to ACIP that the Secretary asked PACCARB to provide guidance on best ways to incentivize the development of therapeutics, rapid diagnostics, and vaccines. In order to address this charge, PACCARB is in the process of establishing three WGs, including one that will be dedicated to understanding these issues for vaccines.

In terms of activities within the NVPO office, NVPO is in the process of finalizing a mid-course review of its 2010 National Vaccine Plan (NVP). This analysis represents a comprehensive stakeholder engagement to help identify and build consensus on priority areas thought to have the greatest potential impact for the remaining five years of the NVP. NVPO hopes to have the results available for distribution by the summer of 2016. The results will be used to guide the development of the 2016-2020 implementation plan.

As part of its effort to support adult immunization, NVPO in partnership with American Academy of Pediatrics (AAP), the Gerontological Society of America (GSA), and the National Foundation for Infectious Diseases (NFID) co-hosted the 3rd Immunization Congress: Financing Across the Lifespan on April 27-28, 2016 in Washington, DC. The purpose of this Congress was to identify the financial challenges facing different physician types in providing vaccines in their offices to their patient populations. The Immunization Congress is in the process of publishing the proceedings, which will be available soon.

After a highly competitive independent review, NVPO has awarded a cooperative agreement to Emory University in support of their research project titled, "Transforming Vaccine Hesitancy into Confidence—Research to Address Parents' Vaccine Decision-Making and Inform Development of Novel Immunization Communication Education Strategies." This award stems from NVAC's recommendations pertaining to vaccine confidence and Goal 3 in the NVP, which addresses vaccine communication.

Dr. Kimberly Thompson was recently appointed to serve as the incoming Chair of NVAC. NVAC convened its last meeting June 7-8, 2016 in Washington, DC. The agenda included a number of discussions on mechanisms to overcome economic and scientific challenges to vaccine research and development. There was an update on efforts to improve human papillomavirus (HPV) vaccinations among adolescents. Updates were presented by the NVAC Maternal Immunization WG and the Mid-Course Review WG. Both of these WGs plan to finalize their analyses for discussion during the September 2016 NVAC meeting.

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Introduction

Arthur Reingold, MD
University of California, Berkeley
Chair, ACIP Cholera Vaccine Work Group

Dr. Reingold reminded everyone that the Cholera Vaccine WG was formed in August 2015 with the relatively specific mandate of preparing for the licensure of a new cholera vaccine for use in the US among travelers. During the October 2015 ACIP meeting, the WG presented an overview of cholera background and epidemiology. During the February 2016 ACIP meeting, PaxVax presented Vaxchora™ clinical data and the Cholera Vaccine WG presented a Grading of Recommendation Assessment, Development, and Evaluation (GRADE) evaluation.

FDA approved Vaxchora™ (CVD-103 HgR) vaccine on June 10, 2016 for prevention of cholera caused by serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas. Vaxchora is the only FDA-approved vaccine for the prevention of cholera.

The Cholera Vaccine WG activities since February 2016 have included summarization of additional data on special populations (pregnant women, breastfeeding women, immunocompromised people, and children), shedding and transmission of vaccine strain, duration of protection; and development of proposed recommendations.

Dr. Reingold indicated that during this session, Dr. Karen Wong from CDC would provide a cholera vaccine update and proposed recommendations, followed by a vote on use of this vaccine.

Cholera Vaccine Update / Proposed Recommendations

Karen K. Wong, MD, MPH
Medical Officer
Division of Foodborne, Waterborne, and Environmental Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Wong reminded everyone that cholera is caused by toxigenic *Vibrio cholerae* O1. It causes watery diarrhea that may be severe and rapidly fatal without proper treatment. Cholera is endemic in more than 50 countries, and may also cause epidemics. Rehydration can reduce fatality rate to less than 1%. In the US, most cases occur among travelers to cholera-affected areas. Cholera is rare; however, an increase in cases in travelers from Haiti was observed after the epidemic began in October 2010. Safe food and water and personal hygiene measures are key to prevention. Populations who may be at higher risk of poor outcomes from cholera include travelers without ready access to rehydration therapy and medical care and travelers with a condition that carries increased risk of poor clinical outcomes from cholera, such as blood type O, pregnancy, immunocompromising conditions, cardiovascular disease, and renal disease.

CVD 103-HgR is a live attenuated single-dose oral cholera vaccine that protects against toxigenic *V. cholera* infection. More than 500,000 doses of the previous formulation were distributed before manufacture ceased for business reasons. The vaccine was redeveloped as Vaxchora™, hereafter referred to as the "new formulation" of the vaccine. Vaccine efficacy (VE) has been assessed by immunogenicity and protection against oral cholera challenge.

During the February 2016 ACIP meeting, the WG presented its GRADE review and concluded that CVD 103-HgR vaccine is safe and effective for prevention of infection with toxigenic *V. cholerae O1*. The overall evidence type was 2. For Safety outcomes, the evidence type was 3. For Efficacy, the evidence type was 1.

No data exist on the use of CVD 103-HgR vaccine in pregnant or breastfeeding women. Pregnant women are at risk of poor outcomes from cholera infection. The vaccine is not absorbed systemically; therefore, maternal exposure to CVD 103-HgR is not expected to result in exposure of the fetus or breastfed infant to the vaccine. No data exist on the use of the new vaccine formulation in immunocompromised populations. However, one study of the vaccine formulation in HIV+ adults in Mali found that vibriocidal seroconversion was slightly lower among HIV-positive than HIV-negative participants (58% versus 71%). No differences were found between vaccinated and comparison populations for any systemic adverse events (AEs).

No data exist on the use of the new vaccine formulation in children. However, limited data exist on use of the older formulation. There were 10 studies that included participants 3 months to 17 years of age. Studies were conducted in Ecuador, Chile, and Indonesia. None were in the US. There were no pediatric challenge studies. The vibriocidal antibody responses corresponded to VEs between 29% to 98%, and no association was detected between CVD 103-HgR and any systemic or serious adverse events (SAEs).

Some data exist on the shedding of the new vaccine formulation strain. In two randomly allocated study groups combined, 11.1% of subjects shed the vaccine strain in stool at any point up to 7 days post-vaccination [Chen WH, Greenberg RN et al. Clin Vaccine Immunol. 2014;21(1):66–73].

In a study of the new vaccine formulation, the vaccine strain was not isolated from stools of 28 household contacts cultured 7 days post-vaccination. With the older formulation, the vaccine strain was isolated from stool in less than 1% of household contacts cultured up to 5 days post-vaccine. It is important to note that both studies may miss transmission events that would be detected after 5 or 7 days. Seroconversion was detected in 3.7% of family contacts when tested at 9 or 28 days [Chen WH, Greenberg RN et al. Clin Vaccine Immunol. 2014;21(1):66–73; and Simanjuntak CH et al. Journal Inf Dis. 1993;168:1169-76].

Duration of protection has been assessed from cholera challenge studies. For the new formulation, VE for protection against severe diarrhea was evaluated up to 3 months post-vaccination at 79.5%. For the older formulation, VE for protection against diarrhea of any severity was evaluated up to 4 to 6 months post-vaccination and approached 100% [Tacket CO et al. J Infect Dis. 1992 Oct;166(4):837-41]. The duration of the immune response has been evaluated for the new formulation. Vibriocidal antibody seroconversion was detected in 90.4% of vaccinees up to 180 days, or 6 months, post-vaccination. No data exist on re-immunization with the new vaccine formulation [Chen WH, Greenberg RN et al. Clin Vaccine Immunol. 2014;21(1):66–73; and Chen WH, Cohen MB et al. Clin Infect Dis. 2016 Jun 1;62(11):1329-35].

FDA announced Vaxchora™ approval on June 10, 2016 for use in adults 18 through 64 years old traveling to cholera-affected areas. The package insert states certain limitations of use. The first two concern people who may already be immune: 1) effectiveness is not established in persons living in cholera-affected areas; and 2) effectiveness is not established in persons with pre-existing immunity due to previous exposure to *V. cholerae* or receipt of a cholera vaccine. The package insert also states that the vaccine is not shown to protect against disease caused by non-O1 serogroups.

The package insert states that safety and effectiveness are not established in immunocompromised persons. The vaccine strain may be shed in the stool of recipients for at least 7 days. It says to use caution when considering whether to administer Vaxchora™ to individuals with immunocompromised close contacts. It also mentions the establishment of a pregnancy exposure registry, and states that safety and effectiveness are not established in persons younger than 18 years of age or those 65 years of age and older.

The WG had certain considerations for formulating the recommendation option. From the GRADE review, the evidence supports the safety and efficacy of the vaccine. In terms of the risk, cholera among travelers is rare but can be severe. Most travelers to cholera-affected areas are at low risk of severe infection. The WG felt that a Category A recommendation for a clearly defined population would be easier for clinicians to interpret and implement. The WG's approach to the recommendation option was to propose a Category A recommendation for a defined subpopulation of travelers. This proposed recommendation would require assessment of the individual traveler's risk factors and travel plans. The WG felt that the recommendation should be clear that vaccine is not routinely recommended for most travelers due to the low risk of cholera. Given that the duration of protection beyond 3 to 6 months is not known at this time, the WG included no formal recommendations for re-immunization in the proposed option. It is important to assess data on re-immunization as it becomes available and to update the recommendation at that time.

Dr. Wong indicated that the proposed recommendation for prevention of severe cholera among travelers consisted of personal protective measures and use of CVD 103-HgR vaccine. The vaccine portion would be a Category A recommendation. The vaccine recommendation would require travel to an area of active toxigenic *V. cholerae O1* transmission <u>AND</u> increased risk of exposure to toxigenic *V. cholerae O1* <u>OR</u> increased risk of poor outcome if infected. She presented the following text of the proposed recommendation:

Personal Protective Measures

- ❑ All travelers to cholera-affected areas should follow safe food and water precautions and proper sanitation and personal hygiene measures as primary prevention strategies against cholera infection.
- ❑ Travelers who develop severe diarrhea should seek medical attention, particularly rehydration therapy, promptly.

Use of CVD 103-HgR Vaccine

1. Vaccination against cholera is not routinely recommended for most travelers who are at low risk of exposure to toxigenic *V. cholerae* O1. Prevention of cholera and other diarrheal diseases primarily depends on following safe food and water precautions and personal hygiene measures.

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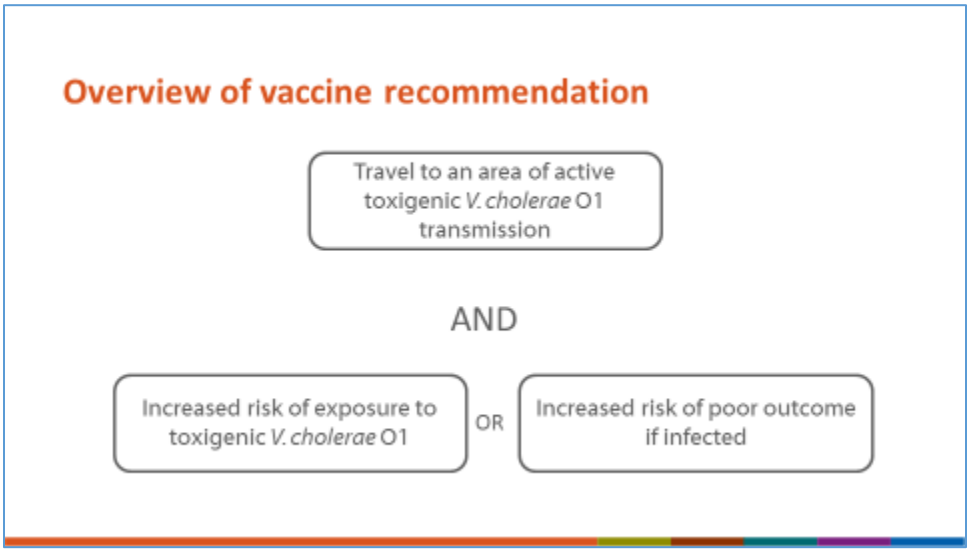
2. The decision to vaccinate should be made after detailed assessment of the individual traveler's risk of exposure to toxigenic *V. cholerae* O1 and the traveler's risk of severe outcomes if infected.
3. CVD 103-HgR vaccine is recommended for travelers to an area of active cholera transmission
    a. who are at increased risk of toxigenic *V. cholerae* O1 exposure, or
    b. whose individual risk factors or travel situations carry increased risk of poor clinical outcome if infected.
    c. These populations include:
        - People with increased risk of exposure to toxigenic *V. cholerae* O1, which can include:
            - Travelers, including those visiting friends and relatives, who are unable to consistently follow safe food and water precautions and personal hygiene measures in an area of active toxigenic *V. cholerae* O1 transmission
            - Healthcare personnel and others who have direct contact with body fluids (vomitus or stool) from cholera patients
        - People with increased risk of poor clinical outcome if infected, which can include:
            - Travelers who may be without rapid access to adequate rehydration and medical care
            - Travelers with a condition known to carry increased risk of poor clinical outcomes from cholera, such as low gastric acidity or blood type O
            - Travelers with chronic medical conditions, including but not limited to travelers with conditions such as cardiovascular or kidney disease who would tolerate dehydration poorly

There would be 2 footnotes:

> [1]An area of active cholera transmission is defined as a province, state, or other administrative subdivision within a country with endemic or epidemic cholera caused by toxigenic *V. cholerae* O1 and includes areas with cholera activity within the last 1 year that are prone to recurrence of cholera epidemics; it does not include areas where rare sporadic cases have been reported. Most travelers from the United States do not visit areas with active cholera transmission. The vaccine is not routinely recommended for most travelers from the United States.
>
> [2]Long-term travelers and frequent travelers to areas of active cholera transmission may also be at increased risk of exposure, because the cumulative risk of exposure to unsafe food or water is presumed to be higher with longer duration of travel. However, data are limited on the duration of protection beyond 3–6 months afforded by vaccination with CVD 103-HgR.

To review, the first section about personal protective measures talked about following safe food and water and personal hygiene precautions, and seeking medical attention promptly for severe diarrhea. The section about use of vaccine stated that the vaccine is not routinely recommended for most travelers. It recommended detailed assessment of the traveler's risk of exposure and risk of severe outcomes. It stated that the vaccine is recommended for travelers to an area of active cholera transmission who are at increased risk of exposure, or whose risk

factors or travel situations carry increased risk of a poor clinical outcome if infected. Examples were given of populations who meet these criteria.



Discussion Points

Dr. Messonnier said her understanding was that the definition of "travelers" means adults, children were excluded, and pregnant women were not excluded.

Dr. Wong responded that it means adults for the indicated age range of 18 through 64 years of age. The data on pregnant women are limited or non-existent, and the WG would expect to elaborate on that in the recommendation. However, the recommendation does not exclude recommending pregnant women.

Dr. Belongia wondered if it was true in every country where cholera transmission is endemic that 99% of cases are due to O1 and a small proportion are due to O139, or if there are areas where O139 is more of an issue.

Dr. Wong indicated that O139 is more common in areas of Asia and Southeast Asia, but most cholera throughout the world is O1.

Dr. Walter questioned whether there is any information and guidance on appropriate timing of vaccination prior to travel, and if there is an upper limit.

Dr. Wong replied that the recommendation is 10 days prior to travel, and that she did not believe that there is an upper limit.

Dr. Moore said she appreciated the concrete definition of who should receive the vaccine, and wondered whether CDC would help them in implementing this by consistently updating its travel site with the specific areas that meet the criterion for active transmission. She could understand clinicians being challenged to figure out which areas meet the criterion for active transmission. This would be simple for the website to keep current.

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Dr. Wong responded that the various mechanisms to report cholera epidemiology can be incomplete, and cholera epidemiology can change quickly. Therefore, discussion is underway with CDC's Travelers' Health Branch (THB) regarding how that website can be used to help clinicians assess where areas of active cholera transmission are.

Dr. Kempe suggested in the guidelines to include a linkage that will make if very easy to connect to this information. Another implementation-related issue is low gastric acidity. She asked whether that included people on chronic acid blockers, and thought some definition of that would be helpful.

Dr. Wong confirmed that low gastric acidity could have many causes, including medications. Individuals with low gastric acidity are known to be at risk for more severe outcomes. That is going to be a potentially large segment of the population. However, restricting the recommendation to areas of low transmission will confine this to a narrow population to begin with.

Dr. Kempe thought that if this would include people on chronic Prilosec®, this should be specified in the recommendation.

Dr. Belongia asked whether there was any recommendation regarding co-administration with oral typhoid vaccine.

Dr. Wong responded that there are no data regarding co-administration with the new vaccine formulation, which is stated in the package insert. There are studies with the older formulation that were presented during the last ACIP meeting that found no interaction when co-administered with typhoid vaccine.

Dr. Messonnier noted that the defining criteria come from defining this as only people traveling places where cholera is raging. Regarding the second criterion, she wondered whether any thought had been given to the fact that combining the proportion of those travelers who were either blood type O or for some reason were on acid suppressing therapy would mean that most people traveling to a cholera-endemic area would meet the second criterion. If so, perhaps the recommendation would be simpler by merely focusing on the cholera-endemic area.

Dr. Wong replied that this point was discussed extensively within the WG. Blood type O is very common, as are medications that cause low gastric acidity. The rationale was that defining the area of active cholera transmission would be the initial narrowing filter. There was discussion regarding the possibility of including only that point and the increased risk of exposure.

Dr. Reingold added that the WG spent a lot of timing talking about the fact that half the population is blood group O. In the recommendation, the attempt was to point to the fact that the number of people traveling to areas with substantial transmission is limited. Most travelers are not going to be in a situation where they are at risk of cholera or severe dehydration.

Dr. Romero asked whether there were any data on co-administration of this vaccine with trivalent or bivalent oral polio vaccine.

Dr. Wong responded that there were no data pertaining to the new formulation, but there are with regard to the older formulation that were presented during the last ACIP meeting. There were no interactions.

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Recognizing that children are not included in the current language under consideration, Dr. Kimberlin (AAP) asked whether Dr. Wong was aware of any studies ongoing or planned in the pediatric population that might one day inform use of this product in people younger than 17 years of age.

Dr. Wong requested that someone from PaxVax respond to this question.

Dr. Danzig (PaxVax) indicated that PaxVax plans to start a pediatric study in 2017 in 2 through 18 year olds. The prior study on oral polio vaccine showed no interaction with CVD 103-HgR and the liquid formulation of the typhoid vaccine. The oral typhoid vaccine would not be given co-administered with any buffer. PaxVax would be worried more about the typhoid concomitant administration, but there was no interaction with the bacteria.

Dr. Rubin asked whether there was any intent to offer guidance for administration of the vaccine to recipients who have a household or occupational exposure to immunocompromised persons. The FDA wording is “use with caution.” He wondered whether they should amplify on that to say it should or should not be used in such cases.

Dr. Wong indicated that the WG has not yet decided what should be said about people who may have immunocompromised household members. The package insert does indicate to “use caution” and there are data from the older formulation to show that transmission can occur.

Dr. Middleman (SAHM) noted that many of the young adults and adolescents she sees do not know their blood type. She wondered whether there were any data about whether people typically know their blood type and if not, whether there should be a recommendation for people to get a type and cross before deciding whether to get the vaccine.

Dr. Wong indicated that the WG discussed this extensively. There is no recommendation currently in the wording that clinicians should test blood type as part of the decision-making process. The WG has discussed that blood type O is very common, and people can assume that they are blood type O unless they know otherwise. This is probably an area for clinician judgment and may depend upon the person and what their other risk factors may be.

Dr. Baker expressed her appreciation for the details, data, and good questions / answers. However, she observed that the recommendation was very complicated. While she did not have a solution and knew the WG tried to be as transparent with the data as possible, it reminded her of a Category B recommendation in which the burden is on the physician to have a discussion with the patient. Even in a travel vaccine situation, there is a lot of finesse. She thought the recommendation was pretty complicated to be a Category A if the goal was for the vaccine to be used for people at risk, because it will be a large number of people.

Dr. Wong emphasized that the WG’s rationale was to make a clear and narrow recommendation.

Dr. Zahn (NACCHO) asked how rare travel-associated cholera is in terms of numbers of reported or identified cases. He also wondered whether there was an issue for persons in need of malaria prophylaxis in addition to potential cholera exposure.

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Regarding how rare is rare, Dr. Wong noted that cholera is underreported. Illness is often mild or moderate and self-limited, so it does not come to attention. Because of the disease duration and incubation period, disease may occur when people are still outside of the US. That being said, there may be about 100 cholera cases per year, though only a handful may be reported to CDC surveillance as laboratory confirmed infections. But, increases have been seen after certain events such as the Haiti epidemic when there were more than 40 cases reported in one year. There have also been some outbreaks such as the one that occurred on a plane with travelers returning to the US. In terms of oral prophylaxis, with the older formulation there was a study in which various antimalarial prophylaxis regimens were assessed. It was found that chloroquine may reduce the immunogenicity of the vaccine. There are no studies with the new formulation, but the package insert recommends against co-administration with chloroquine or at least spacing it out.

Dr. Mahon (SME) said she thought Dr. Baker's point was really good. There was strong feeling among the WG members that a Category A recommendation would be much easier to implement and that they should do as much of the work of defining that as possible rather than deferring too much to the clinician. The sense of the WG would probably be that if there is a way to make the wording clearer and keep it a Category A recommendation, perhaps that would be more useful to the clinician.

Dr. Baker commented that CDC is such a tremendous source of what countries / locations are at risk for severe cholera, that information will be readily available for people to look up.

Dr. Reingold said that he recently had to advise his daughter when they were traveling through Southeast Asia whether to get Japanese Encephalitis Vaccine (JEV), the areas at risk, and how great the risk was in terms of their activities, the benefits, et cetera. He thought in some ways, cholera was very similar. It is very difficult to give a blanket recommendation to all travelers, and a lot of the burden is going to fall on physicians in travel clinics and based on good data from CDC and elsewhere about where active transmission is occurring. The WG could not come up with a way to get around that problem, so he said they would be delighted to hear alternative suggestions.

Regarding the surveillance issue and the fact that cholera is underreported, Dr. Thompson (NVAC) requested further discussion about the global surveillance quality with respect to identifying areas of active transmission and the challenge on the temporal side, which is that travelers get vaccinated before they go, but do not know what is going to occur while on travel. She wondered how to deal with the fact that there could be an active transmission in an area upon arrival that was not occurring prior to departing the US.

Dr. Wong replied that global cholera surveillance is definitely patchy. There is a WHO report, but reporting to that is certainly incomplete. In terms of what could happen if an outbreak occurs after a traveler arrives in an area, one of the primary points in the recommendation is that the key to prevention is following safe food and water precautions and personal hygiene measures.

Dr. Savoy (AAFP) pointed out that most family practice offices do not give this vaccine, but they may have patients who ask them whether they should go to a travel clinic to get it. With a link to a graphic that is easy to follow, it would not be that complicated to determine whether someone needs to go to a travel clinic based on where they are traveling.

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Dr. Wong said when providing examples, they would want to offer vignettes for physicians to help them understand what increased risk would look like.

Dr. Kempe agreed. She was concerned that a bullet about blood type and low gastric acid would result in a lot of question and confusion, and said she would like to debate the downside of removing it.

Dr. Grogg (AOA) said that having been to Haiti during the epidemic, he was excited to have this vaccine available. The AOA has always recommended, if planning to travel to an area for an extended period where there is cholera, obtaining the vaccine in that country because the US did not have the vaccine. He thought more clarification was needed with regard to co-administration of Yellow Fever (YF), typhoid, malaria, et cetera. That could be in the form of a hyperlink. He also inquired as to the cost of the vaccine.

Dr. Wong replied that the WG would like to make the proper administration procedures as clear as possible for clinicians. The thought was to elaborate on a number of the issues mentioned in the text of the full recommendation report. Regarding the earlier comment about whether to remove the specific mention of blood type O and low gastric acidity, the way the recommendation is structured, the category of “Increase Risk of Poor Outcome” would have to be eliminated or change what it is called if blood type O and low gastric acidity were removed. She called upon PaxVax to respond to the question regarding cost.

Dr. Mark Meltz (PaxVax) indicated that the price is anticipated to be between $200 to $300 per single dose, which is consistent with other travel vaccines on a per course basis.

Dr. Riley added that the other aspect of increased risk for poor outcome that the WG discussed extensively was the ability to be treated. If someone could be rehydrated safely, the risk of death would be reduced to less than 1%. It would be incumbent on the physician to find out all of the risk factors and determine the risk / benefits, especially for pregnancy where there are no data about safety.

Dr. O’Leary (PIDS) requested information regarding the magnitude of increased risk with blood type O and low gastric acidity.

Dr. Wong indicated that while she did not have those numbers with her, gastric acidity is reduced immediately and basically stays very low for people on an inhibitor. In terms of blood type O, the risk is for cholera gravis, which is severe cholera. Often, cholera is a mild and self-limited illness that does not even require treatment. However, cholera gravis is the rapidly dehydrating form of the disease with the loss of liters of diarrhea very quickly. People with blood type O are at increased risk for that severe, potentially life-threatening type of cholera.

Dr. O’Leary (PIDS) clarified that he was asking for the magnitude of that risk. Is it two-fold, five-fold, 20% higher?

Dr. Wong responded that she did not remember the exact numbers, but it is a substantially increased risk of several-fold.

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Dr. Mahon (SME) inquired as to whether the recommendations for healthcare personnel (HCP) where there is discussion about having direct contact with body fluids it meant unprotected without personal protective equipment (PPE), or even if they have that on they should still be immunized.

Dr. Wong replied that the WG had not discussed that level of detail.

Dr. Romero was not sure that the physician attending to the traveler in the US would have a good idea of how rapid or good access they would have to medical care in the area to which they plan to travel. If rapid / good access to medical care is going to be used as a determining factor to give the vaccine or not, this needs to be further considered. He does not know what the access to medical care is for many of the pediatric patients he is asked to offer advice for when traveling to South America, Asia, or Africa.

Dr. Michael Levine (Co-Inventor of CVD103-HgR) said that regarding the question about blood group O, it is important to take into account that blood group O does not increase the risk of infection or diarrhea. It increases the chance of cholera gravis, a severe cholera that can kill someone if they do not get to rehydration promptly. When he teaches, he likes to use the example of the lowest prevalence of blood group O in the world which is in the Gangetic Delta. In a lovely review paper that Roger Glass wrote a few decades ago, he pointed out that in this home of ancestral cholera with, he thinks, the Darwinian lowest prevalence of blood group O, two-thirds of the cases of cholera gravis are in blood group O. In volunteers, if one gives 1 million or 100 million organisms without buffer, one does not have positive cultures. One does not have diarrhea. If 1 million organisms are given with buffer, there is a 90% attack rate. Persons who are blood group O have a much greater propensity to develop severe cholera. Even an inoculum as low as 1000 organisms will give a 67% attack rate if the buffer is given. In terms of risk, Dr. Levine emphasized that when there are large outbreaks, particularly in the Western Hemisphere (as in Peru, Ecuador, and Columbia in 1991 and Haiti in 2010), the consequence for US travelers increases greatly and bad things can occur. It is when there is no access to healthcare that people are in danger. Cholera is different. Everyone knows about traveler's diarrhea. Cholera is really very special. When someone is purging at a liter an hour, which could happen very quickly in the progression, in three hours they have lost the equivalent of the entire plasma volume. In five hours, they have lost the equivalent of their entire blood volume and they are potentially near death. This is not common, but it is like tornados. They are rare. Most people who live in tornado areas have not experienced it, but when it happens it can be very devastating. There is a nice study that Dave Taylor did in the 1990s when he was assigned in Peru. He cultured the American workers at the American Embassy, many of whom had bad traveler's diarrhea. When the attack rate is annualized, it is like endemic disease in the developing world. Those folks all had easy access, but it shows how much more common cholera really is when one does very active surveillance, including bacteriologic culture.

Regarding the relative increased risk of people with blood group O or with low gastric acidity, Dr. Belongia wondered what some approximation of the risk would be among people who do not have those risk factors. Is the additional complexity really needed in the recommendation? Perhaps ACIP should state that they believe the vaccine should be acquired simply due to travel to an area where the risk is non-trivial, regardless of risk factors, because there is a still a risk of developing severe cholera. Is the risk so low for someone who is not blood group O or does not have low gastric acidity that they do not need to worry about it? Or if the risk is not that low, perhaps the complexity of these additional factors is not needed.

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Dr. Karron thought it was important, if the recommendation was stratified, to include the increased risk of poor outcome in part as an educational measure for physicians. It may be that individuals who are on protein pump inhibitors might not want to take those if going to a cholera-endemic area. It is helpful to educate the physicians about that. It may be worth doing blood typing. She wondered what the impact would be with removal of both narrowing categories, which would leave travel to an area of active transmission.

Dr. Mahon (SME) emphasized that the WG spent a lot of time discussing this, and their attempt was to narrow and target the recommendation as much as possible. However, as had been pointed out, it does not narrow it that much. She personally thought it would be reasonable to strike the bottom two categories and to include educational material in the recommendation itself if it would be easier to implement. The WG was driven very much by the travel medicine perspective of trying to understand exactly who would benefit most from this recommendation. She thought the sense of the clinicians was that this is implementable and people would not be vaccinated who would not benefit as much. Most people who meet the first criterion are going to meet one or the other of the second criteria, so it is not going to be that big of a difference.

Ms. Pellegrini said she was trying to think about this from the traveler's perspective. It seemed like the recommendation was most focused on preventing the most severe cases—the potentially fatal cases. If she was a traveler, she would be interested in obtaining this vaccine to prevent herself from getting *any* cholera. With the recommendation as stated, they seemed to be saying they were okay with the mild to moderate cases. She would be happy to remove the qualifiers in order to prevent a greater percentage of cases, including the mild to moderate ones.

Dr. Moore said that one counterpoint to that perhaps was, as people are assessing travel, it is $200 to $300 for this vaccine. People also may be paying $200 or $300 for YF and other vaccines, and those are typically out-of-pocket costs. There may be value to including the additional criteria so that people who really should get this vaccine understand that they really should get it, and those who do not have higher risk factors and will have access to other measures can make a decision not to get the vaccine.

Dr. Bennett requested that Dr. Mahon respond to the difference between having these two criteria in the recommendation versus having them in the narrative about who is at highest risk.

Dr. Mahon (SME) said she thought it was important to remember that everyone is at low risk, even in these categories. Only several dozen cases of travel-associated cases are seen in the US every year. Although it is possible that other people are getting sick while they are still abroad or are not being captured by the surveillance systems, the risk is still pretty low. The pros and cons were well-articulated, and these are the groups who would benefit the most from the vaccine. However, there is additional complexity in implementation that could lead to confusion, blood typing that could be a barrier, et cetera. Personally, she thought either way was reasonable and it would be possible to begin with this or start without it and try to assess the situation over time.

Dr. Reingold agreed that either way could work. To him the parallels were somewhat similar to JE because it is highly specific within a region, when traveling to an area where there are pigs and mosquitos.

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Dr. Rubin suggested striking the lower right-hand part of the recommendation and having that as guidance, and keeping it simple in terms of being at increased risk based on itinerary. It is a dialogue with the patient in the travel provider's office that occurs each day. The other risk factors would enter into the conversation. As Dr. Romero said, it is difficult to know a patient's access to rapid rehydration in the area to which they plan to travel. This would include essentially everybody in the lower right-hand corner anyway.

Regarding the issue of the blood group, Dr. Sun referred to the pivotal trial for the approval of this vaccine, in which an assessment was made of whether a patient had blood group O or not and vaccine efficacy was evaluated. At the 10-day challenge versus the 3-month challenge, at 10 days vaccine efficacy for blood group O was 84% and for non-group O was 100%. At the 3-month challenge time point, the efficacy for the O group was 78% and for non-group O was 83%.

Dr. Mahon (SME) said she thought if the committee wanted to strike the specifics, it would be best to strike both rather than just the right. The thinking was that some people are at higher risk of exposure and, therefore, at higher risk of illness and severe illness and some people at lower risk of exposure, but if they did get exposed, would be at a high risk of severe illness. They thought of the two as going together.

Vote: Cholera Vaccine Recommendations

Dr. Reingold motioned to approve the recommendation, striking the bottom two boxes and placing that information into the lengthy caveats, flow charts, and examples to inform clinicians. Dr. Walter seconded the motion. The motion carried unanimously with 15 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

15 Favored:	Belongia, Bennett, Ezeanolue, Harriman, Harrison, Karron, Kempe, Moore, Pellegrini, Romero, Reingold, Riley, Rubin, Stephens, Walter
0 Opposed:	N/A
0 Abstained:	N/A

Meningococcal Vaccines

Introduction

Lorry Rubin, MD
Chair, Meningococcal Work Group
Advisory Committee on Immunization Practices

This being his final meeting, Dr. Rubin said that he wanted to thank everyone for allowing him to participate in ACIP for the last four years, which he certainly enjoyed and from which he learned a lot.

He reminded everyone that as Dr. Sun mentioned earlier, a revised dosing schedule was approved for Trumenba®, Pfizer Vaccines' MenB-FHbp vaccine. The dosing schedule was approved by FDA on April 14, 2016 to change the 3-dose schedule of administration to a 0.5 mL

dose at 0, 1-2, and 6 months versus the previous 0, 2, and 6 months schedule, as well as the approval of a 2-dose schedule with administration of a 0.5 mL dose at 0 and 6 months. The revised schedule indicates that the choice and dosing schedule may depend upon the risk of exposure and the patient's susceptibility to serogroup B meningococcal (MenB) disease.

Dr. Rubin indicated that the presentation topics for this session would include the following:

- ❑ Updates to the MenB-FHbp dosing schedule, including discussion on potential policy options for 2-dose and 3-dose schedules, with no vote planned

- ❑ Use of MenACWY vaccines in human immunodeficiency virus (HIV)-infected persons based on previous discussion during the February 2016 meeting, with anticipation of ACIP and VFC votes during this session

Focusing on the quadrivalent vaccine and HIV, two policy options were to be raised for discussion with ACIP during this session:

- ❑ Human Immunodeficiency Virus (HIV)-infected persons aged ≥2 months should routinely receive MenACWY vaccine* (Category A)

OR

- ❑ Human Immunodeficiency Virus (HIV)-infected persons aged ≥11 years should routinely receive MenACWY vaccine** (Category A)

  [*Includes MenACWY-D (Menactra®), MenACWY-CRM (Menveo®), and Hib-MenCY-TT (MenHibrix®); **Includes MenACWY-D (Menactra®) and MenACWY-CRM (Menveo®)]

Dr. Rubin reported that the majority of the WG members support vaccinating HIV-infected persons beginning at 2 months of age. The cost-effectiveness and GRADE analyses were based on vaccinating HIV-infected persons aged ≥2 months.

Specific topics during this session included:

- ❑ Update: Trumenba® Label
- ❑ Summary of WG Discussion: Trumenba® Label
- ❑ Cost-effectiveness of MenACWY in HIV-Infected Persons
- ❑ GRADE for MenACWY in HIV-Infected Persons
- ❑ Considerations for use of MenACWY in HIV-Infected Persons
  - ➢ Proposed Recommendations / Vote
  - ➢ VFC Vote

Update: Trumenba® Label

Dr. Laura York
Medical Development
Scientific and Clinical Affairs
Pfizer

Dr. York presented an update on Trumenba®, which was licensed in October 2014 and received FDA approval through the accelerated approval regulations to be used in a 3-dose series of 0, 2, and 6 months for prevention of meningococcal B disease in individuals 10 through 25 years of age. Recognizing that there are challenges with a 3-dose series, Pfizer continued to assess the data and have discussions with FDA to evaluate the potential for receiving a 2-dose schedule and the benefit that would be provided by that. As Dr. Rubin noted, there has now been a US label change. The vaccines were approved through an Accelerated Approval to provide access for outbreaks. Now thought is being given to the use of this vaccine in the two recommendations that ACIP already has in place.

As Dr. Rubin pointed out, the dosing schedule was approved by the FDA on April 14, 2016 to change the 3-dose schedule of administration to a 0.5 mL dose at 0, 1-2, and 6 months versus the previous 0, 2, and 6 months schedule, as well as the approval of a 2-dose schedule with administration of a 0.5 mL dose at 0 and 6 months. The revised schedule indicates that the choice and dosing schedule may depend upon the risk of exposure and the patient's susceptibility to meningococcal serogroup B disease. Dr. York indicated that Pfizer had come to ACIP because providers do need guidance on how best to use these schedules.

The data that supported the 2-dose label was from a pivotal study that was included in the licensure, B1971012, that evaluated the safety, tolerability, and immunogenicity of 2-dose and 3-dose schedules. These data were presented to ACIP previously prior to the initial approval. This study assessed two 3-dose schedules: 0, 1, 6 and 0, 2, 6 and then assessed schedules of 0, 6 months; 0, 2 months; and 0, 4 months to evaluate how the interval may impact the immune response. This was a Phase II study conducted in Europe in the Czech Republic, Finland, Germany, and Poland in male and female adolescents 11 through 18 years of age. The primary endpoint was to determine the proportion of subjects achieving a human complement serum bactericidal antibody (hSBA) titer of at least 1:8 or over against each of the 4 primary strains used to measure the response that is solicited by Trumenba®.

In terms of the immunogenicity results, this study shows the benefit of Trumenba® and the effect of the dosing schedule. The 0, 1 schedule is assessing the data within the 0, 1, 6 three-dose series to provide more information in terms of interval. With short intervals with a goal to raise immunity very rapidly, there is a good immune response to the four strains. These strains are representative of the prevalent strains in the US. They have antigens on them that differ from what is in the vaccine antigen, so they will display the ability of the antibody to recognize across a diversity of that antigen and across the diversity of meningococcal B.

When two doses were given in a short interval, there were robust immune responses, but they were less than if the interval is extended. This has been observed with other vaccines. Extending the interval between doses can show an improved immune response. This depends upon whether the goal is to illicit immunity rapidly in the case of an outbreak, or whether there is low risk of exposure and being able to extend that to 6 months and use two doses to have a high proportion of individuals who will respond to the representative strains.

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The 0, 2, 6 and 0, 1, 6 schedules were very comparable, which permitted moving to a schedule with more flexibility. Looking at the responses to each of the strains, there is similarity between the 0, 6 and the 3-dose series as well. Therefore, substantial benefit is provided with a 2-dose schedule on a 0, 6 interval in comparison to the 3-dose schedule.

The composite response is an evaluation of the number of individuals who have a response to all 4 strains. This offers predictive measures of what the response will be against virtually any meningococcal strain that will now be tested in the hSBA. It is a very good predictive value. In terms of 4-fold responses, there is a discernable difference between providing vaccine in a short interval versus the longer interval of 0, 6 and there is comparability in terms of the 0, 6 two-dose response and the three-dose schedules. While there are differences in this, if two doses are given very close together and a third dose is administered, the responses will be maximized.

The 0, 6 schedule does provide substantial benefit. In terms of "before vaccination," individuals may have background response to a particular strain, but the requirement is to respond to all four strains. So vaccination provides a benefit in terms of antibody that is solicited, which will now recognize across that diversity. There is comparability, or at least similarity, between the 2-dose schedule and the two 3-dose schedules. Very often, the confidence intervals overlap for some of the strains and may not for others, but they are very close.

This is also true in terms of the geometric mean titers (GMTs). There are differences in the titers achieved against the strains, but there are noticeable differences in the GMT that is actually achieved with 2 doses given very close together as opposed to the 0, 6 interval. Again, these are similar in terms of the GMT of the 2-dose compared to the 3-dose schedule.

Two isolates from one of the US outbreaks are almost virtually the same molecularly. These data show that there are differences in terms of strains in this in vitro assay, but the predictive value seen in a composite is shown in this. The predictive value of the 0, 6 schedule in terms of a composite is over 70% response, with a 70% to 80% response rate in terms of the 3-dose schedules. On a 0, 6 schedule against Strain 1, over 90% of individuals achieve a titer of 1:4, which is a protective value. In the 0, 2, 6 schedule the 2-dose and 3-dose schedules show 90% on this particular strain. The second strain is very similar molecularly, but acts differently in the in vitro situation. These are exploratory assays that are not very well-validated, but they do show the predictive value of 70% on a 0, 6 schedule and about 80% on a 3-dose schedule.

In terms of duration of protection, differences can be discerned in these data. Those data will be provided to the WG and ACIP before the October 2016 ACIP meeting, and certainly will be provided to the WG as soon as all of the cohorts within that study are collected and the testing done. Pfizer has followed persistence in this study for four years and then followed with a booster. Those data will be submitted to the WG and ACIP as well.

Regarding safety, there are no changes in the US Prescribing Information (USPI) in terms of the reactogenicity, et cetera. There are no changes within that document other than noting that a second or third dose of Trumenba® is virtually the same in terms of the safety profile. Pfizer has continued the evaluation of post-dose 2 and post-dose 3. Based on the cumulative safety summary of the 11 trials with over 15,000 subjects receiving MenB-FHbp, there is no distinction between the second and third dose. MenB-FHbp has demonstrated an acceptable safety profile. The most common local and systemic reactions were injection site pain, headache, fatigue, and muscle pain. Reactogenicity events were mostly mild and moderate. Median duration was 2 to 3 days for local reactions and 1 to 2 days for systemic reactions. There was

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no potentiation of reactions with subsequent doses. MenB-FHbp has demonstrated an acceptable safety profile when co-administered with MCV4/Tdap, dTaP-IPV, or HPV4. Similar proportions of newly diagnosed chronic medical conditions, autoimmune diseases, and neuroinflammatory conditions were reported in MenB-FHbp recipients and controls. Rates of SAE were similar between MenB-FHbp recipients (1.6%) and controls (1.9%).

In summary, Trumenba® (MenB-FHbp) was granted FDA approval under Accelerated Approval regulations in October 2014 for use in a 3-dose series (0,2,6 months) for the prevention of invasive meningococcal disease caused by serogroup B in individuals 10 years through 25 years. On April 14, 2016, FDA approved a label change under the same regulations with a flexible 3-dose schedule (0, 1-2 months and 6 months) and a 2-dose schedule (0, 6 months). Both schedules have been determined to be safe and effective. ACIP guidance to providers is needed on the use of the FDA-approved dosing schedules for MenB-FHbp within the context of current vaccine recommendations for the prevention of MenB disease for use in individuals ≥10 years at increased risk of disease and in adolescent and young adults.

Summary of WG Discussions: Trumenba® Label

Jessica MacNeil, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. MacNeil provided a summary of the WG's discussions pertaining to the revised dosing schedule for MenB-FHbp or Trumenba®. On April 14, 2016, FDA approved updates to the Dosage and Administration section for MenB-FHbp. The changes allow for administration of both a 3-dose schedule at 0, 1-2, and 6 months, and a 2-dose schedule at 0 and 6 months. Additionally, the package insert now includes the following statement, "The choice and dosing schedule may depend on the risk of exposure and the patient's susceptibility to meningococcal serogroup B disease."

The current ACIP recommendations for the use of MenB are as follows:

- ❑ Certain persons aged ≥10 years who are at increased risk for meningococcal disease should receive MenB vaccine (Category A)[1]
- ❑ A MenB vaccine series may be administered to adolescents and young adults aged 16 through 23 years to provide short-term protection against most strains of serogroup B meningococcal disease (Category B)[2]

In the MenB Policy Notes, additional guidance is provided that states the following, which is consistent with the original licensing of these vaccines:

- ❑ MenB vaccine should either be administered as a 3-dose series of MenB-FHbp (Trumenba®) or a 2-dose series of MenB-4C (Bexsero®)[1,2]

[[1]Folaranmi T., et al. Use of Serogroup B Meningococcal Vaccines in Persons Aged ≥10 Years at Increased Risk for Serogroup B Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR; June 12, 2015; Vol. 64, No. 22, p 608-612; [2]MacNeil JR, et al. Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices, 2014. MMWR; October 23, 2015, Vol. 64, No. 41, p 1171-1176].

Ms. MacNeil then summarized the WG's interpretation of data presented on the immunogenicity and safety data for the 2-dose schedule of MenB-FHbp at 0 and 6 months, as well as the proposed policy options language, and the WG's discussion. As a reminder, several dosing schedules were evaluated for MenB-FHbp including two 3-dose schedules and four 2-dose schedules.

Based on the immunogenicity data presented by Dr. York, overall among the 2-dose schedules evaluated, the 0, 6 month schedule had the highest percentage of responders and GMTs and is most similar to a 3-dose schedule. However, the proportion of subjects demonstrating at least a 4-fold rise in hSBA titers is lower with a 2-dose schedule at (0, 6 months) compared to either 3-dose schedule:

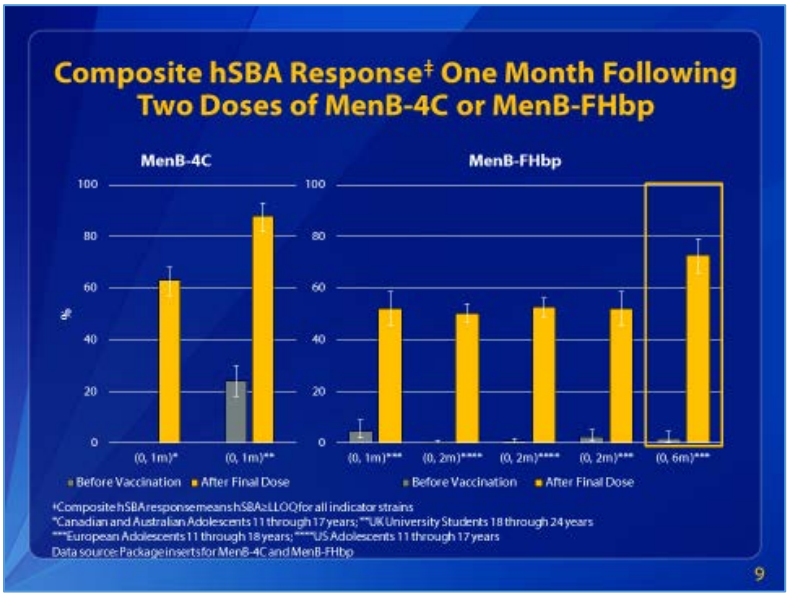
- ❑ 2-dose schedule (0, 6 months): 73.5% (68.5-78.1)*
- ❑ 3-dose schedule (0, 1, 6 months): 83.1% (78.6-86.9)*
- ❑ 3-dose schedule (0, 2, 6 months): 81.7% (77.3-85.7)*

[*Composite response (hSBA titer ≥1:8** for all 4 strains) 1 month post-last dose; **hSBA ≥1:16 for A22 expressing strain].

Similarly, the GMTs are lower with a 2-dose schedule at 0 and 6 months compared to either 3-dose schedule. For some of the strains, the 95% confidence intervals do not overlap. The WG felt that these lower GMTs suggest not as strong of an immune response to the 2-dose MenB-FHbp compared to 3 doses.

Although comparing hSBA responses following 2 doses of MenB-4C or MenB-FHbp is somewhat like comparing apples to oranges because of differences in the strains tested and the study population, the WG did feel that these were important data to consider as part of this discussion.

The following graphic shows the composite hSBA response one month following two doses of MenB-4C on the left and MenB-FHbp on the right, with varying intervals between those two doses:



In general, the responses following 2 doses of MenB-FHbp are similar and are slightly lower than the response following 2 doses of MenB-4C.

Preliminary antibody persistence data following the 2-dose schedule of MenB-FHbp was recently shared with the WG, and it is anticipated that more complete antibody persistence data may be available to be shared with the full ACIP in October 2016.

As presented to ACIP previously, the MenB vaccines are generally more reactogenic than other vaccines given during adolescence. The most common AE reported is pain at the injection site. Overall, the safety and tolerability profiles are similar for the 2-dose and 3-dose schedules of MenB-FHbp.

After reviewing these data, the WG has discussed several different policy options. For persons at increased risk and for use during outbreaks a preference for a 3-dose schedule of MenB-FHbp would be stated. For healthy adolescents, there are two options: 1) a 2-dose schedule of MenB-FHbp at 0 and 6 months or the 3-dose schedule could be given; or 2) a preference for a 3-dose schedule of MenB-FHbp could be stated and guidance could be provided that if someone receives their second dose of MenB-FHbp 6 months after the first dose, no additional doses are needed.

Based on the WG's discussion, there was strong consensus among WG members to express a preference for a 3-dose schedule for persons at increased risk, including outbreaks, in order to provide early protection and maximize the immune response. There also was a strong preference for a 3-dose schedule for healthy adolescents. For people who want to maximize protection, 3 doses are preferred. Both the 2- and 3-dose schedules take 6 months to complete. Guidance could be provided that if someone receives their second dose of MenB-FHbp 6 months after the first dose, no additional doses are needed.
Additional data are anticipated to be available for ACIP to consider in October 2016, which include the following:

- ❑ Results of antibody persistence following a 2-dose (0, 6 month) schedule
- ❑ Results from an independent evaluation of hSBA data for MenB-FHbp and MenB-4C against several US outbreak strains, which clearly show the benefits of a third dose of MenB-FHbp
- ❑ Results of a study on the impact of MenB-FHbp on carriage among US college students

In addition to hearing ACIP's feedback about the data presented, during the discussion the WG also hoped to obtain: 1) feedback on whether ACIP is in agreement with the WG's proposal to express a preference for the 3-dose schedule of MenB-FHbp in persons at increased risk, including outbreaks and healthy adolescents; and 2) whether there are additional data beyond data proposed for October 2016 that ACIP would like to see.

Discussion Points

Dr. Kempe asked whether there were plans to compare the cost-benefit for 2 versus 3 doses in healthy adolescents in terms of evaluating the additional potential benefit of the third dose.

Ms. MacNeil indicated that the WG had not planned to perform an analysis comparing the cost-benefit for 2 versus 3 doses, but could discuss this.

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Regarding the preference of the 3-dose schedule for healthy adolescents, Dr. Karron asked whether there is clear evidence that 3 doses maximizes protection relative to 2 doses.

Ms. MacNeil indicated that based on the immunogenicity data, there is a slight increase with 3 doses versus 2.

Dr. Karron asked for clarification about whether the confidence intervals overlap when the doses are given at 0 and 6 months, and Ms. MacNeil confirmed that they do. Therefore, Dr. Karron thought ACIP should consider this as an issue as well as with regard to the wording of the recommendation. She did not know that they had data to suggest that 3 doses maximizes protection over 2 doses in a healthy adolescent population.

Dr. Reingold asked who would be left such that there would not be a preference for a 3-dose schedule if those at increased risk in outbreaks and healthy adolescents were subtracted out.

Ms. MacNeil replied that there would be a preference for everyone for whom there is a current recommendation.

Dr. Grogg (AOA) asked Dr. York for clarification regarding whether the subfamilies that are tested and give a robust response were the same strains in the vaccine. If so, this would indicate to him that there is cross-protection.

Dr. York responded that this was correct. Strains were selected that would have antigens expressed that differed from the vaccine components. The assumption is that there is cross-protection. Instead of trying to match it to show a response to a vaccine, Pfizer approached this to show the breadth of the ability of the antibody to recognize across a diversity of US strains.

Dr. Stephens said it would be helpful to know about predicted strain coverage across US strains, for example. He requested that Dr. York elaborate on those data.

Dr. York indicated that Pfizer has performed exploratory analyses on outbreak strains in the US and France, which she presented during the last ACIP meeting. With the 2-dose and 3-dose, it is really quite predictive. Some strains are more difficult to develop in these assays, but the composite provides an idea of the minimum. It varies depending on the strain, regardless of the FHbp antigen.

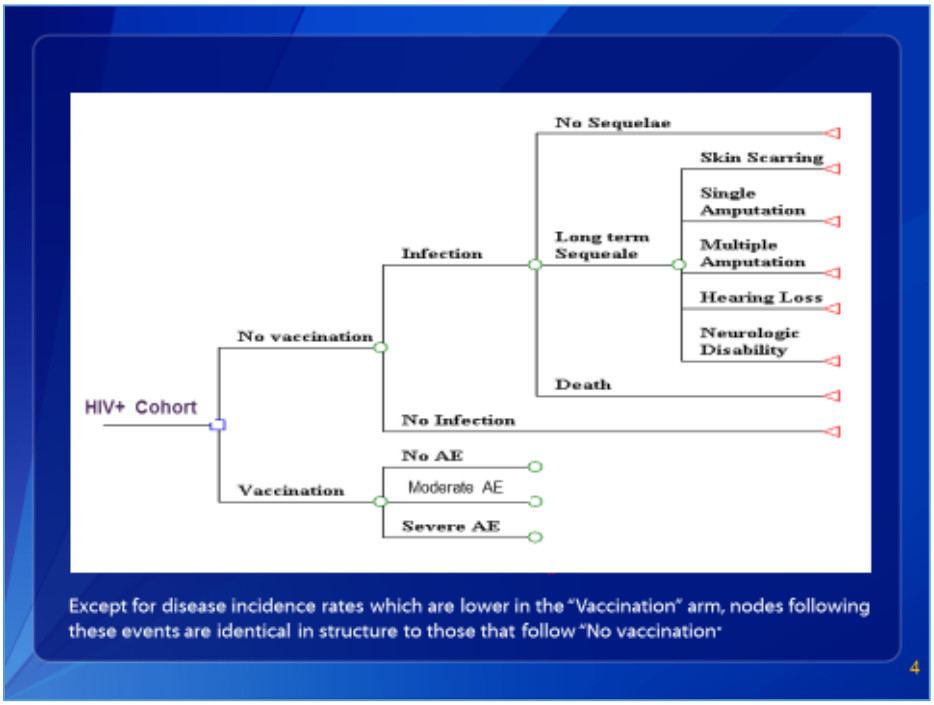
Cost-Effectiveness of Meningococcal Vaccination in HIV-Infected People in the US

Ismael Ortega-Sanchez, PhD
Senior Health Economist
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Ortega-Sanchez indicated that following the ACIP Guidance for Health Economics Studies, this study was reviewed by CDC. The review provided important observations that were addressed for this presentation, with explicit responses to some comments included at the end. The purpose of this study was to analyze the effectiveness and cost-effectiveness of a potential vaccination program for persons living with HIV against meningococcal disease with a primary series of MenACWY followed by lifelong 1-dose boosters every 5 years. For people less than 7

years of age, the booster dose would be every 3 years. The societal perspective was used for this analysis.

For this study, the investigators resorted to the previously constructed decision tree model to compare the strategies, with vaccination and without vaccination for each cohort:



For the complete number of cases as well as the number of deaths and survivors with sequelae, the model includes nodes that describe infection and non-infection and specific outcomes. A similar model was presented to this committee in the past. To deal with key uncertainties, the decision tree model also is designed with a Monte Carlo simulation analysis. This simulation allows for calculation of not only the most likely or base case estimate for health benefits and costs, but also the ranges around these estimates. For that, an age-specific HIV+ population is included that is comprised of approximately 934,000 HIV+ subjects distributed by age. Each age group is followed until 70 years of age, which is the timeframe. Benefits of vaccination are over the age-specific life expectancy, for which a discount rate of 3% is used for both costs and benefits.

Once the core of the model was set, the best available data were used, including the following:

- ❑ Age-specific HIV+ population (2013)
- ❑ Age- year- and Mening ACWY serogroup-specific incidence rates (2005-2014)
- ❑ Age- and Mening ACWY serogroup-specific case fatality ratios (2005-2014)
- ❑ Proportion of survivors with sequelae by condition after meningococcal disease

The model uses data for people living with HIV by age from the *HIV Surveillance Report, 2014*. It is quite important for modeling vaccine to determine the proportion of people living with HIV in Stage 3. For the lower bound, the data used was the proportion of new Stage 3 diagnoses for 2013, while the upper bound was based on the Revised Surveillance Case Definition for HIV Infection, which is based on CD4 counts. The assumption was made that the average life

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expectancy of people living with HIV is similar to the general population for the upper bound, and about a 7-year reduction in people living with HIV in the lower bound.

There are two important characteristics regarding the incidence data of people living with HIV who are in the model: 1) the proportion of cases who are HIV+ are from Active Bacterial Core surveillance (ABCs) and incidence data from the National Notifiable Diseases Surveillance System (NNDSS), with additional serogroup data from ABCs and state health departments; and 2) incidence data for 0 to 19 years is from NNDSS, with additional serogroups data from ABCs and state health departments for the general population regardless of HIV status.

Strategies of vaccination with MenACWY in the US are as follows:

- ≥2 years of age:
  Primary series: 0, 2 months
  Boosters: life-long boosters required
  Current booster recommendations: 3 years if age <7 years at previous dose and 5 years if age ≥7 years at previous dose

- <1 year of age:
  Primary series: 2, 4, 6, 12 months
  Boosters: same as above

- 1-2 years of age:
  Primary series: 0, 3 months
  Boosters: same as above

One key component is the initial VE based on CD4 counts. The specific efficacy used in the model was:

- High CD4 count with 2 doses series: 75% (37% to 91%)
- Low CD4 count with 2 doses series: 37% (24% to 60%)

The initial efficacy was based on combined efficacy from the Open-Label Trial of Safety and Immunogenicity of Meningococcal Groups A, C, Y, and W.

In the same way, the coverage rate was assumed for primary series and any booster dose as follows:

- Primary series (2 or 3 doses): 65% (40% to 80%)
- Booster dose (every 5 years): 45% (30% to 65%)

Rates of coverage for the primary series and booster assumptions were based on various sources.

The second component of VE regards how initial protection wanes over time. For preliminary assumptions, linear and exponential decay curves were fitted to antibody waning through available SBA data. Such waning was adjusted for low and high CD4 counts and for the first and second dose in the series. A key assumption in the model is that the efficacy of each and any booster dose is assumed to follow a similar waning protection pattern.

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Therefore in the model, the meningococcal disease incidence and vaccination were modeled using the following expression:

$$MDI_{vacc} = MDI_{no\ vacc} * [1-(Vcov * IntVEff * Residual_t)]$$

Where:

- MDI_{vacc} = Meningococcal disease incidence under vaccination
- $MDI_{no\ vacc}$ = Meningococcal disease incidence without vaccination
- *Vcov* = Vaccination coverage
- *Int VEff* = Initial vaccine efficacy
- $Residual_t$ = Residual vaccine efficacy (0-100%) *t* years after vaccination *t* = 0,…,T

No indirect effects were introduced into the model, because it is considered a vaccination primed to a target population. Once the disease incidence is calculated with vaccination and with no vaccination, the health outcomes were estimated. First, mortality was estimated using the case fatality ratios (CFRs) specific for serogroups ACWY in HIV+ persons based on NNDSS meningococcal cases with and without reduction as observed in ABCs data for HIV+ cases for the US, 2005-2014. Second, the proportion of survivor cases with sequelae was calculated by type of condition. The following table shows the rates of sequelae by type of condition, with point values and ranges that were used in previous analyses:

Skin Scarring	7.6 (0 - 19)
Single Amputation	1.9 (0.5 - 10)
Multiple Amputations	1.2 (0.02 - 6)
Hearing Loss*	8.8 (2 - 20)
Significant Long-Term Neurologic Disability**	2.1 (0.02 - 11)

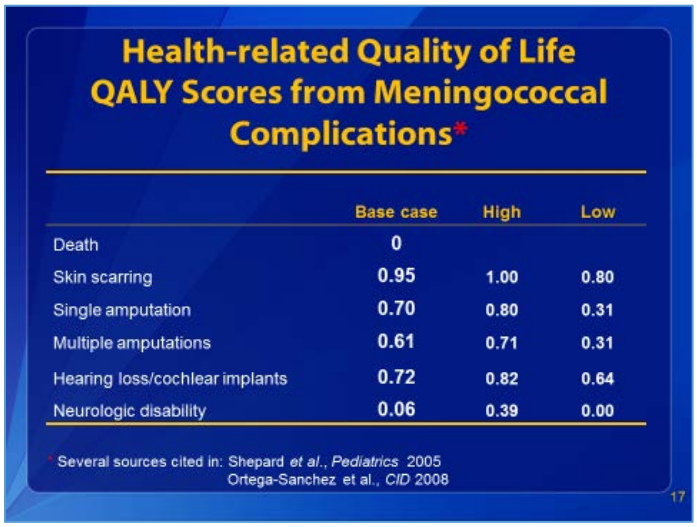
*Edwards *et al*. Complications and sequelae of meningococcal infections in children. J Pediatrics 1981; 99:540-5
**Baraff *et al*. Outcomes of Bacterial meningitis in children: a meta-analysis PIDJ 1993;12:389-94

Once outcomes of meningococcal disease were defined, the quality-of-life lost to each of these complications must be assessed. However, the baseline [1]Health Utility Index must be adjusted to take into account the underlying HIV infection and the perceived quality-of-life among people living with HIV. That is done before any meningococcal infection and the impact of the specific complications. Therefore, the baseline scores for people living with HIV are adjusted using the marginal effects from HIV, which are taken from a study on the [2]health-related quality-of-life of people living with HIV versus the general population. The adjustments are done by age, sexuality, CD4 counts, and date of diagnosis [[1]Health Utilities Index, Mark 3, (HUI-3) combined for males and females. Sources: (1) http://www.healthutilities.com/HUINormsKeyTable.htm (2)

http://www.chepa.org/Files/Working%20Papers/01-02.pdf; and [2]Adjusted for Age, Sexuality, CD4 counts (AIDS) and Date of diagnosis. Source: Miners et al. "Health-related quality-of-life of people with HIV in the era of combination antiretroviral treatment: a cross-sectional comparison with the general population. The Lancet V1, (1), October 2014, e32–e40]:

AGE (in years)	Health Utility Index General Population[1]	Marginal Effect in Utility Score from HIV[2]	Health Utility Index People Living with HIV
<24	92.2%	-11.0%	81.2%
25-34	92.2%	-11.0%	81.2%
35-44	92.3%	-13.0%	79.3%
45-54	91.5%	-13.0%	78.5%
55-64	88.1%	-14.0%	74.1%
65-74	86.4%	-14.0%	72.4%
75-84	83.9%	-14.0%	69.9%
85+	78.5%	-14.0%	64.5%

Once the baseline for quality-of-life is adjusted for people living with HIV, the related quality-of-life scores are applied for specific meningococcal complications as shown in the following table, which is done to estimate the quality adjusted life years (QALYs) lost to meningococcal to disease or the QALYs saved with vaccination:



Health-related Quality of Life QALY Scores from Meningococcal Complications*

	Base case	High	Low
Death	0		
Skin scarring	0.95	1.00	0.80
Single amputation	0.70	0.80	0.31
Multiple amputations	0.61	0.71	0.31
Hearing loss/cochlear implants	0.72	0.82	0.64
Neurologic disability	0.06	0.39	0.00

* Several sources cited in: Shepard *et al.*, *Pediatrics* 2005
Ortega-Sanchez et al., *CID* 2008

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The following chart is intended to illustrate what goes into cost calculations for the various outcomes of cases of meningococcal disease in this model:

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Components of Cost of Disease Calculation

Outcome	Acute phase: Med care (mening)	Acute phase: Caregivers' Work-Loss	Acute phase: Med care sequelae	Lifetime: Lifetime care (rehab, long term care)	Lifetime: Productivity Loss
No Sequelae	√	√			
Death	√	√			√
Skin scarring	√	√	√		
Single amput	√	√	√	√	
Multi amput	√	√	√	√	√
Hearing loss	√	√		√	√
Neuro seq	√	√		√	√

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Finally, the vaccine costs were based on the March 2016 public and private sector prices of Menveo or Menactra®. The cost of the vaccination program includes the cost of the dose, the cost of administration, and the proportion of waste due to vaccination problems. Note that the rates of AEs included in the vaccination program were taken from the United Kingdom (UK) experience with meningococcal C conjugate (MCC) vaccine.

Regarding the preliminary results, the baseline per age group of HIV+ persons with no vaccination are shown in this table:

Baseline per Age Group of HIV+ No Vaccination, Mean Estimates*

	Cases	Deaths	QALYs lost**	Disease Costs**
<13 years	2.0	0.4	5.8	$ 466,000
13-14 years	0.6	0.1	2.5	$ 176,000
15-19 years	4.6	0.9	21.2	$ 1,566,000
20-24 years	23.4	4.4	101.2	$ 8,524,000
25-29 years	34.2	6.3	118.1	$ 12,080,000
30-34 years	38.6	7.0	119.1	$ 13,763,000
35-39 years	40.2	7.3	118.7	$ 9,074,000
40-44 years	49.9	9.3	156.5	$ 11,557,000
45-49 years	56.7	10.6	162.4	$ 13,143,000
50-54 years	44.4	8.8	134.7	$ 10,168,000
55-59 years	27.0	5.2	76.2	$ 6,288,000
60-64 years	11.5	2.3	33.8	$ 2,646,000
65+ years	5.4	1.2	16.9	$ 1,278,000
All HIV+	**338**	**64**	**1067**	**$ 90,728,000**

* Mean values from Monte Carlo simulation
** Discounted at 3% rate, disease costs rounded to the nearest thousand

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Note that because of the small numbers of people living with HIV in some age groups and because of the low incidence and mortality rates of meningococcal disease, the number of cases, deaths, and QALYs lost are very small. The age groups with the highest meningococcal disease burden are observed from 20 through 24 years of age and from 50 through 59 years of age.

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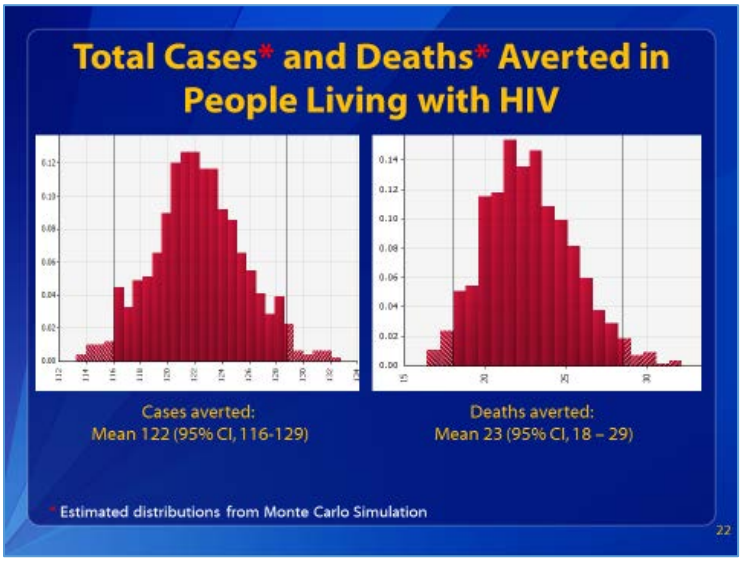
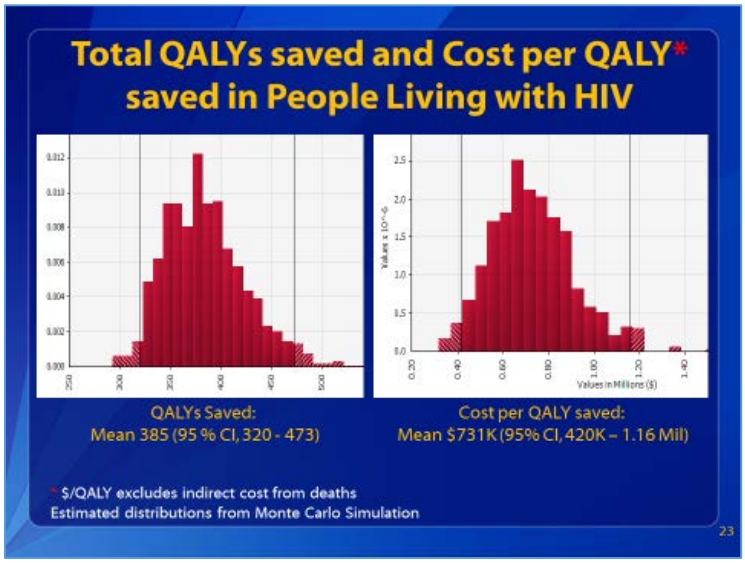
Once a vaccination program is implemented in the model, the total number of meningococcal cases and deaths averted in people living with HIV are shown below:



These estimated distributions are from Monte Carlo simulation. Based on this simulation, the mean number of cases averted was 122 and the mean number of deaths averted was 23.

Once the vaccination program is implemented in the model, the total cost of QALYs saved in people living with HIV vaccinated against MenACWY are shown below:



The average number of QALYs saved is 385 and the cost is about $730,000 per QALY. However, it is important to look more closely at which specific age groups of people living with HIV have high impact from vaccination. The following table shows the base case by age group, the number of cases, deaths prevented, and number of QALYs saved:

Cases, Deaths Prevented & QALYs Saved Baseline Estimates* by Age Group

Age	Cases saved (5th - 95th)		Lives saved (5th - 95th)		QALYs saved (5th - 95th)**	
<13 years	0.8	(0.8 - 0.9)	0.1	(0.1 - 0.2)	2.1	(1.8 - 2.5)
13-14 years	0.2	(0.2 - 0.2)	0.0	(0.0 - 0.1)	0.9	(0.7 - 1.0)
15-19 years	1.6	(1.5 - 1.70	0.3	(0.3 - 0.4)	7.3	(6.1 - 8.6)
20-24 years	8.5	(8.2 - 9.0)	1.6	(1.4 - 1.8)	37.8	(32.0 - 45.2)
25-29 years	12.2	(11.8 - 12.6)	2.2	(1.9 - 2.6)	42.4	(41.2 - 58.1)
30-34 years	13.8	(13.2 - 14.4)	2.5	(2.1 - 3.0)	42.5	(34.3 - 53.2)
35-39 years	14.4	(13.8 - 15.0)	2.6	(2.1 - 3.1)	42.4	(33.8 - 54.0)
40-44 years	18.0	(17.1 - 18.8)	3.3	(2.7 - 4.1)	57.5	(44.7 - 74.9)
45-49 years	20.5	(19.5 - 21.5)	3.7	(3.0 - 4.7)	57.2	(45.1 - 73.2)
50-54 years	15.9	(15.0 - 16.9)	3.1	(2.4 - 3.9)	46.3	(37.0 - 57.6)
55-59 years	10.0	(9.3 - 10.7)	1.9	(1.4 - 2.5)	28.0	(20.7 - 36.3)
60-64 years	4.2	(3.8 - 4.6)	0.9	(0.6 - 1.2)	12.4	(8.6 - 17.6)
65 + years	2.2	(2.0 - 2.5)	0.5	(0.3 - 0.8)	7.1	(4.2 - 11.3)
All HIV+	122	(116 - 129)	26	(18 - 29)	385	(320 - 458)

* Mean, 5th and 95th percentiles from Monte Carlo simulation
** Discounted at 3% rate

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As expected, the age groups where the highest vaccine impacts are observed are among those 20 through 24 years of age to 50 through 59 years of age.

To get an idea of the costs, the following graphic shows the base case for cost of disease with vaccination and the cost of vaccination program for each age group. Also shown are the base case net costs by age group:

Disease, Vaccination and Net Costs Baseline Estimates* by Age Group

Age	Disease Cost with Vax	Vaccine Cost	Net Cost **
<13 years	$ 297,000	$ 1,156,000	$ 1,081,000
13-14 years	$ 115,000	$ 353,000	$ 330,000
15-19 years	$ 1,024,000	$ 2,615,000	$ 2,417,000
20-24 years	$ 5,397,000	$ 14,437,000	$ 13,314,000
25-29 years	$ 7,767,000	$ 24,677,000	$ 23,115,000
30-34 years	$ 8,836,000	$ 29,675,000	$ 27,787,000
35-39 years	$ 9,285,000	$ 32,248,000	$ 30,141,000
40-44 years	$ 11,605,000	$ 41,692,000	$ 38,856,000
45-49 years	$ 12,591,000	$ 51,903,000	$ 48,465,000
50-54 years	$ 9,506,000	$ 47,168,000	$ 44,353,000
55-59 years	$ 5,288,000	$ 29,039,000	$ 27,121,000
60-64 years	$ 2,117,000	$ 14,007,000	$ 13,170,000
65 + years	$ 896,000	$ 8,505,000	$ 8,022,000
All HIV+	$ 74,766,000	$ 298,373,000	$ 279,050,000

* Values from Monte Carlo simulation, discounted at 3% and rounded
** Net costs exclude all indirect or productivity costs

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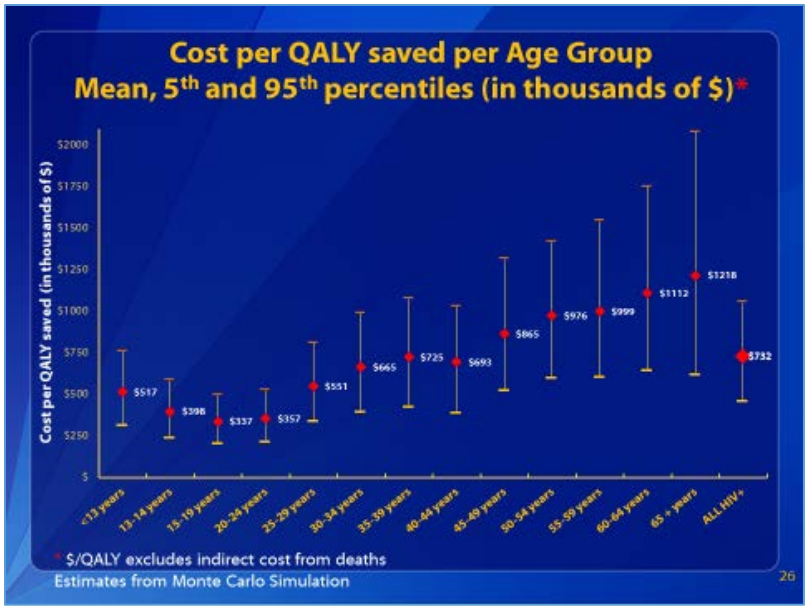
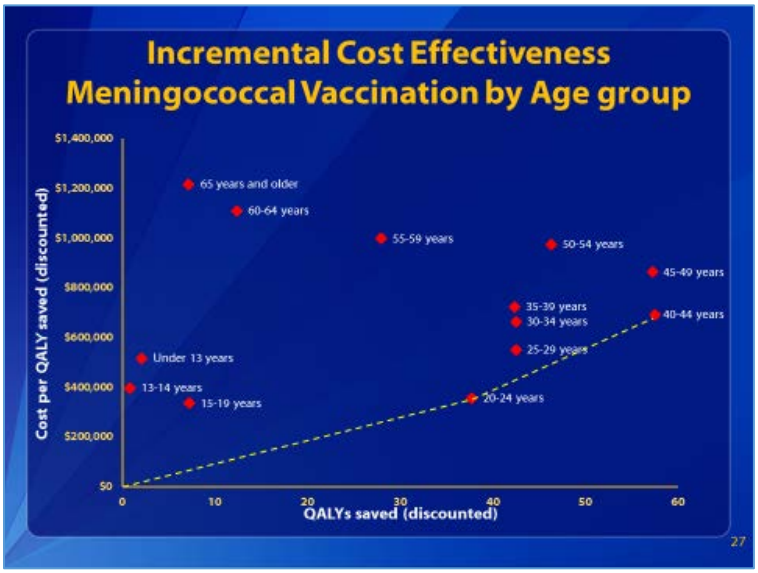
The following graphic presents the cost-effectiveness analysis among all age groups. The diamonds are the mean values from the Monte Carlo Simulation, and the 5th and 95th percentiles are the ranges in bars. Note the U-shape when age is changing:



In order to see the incremental cost-effectiveness of meningococcal vaccination by age group, economists use the following type of graph that shows the cost per QALY in the Y-axis and the QALYs saved on the X-axis and draws a line to the one that has the lowest slope, which is considered to be the most cost-effective intervention:



Based on this graph, the age groups that provide the most QALYs are those that range from 20 through 24 to 40 through 50 to 54 years of age. The people on the left-hand side are providing less QALYs saved, which is due to the small numbers in those age groups living with HIV and the lowest incidence and mortality rates.

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When specific scenarios are selected and some of the variables are changed in the base case assumptions, changes can be seen in those assumptions and the QALYs and costs per QALY saved as shown in the following table:

Cost-Effectiveness Selected Scenario Analyses*

	QALYs saved	Cost-per-QALY saved
Base-case	**385**	**$732,000**
Life Expectancy in people living with HIV -- 7 year lower than GP	327	$819,000
Proportion of HIV people in Stage 3 – 14% based in CD4 counts	321	$841,000
Waning of vaccine efficacy -- lower 5th percentile	296	$901,000
Initial vaccine efficacy -- 37% as for low CD4 count	231	$1,119,000
Baseline health-related quality of life similar to general population	447	$595,000

* Preliminary estimates from Monte Carlo simulation

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The following table provides a base case comparison for cost per QALY among some vaccination programs recommended and some not recommended:

$/QALY of Selective Vaccines in the US Base-case Comparisons

Vaccine	Target group	Cost per QALY gained (compared to no vaccination)
Hepatitis B	College freshmen	<$0 (cost-saving) to ≈ $10,000
Hepatitis A	College freshmen	<$0 (cost-saving) to ≈ $15,000
Pneumococcal (PCV13)	Adult persons with HIV/AIDS	≈ $4,000
Meningococcal (MCV4)	All 11- to 17-year-olds (with herd immunity)	≈ $94,000
Meningococcal (MCV4)	MSM in New York City (with, without herd immunity)	≈ $66,000 to >$177,000
Meningococcal (MCV4)	2-dose, all 11 & 16-year-olds	$212,000
Meningococcal (Hib MenCY)	4 doses, all infants at 2, 4 , 6 and 12-15 mons	≈215,000 ($90,000 to >$450,000)
Meningococcal ACWY	**All persons living with HIV in the US**	**$732,000 ($337,000 to $1,218,000)**
Meningococcal (MenB)	Series @16 years	≈$4.1 Million
Meningococcal (MenB)	Series, all freshman college in 4yr and 2yr programs	≈$9.4 Million

Sources: Ortega-Sanchez et al. *Pediatrics* 2008 Jan;121 Suppl 1:S63-78
Cohn et al., *MMWR*, 2013 Mar 22;62(RR-2):1-28.
Simon et al. *J Acquir Immune Defic Syndr*. 2016 Feb 1;71(2):146-54.
Cho et al. Vaccine 2013 Dec 5; 31 (50): 6011-6021

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There are a number of limitations in the analysis. Data on incidence and mortality among people with HIV are limited. Data on *initial* VE are from serology and immunogenicity. Data on duration of VE also is limited, though strong assumptions have been used to try to determine the best estimates.

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As mentioned earlier, following the ACIP Guidance for Health Economics Studies, there were a number of comments / suggestions made by the reviewers inside the CDC. The comments provided for Parts 1 and II, along with the responses from the investigators, were as follows:

Part I

Comment 1. "[C]oncerns about the numbers presented for the number of people living with AIDS:

Using the "Revised Surveillance Case Definition for HIV Infection - United States, 2014" we re-estimated the percentage range of people living with HIV in stage 3, along with a scenario analysis

Comment 2. The reduction in cases of disease as a result of vaccination does not seem to line up with the assumptions about vaccine efficacy, vaccine coverage, and waning of protection:

We reviewed the model calculations for formulas and parameter values and health outcomes and costs were re-estimated

Part II

In Comments 3 to 9. Reviewer provided "minor" or "editorial" comments which were addressed in these slides and in the technical report

In conclusion, routine vaccination of people living with HIV with a primary series plus periodic boosters against Meningococcal ACWY disease is relatively costly. Disease cases, deaths (both with relatively low numbers), and vaccine costs of lifelong booster doses drive the analyses. Although costly, additional cases could be prevented by all vaccination strategies.

Discussion Points

Dr. Thompson (NVAC) asked whether less waning than the base case was evaluated, and related to that whether people who wane, wane back to the same level as fully susceptible individuals with respect to their risks for the specific outcomes or sequelae.

Dr. Ortega–Sanchez replied that the assumptions about waning were taken from the open-label immunization data, most of which were for children and adolescents that were extrapolated to the other age groups. For the sensitivity analysis, consideration was given to what would happen if the waning was faster, which was following the 5th percentile. The number of QALYs saved and the cost per QALY changed in the direction expected. Only 296 QALYs saved and a cost of $901,000 per QALY. The assumptions can be changed. In fact, he has been performing a number of experiments with that assumption because it seems to be the one that drives the analysis. Again, the data are limited and the ranges provided to each one of the mean points are supposed to be included in some of the uncertainty that was observed in the variables.

Dr. Reingold asked for an approximate number needed to vaccine (NNV) to prevent one case, and a reasonable number of assumptions about duration of protection and if there is full coverage, approximately how many cases and deaths would be prevented per year in the US.

Dr. Ortega–Sanchez responded that the model is allowing him to calculate the NNV and he has been assessing those estimates. Some of the age groups were so small that more people than

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in the age groups would need to be vaccinated in order to prevent one case in those age groups. For example, for those less than 13 years of age, he had to determine how to distribute all 2415 cases among all of those 12 years, and then try to include the incidence data to come up with cases. Not all 2415 would be vaccinated, because there are assumptions about coverage. The NNV to prevent one case among one of these age groups was higher than the 2415, for example. It is basically the same for some of the other age groups. He can provide those data, and some data were provided in the extra slides to support the assumptions. He was not able to provide the estimate year-by-year of cases and deaths averted, because this cohort was followed for 70 years. In 70 years, about 122 cases would be prevented. That is approximately 45% of the total number of cases observed in the same period. If that is distributed by year, the numbers are very small.

Dr. Messonnier pointed out that this information was going to be discussed in the upcoming GRADE presentation.

While Dr. Whitely Williams (NMA) thought this was an excellent effort to try to answer the question, the modeling did not take into account the social background and environment of this population. For example, there was an outbreak of meningococcal meningitis in Chicago. Of the 7 cases, 6 were HIV-infected and 1 was not. She said she made this comment because eventually, had the investigation not used the infrastructure that was in place to support persons with HIV infection, it would have been difficult to understand what was occurring with that outbreak and it potentially could have spread to the general population. Obviously, it was good that there was a social support and environment existed in order to be able to recognize and control that outbreak, she though they needed to be very careful about the modeling to come to a conclusion that this would be very expensive in terms of the use of this vaccine in this particular population.

GRADE for MenACWY Vaccines for HIV-Infected Persons

Monica Patton, MD
National Center for Immunization and Respiratory Diseases
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Dr. Patton presented the WG's GRADE process for the MenACWY vaccines for HIV-infected persons. She reviewed the study question and presented a modified assessment of disease burden data, an assessment of evidence for outcomes, and the WGs determination of overall evidence type. The first step in the GRADE process is to formulate the study question. The overall question for this analysis was, "Should MenACWY vaccines be administered routinely to all HIV-infected persons aged 2 months and older for prevention of meningococcal disease?"

There are three conjugate vaccines licensed for use in the US. Menactra® covers serogroups A, C, W, and Y and is licensed for use among persons aged 9 months to 55 years. Menveo® covers serogroups A, C, W, and Y and is licensed for use among persons aged 2 months to 55 years. Menhibrix® covers serogroups C, Y, and *Haemophilus influenzae* type b and is licensed for children aged 6 weeks to 18 months.

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The following table summarizes the outcomes that were chosen for the question:

Assessment	Outcome
Modified assessment of disease burden data	Cases/Incidence
	Mortality
Quality of evidence assessed using standard GRADE approach	Short-term immunogenicity against serogroups A, C, W, Y -4 weeks after 1st dose (week 4) -4 weeks after 2nd dose (week 28)
	Persistence in immunogenicity against serogroups A, C, W, Y -48 weeks after 2nd dose (week 72)
	Serious adverse events

The first 2 outcomes were not assessed using GRADE since they are surveillance data. A modified assessment was made of these data. The last 3 outcomes were assessed using GRADE. Dr. Patton first discussed the modified assessment of disease burden data and then described the GRADE process for the outcomes listed.

Because low disease incidence is an important consideration for meningococcal infections among HIV-infected persons, the WG wanted first to evaluate the quality of the meningococcal disease burden data. However, because these are surveillance data and no intervention was tested, they could not evaluate them using the GRADE format. Instead, the disease burden data were assessed for representativeness and completeness.

US meningococcal incidence data come from two sources: ABCs and NNDSS. ABCs is an active laboratory and population-based surveillance system that collects data on cases of meningococcal disease in 10 sites that cover 43 million persons, or approximately 14% of the US population. Because case reports include chart review, HIV status of cases should be included in ABCs data. NNDSS is a passive surveillance system. All states and territories report data for nationally notifiable diseases to NNDSS. However, NNDSS does not contain HIV status. Because cases identified in ABCs are also reportable to NNDSS, these are not independent surveillance systems.

Between 1995 and 2014, a total of 62 meningococcal cases were reported among HIV-infected persons in ABCs, which is approximately 2% of all cases reported to ABCs during that time period. Here we see the cases among HIV-infected person by age group in years and by serogroup:

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Meningococcal Disease Among HIV-Infected Persons, ABCs, 1995–2014

- 62 cases reported among HIV-infected persons
  - 2% of 3951 total cases reported

Age (years)	n (%)	Serogroup					
		B	C	W	Y	Non-groupable	Unknown
0–9	1 (2%)				1		
10–19	2 (3%)	1			1		
20–29	10 (16%)	3	4	1	1		1
30–39	19 (31%)	3	7		6		3
40–49	20 (32%)	4	8	2	4	1	1
50–59	8 (13%)	2	3		3		
60–69	2 (3%)		1		1		
≥70	0 (0%)						
Total n (%)	62 (100%)	13 (21%)	23 (37%)	3 (5%)	17 (27%)	1 (2%)	5 (8%)

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Approximately 80% of cases occurred among HIV-infected persons aged 20 through 49 years and approximately 70% of cases were serogroup C, W, or Y.

A chart review of ABCs data from 2000-2008 was performed in order to determine the incidence of meningococcal disease among HIV-infected persons in the US. A total of 33 cases from HIV-infected persons were included in the chart review. However, because the population of HIV-infected persons in ABCs was unknown due to variable HIV reporting requirements by state during that time period, incidence calculations were limited to the 17 meningococcal cases among HIV-infected persons in ABCs who met the CDC AIDS surveillance case definition because name-based AIDS cases were reported in all states during that time. The analysis found an incidence of 3.5 per 100,000 person years among cases who met CDC AIDS criteria compared to 0.3 per 100,000 person years among all other cases, with a resulting relative risk of 12.9 [Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation*].

However, there are a few things to keep in mind with respect to the quality of data regarding meningococcal disease among HIV-infected persons in ABCs. This is a map of ABC sites in 2014:

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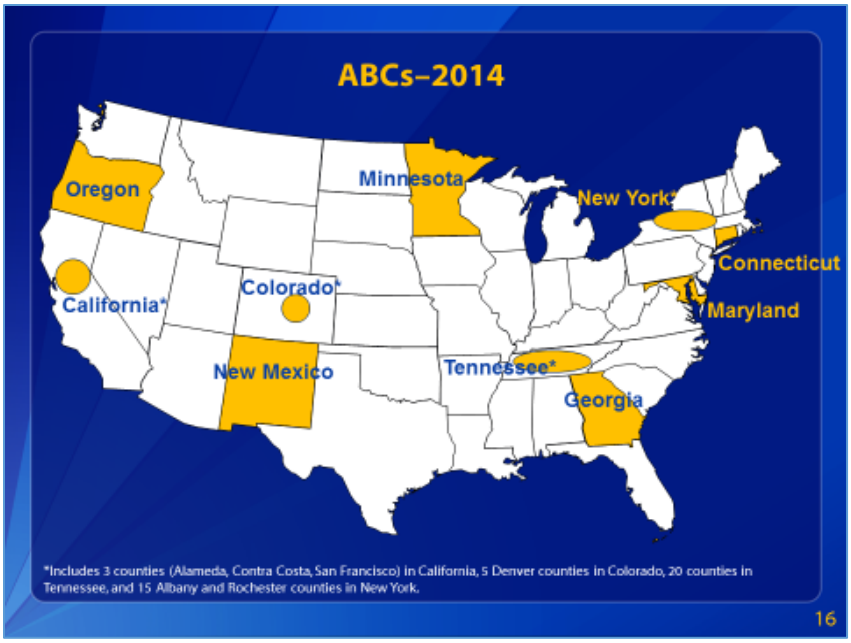

However, the ABCs catchment area during 2000 to 2008 used to calculate the incidence of meningococcal disease among HIV-infected persons is a somewhat different picture. For example, Colorado joined ABCs in 2001 and New Mexico joined in 2004. Additionally, cases were excluded from Maryland in 2000 and New York during the entire study period because of local health information disclosure policies pertaining to HIV infection.

When the proportion of the HIV-infected US population is calculated in the ABCs catchment area by year, the ABCs catchment area represented from 9% to 17% of the HIV-infected US population aged 14 years and older, and the proportion of HIV-infected US children aged 0 through 13 years represented by the ABCs catchment area was even lower, ranging from 6% to 9.8% per year.

Additionally, when considering the quality of surveillance data to identify meningococcal disease among HIV-infected persons, it is important to recognize that HIV testing rates among adults and adolescents are suboptimal. For example, the proportion of adults who had ever been tested for HIV increased from 37% in 2000 to 45% in 2008, and only 12% to 13% of adolescents were ever tested for HIV in 2005 and 2007.

However, despite the limitations of the case / incidence data of meningococcal disease among HIV-infected persons in ABCs, the available estimates are supported by a number of other studies that have investigated the incidence of meningococcal disease in HIV-infected persons as shown in the following table:

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Meningococcal Disease Among HIV-Infected Persons Compared to HIV-Uninfected Persons

Year	Site	Population	No. cases	HIV-infected compared to HIV-uninfected	Serogroup
1996–1999	Australia	All ages	60	5-fold increased rate	B, C
1990–2000	London	All ages	2900	14-fold increased rate	B, C
1988–1993	Atlanta	18–45 years	132	24-fold increased risk	B, C, Y
2003–2007	South Africa	All ages	504	11-fold increased risk	A, B, C, W, Y
2000–2011	New York City	15–64 years	265	10-fold increased risk	C, Y
2011–2013	England	All ages	2353	5-fold increased risk	A, B, C, W, Y

Couldwell DL. Invasive meningococcal disease and HIV coinfection. Commun Dis Intell Q Rep. 2001;25(4):279-280.
Pearson IC, et al. Meningococcal infection in patients with the human immunodeficiency virus and acquired immunodeficiency syndrome. International journal of STD & AIDS. 2001;12(6):410-411.
Stephens DS, et al. Sporadic meningococcal disease in adults: results of a 5-year population-based study. Annals of internal medicine. 1996;123(12):937-940.
Cohen C, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. Aids. 2010;24(9):1359-1360.
Miller L, et al. Elevated risk for invasive meningococcal disease among persons with HIV. Annals of internal medicine. 2014;160(1):36-37.
Simmons RD, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. BMC Med. 2015;13:297.

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Most of these studies were presented to ACIP during the last meeting. It is important to recognize that these studies occurred over a 4-decade time period when many advances in HIV testing, care, and treatment occurred, resulting in studies that span variable HIV testing rates, variable availability of antiretroviral therapy, and variable severity of disease. However, the available studies show a 5- to 14-fold increased rate and a 5- to 24-fold increased risk of meningococcal disease among HIV-infected persons compared to HIV-uninfected persons that, taken together, suggest a possible benefit of MenACWY vaccination for persons with HIV infection.

In terms of mortality among HIV-infected persons with meningococcal disease, case-fatality ratios were analyzed for HIV-infected and HIV-uninfected persons with meningococcal disease in ABCs in the chart review between 2000 and 2008 and overall between 1995 and 2014. There was no statistically significant difference in case-fatality ratios between HIV-infected and HIV-uninfected persons in either analysis, with a case-fatality of 13% among HIV-infected persons compared to 11% of HIV-uninfected persons during 2000 to 2008, and case-fatality ratio of 16% among HIV-infected persons compared to 11% in HIV uninfected persons overall from 1995 to 2014.

Other studies that have assessed case-fatality ratios among HIV-infected and HIV-uninfected persons with meningococcal disease have demonstrated mixed results. While the Australian and South African studies demonstrated higher mortality among HIV-infected persons with meningococcal disease compared to HIV-uninfected persons, the studies from New York and England demonstrated higher mortality among HIV-uninfected persons. There are a number of reasons mortality may be lower among HIV-infected persons in the more recent studies, including the fact that many HIV-infected persons may be engaged in healthcare services where more rapid assessment of symptoms and referral to appropriate medical care may occur. Additionally, HIV-infected persons may receive antibiotic prophylaxis or be on antiretroviral therapy, which may improve survival from meningococcal disease.

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Overall, the representativeness of data on cases and incidence of meningococcal disease among HIV-infected persons in the US is good because, while only 9% to 17% of the US HIV-infected population is represented in ABCS, the resulting data were similar to available studies that assessed meningococcal disease among diverse HIV-infected individuals from multiple countries over a time period that spanned variable HIV testing, care, and treatment. The representativeness of the mortality data is fair because of small numbers in ABC data, few other studies assessing mortality, and mixed results of those studies.

Overall, the completeness of data on cases and incidence of meningococcal disease among HIV-infected persons in the US is good, but there is a potential for missed cases given the many limitations of surveillance data to ascertain meningococcal disease among HIV-infected persons, including that only 9% to 17% of the US HIV-infected population is represented in ABCs, NNDSS does not collect HIV status of cases, and HIV testing is suboptimal. As a result, current data likely underestimate the true incidence of and risk ratio for meningococcal disease among HIV-infected persons. Completeness of mortality data is fair because if cases are missed due to surveillance limitations, those deaths would also be missed. Additionally, there are few studies investigating mortality among HIV-infected persons with meningococcal disease.

In summary, the WG found some limitations to its meningococcal incidence and mortality data. However, they feel that available data likely underestimates the true burden and mortality of meningococcal disease among HIV-infected persons in the US.

Turning to the outcomes evidence of benefits and harms, as a reminder, the study question was, “Should Men ACWY vaccine be administered routinely to all HIV-infected persons aged 2 months and older for prevention of meningococcal disease?” The following table summarizes the outcomes assessed using GRADE:

	Outcome
Benefits	Short-term immunogenicity (4 weeks after 1st dose [week 4])
	Short-term immunogenicity (4 weeks after 2nd dose [week 28])
	Persistence in immunogenicity (48 weeks after 2nd dose [week 72])
Harms	Serious adverse events

The WG compiled data for MenACWY vaccines in HIV-infected persons by outcome and study design. There were a total of 2 studies, both of which were observational, open-label trials. Of note, both studies assessed administration of Menactra®. One assessed administration among 2- to 10-year old children and the other to 11- to 24-year old adolescents and young adults. There are no data available assessing Menveo® or MenHibrix® in HIV-infected persons.

Dr. Patton reviewed the evidence findings for benefits and harms, reminding everyone that these data have been presented during past ACIP meetings. Clinical effectiveness studies of meningococcal vaccines among HIV-infected persons are not feasible because of the low incidence of disease. As a result, SBA titers are used as the immunologic correlate of

protection. Multiple studies have shown that SBA titers correlate with protection against meningococcal disease in healthy persons [Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med. 1969 Jun 1;129(6):1307-26; Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England. Clin Diagn Lab Immunol. 2003 Sep;10(5):780-6].

Based on the body of evidence for MenACWY vaccines in HIV-infected persons, short-term immunogenicity is achieved for serogroups A, C, W, and Y after both the first and second doses. However, immunogenicity for serogroups A, W, and Y is suppressed in HIV-infected adolescents aged 11 through 24 years when compared to HIV-infected children aged 2 to 10 years after the first dose and for all serogroups after the second dose. Additionally, immunogenicity in HIV-infected adolescents is also suppressed when compared to healthy adolescents. Moreover, immunogenicity is suppressed further if there is a low CD4 count or high viral load. Serogroup C demonstrated the lowest rates of response and immunity.

When looking at persistence of immunogenicity at week 72, which is 1 year after receiving the second dose, there were higher levels of seroprotection among HIV-infected children who received 2 doses. However, seroprotection waned rapidly in adolescents, particularly in adolescents with low CD4 counts. Nevertheless, there is a boost response to the second dose.

Both studies assessed SAEs, which were reported from the time of vaccination through 6 weeks post-vaccination. Overall, between 2% and 7% of participants experienced an SAE event, including 4 laboratory events and 8 signs and symptoms including fever, headache, pain, psychiatric symptoms, ocular pain, and a lip lesion. SAE event rates were inversely related to entry CD4 percentage. Two deaths were reported in total, but both were unrelated to the vaccine. Of all SAEs, only ocular pain was judged to be related to the vaccine.

Based on the balance between the benefits and harms for using the vaccine, it can be concluded that the vaccine is immunogenic in HIV-infected children and adolescents in the short-term and is safe. Immunogenicity persists in HIV-infected children up to 72 weeks, but wanes rapidly in adolescents and young adults. Further, immune responses are suppressed with lower CD4 percentages or higher viral loads. The low disease burden lowers the overall benefits.

Regarding the determination of the evidence type for benefits and harms, in GRADE for each outcome, all of the available data are evaluated on the following 5 criteria and a final evidence type is assigned:

- ❑ Risk of Bias (methodological limitations)
- ❑ Inconsistency
- ❑ Indirectness
- ❑ Imprecision
- ❑ Other considerations (publication bias, strength of association, dose response)

The following table describes the algorithm used to determine the final evidence type for each outcome. RCTs start out as an evidence type of 1 and observational studies start out as a 3. The 5 criteria are assessed to determine whether the overall evidence type is moved down or up:

Algorithm for determining final evidence type

Study design	Initial evidence type	Criteria for moving down*	Criteria for moving up*^	Possible final evidence type
Randomized controlled trials	1	**Risk of bias** -1 Serious -2 Very serious **Inconsistency** -1 Serious -2 Very serious **Indirectness** -1 Serious -2 Very serious **Imprecision** -1 Serious -2 Very serious **Publication bias** -1 Likely -2 Very likely	**Strength of association** + 1 Large + 2 Very large **Dose response** + 1 Evidence of a gradient **Direction of all plausible residual confounding** + 1 Would reduce a demonstrated effect, or + 1 Would suggest a spurious effect when results show no effect	1 2 3
Observational studies	3			4

* 1= move up or down 1 level, 2= move up or down 2 levels
^Observational studies that were moved down cannot be moved up.

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No serious concerns were found for risk of bias, and no serious concerns were found with inconsistency for any of the outcomes. Short-term immunogenicity and persistence of immunogenicity were downgraded for indirectness because, while SBA titers are well-described and accepted as the immunologic correlate of protection in healthy persons, they have not been evaluated in HIV-infected persons. No serious concerns were found with imprecision for short-term immunogenicity or persistence of immunogenicity, but SAEs were downgraded for imprecision since the total sample size was not sufficient to detect rare events. No serious problems were found for publication bias. Short-term immunogenicity was upgraded because of a strong strength of association and for dose response. Persistence of immunogenicity was upgraded because of a dose response. The final evidence type turned out to be 3 for short-term immunogenicity after 1 dose, 3 for short-term immunogenicity after 2 doses, 3 for persistence in immunogenicity, and 4 for SAEs. The overall evidence type for all outcomes was 3.

In summary, available studies demonstrate that MenACWY vaccine is immunogenic in HIV-infected children, adolescents, and young adults with immunogenicity that persists more among young children than among adolescents and young adults. The overall evidence type for benefits and harms are Type 3 with short-term immunogenicity after 1 dose, short-term immunogenicity after 2 doses, and persistence in immunogenicity all being type 3 and SAEs being Type 4.

Discussion Points

Dr. Reingold asked where there is an estimate of how many cases could be prevented nationally if this program was fully implemented in terms of the serogroups involved, how many cases there are, and the NNV to prevent a case.

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Dr. Patton replied that she did not have this information.

Dr. Kimberlin (AAP) asked whether there are contemporary US data that document an increased risk of Men ACWY in HIV-infected children in the US.

Dr. Patton responded that they do not have these data. The only information on HIV-infected children in the US is from ABCs. There were only 2 or 3 cases between 1995 and 2014 in ABCs data of meningococcal disease among HIV-infected children. But again, there are very serious limitations to those surveillance data.

Dr. Kimberlin (AAP) said he thought it was only 1 for children under 11 years of age who would not be receiving the vaccine anyway at the standard age of 11.

Dr. Martin (SME) referred to Dr. Ortega-Sanchez's Slide 22, which showed that the cases averted were 122 and the deaths averted were 23. That it, approximately 1 million people total (not per year) would have to be vaccinated to avert 122 cases and 23 deaths.

Dr. Cohn added that a very rough estimate based on the ABCs data, it is likely to be approximately 20 to 30 cases a year occurring among persons with HIV. That is just based on looking at the proportion of the population covered in ABCs, and the number of years in which those cases occurred.

Dr. Reingold said if those numbers were right, dividing by 70 would be about 1.5 cases per year.

In terms of the denominator, Dr. Baker (IDSA) asked how many HIV-infected children there are currently.

Dr. Patton replied that there are approximately 2000 HIV-infected children currently, and it is estimated that there are about 250 new cases of prenatally-acquired HIV per year. One would hope that would be decreasing over time.

Dr. Gorman (NIH) said he was struggling with the data showing the difference in mortality between the four countries. He asked whether they were convinced that the healthcare systems were that different in the four countries in terms of the engagement of the HIV population with antiretroviral therapy, prophylactic antibiotics, and access to healthcare.

Dr. Patton responded that they believe so, because in the two more recent studies, 80% of patients were on antiretroviral therapy. In the two previous studies and the earlier studies, almost no patients were on antiretroviral therapy.

Considerations for Use of MenACWY Vaccines in HIV-Infected Persons / Proposed Recommendations

Jessica MacNeil, MPH
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Ms. MacNeil presented a summary of the WG discussions on meningococcal disease among HIV-infected persons, reminding everyone that HIV is an established risk factor for several bacterial infections. A growing body of evidence supports an increased risk for meningococcal

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disease among HIV-infected persons. ACIP does not currently include HIV-infected persons in the recommendations for routine vaccination of persons at increased risk for meningococcal disease. However, if an HIV-infected person is vaccinated, the recommendations state that they should receive a 2-dose primary series.

During the February 2016 ACIP meeting, the available evidence was demonstrating an increased risk of meningococcal disease among HIV-infected persons, MenACWY vaccine response in HIV-infected persons, and programmatic and other considerations for the use of MenACWY vaccines in HIV-infected persons were discussed. Ms. MacNeil summarized these data and then explained the WG's rationale for the proposed use of MenACWY vaccines in HIV-infected persons and the proposed policy option language for a vote.

There are now five studies which have evaluated the risk for meningococcal disease among HIV-infected persons. Taken together, these studies consistently show an increased risk for meningococcal disease among HIV-infected persons:

1) Stephens DS, Hajjeh RA, Baughman WS, Harvey RC, Wenger JD, Farley MM. Sporadic meningococcal disease in adults: results of a 5-year population-based study. Ann Intern Med. 1995: 123:937-40.

2) Cohen C, Singh E, Wu HM, Martin S, de Gouveia L, Klugman KP, et al; Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA). Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. AIDS. 2010; 24:1351-60.

3) Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation.*

4) Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. Ann Intern Med. 2014; 160:30-38.

5) Simmons RD. et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. BMC Med. 2015; 13: 297.

In addition to showing an overall increased risk for meningococcal disease in HIV-infected persons, these studies also demonstrate that among HIV-infected persons, low CD4 count or high viral load further increases risk. Across the studies, a similar increase in risk was observed for both HIV-infected men and women. One study showed that the overall risk of meningococcal disease in HIV-infected persons is declining along with meningococcal disease incidence in the US. In HIV-infected persons, meningococcal disease is primarily due to serogroups C, W, and Y. Overall, the data on case-fatality ratios for HIV-infected meningococcal disease cases is mixed. However, the more recent studies show a lower case fatality ratio for HIV-infected persons compared to HIV-uninfected persons.

As Dr. Patton reviewed earlier, seroresponse to MenACWY-D (Menactra®) in HIV-infected adolescents is suppressed compared to healthy adolescents and HIV-infected 2- to 10-year-olds. A low CD4 count or higher viral load suppresses the response even further. In addition, the immune response to MenACWY-D wanes rapidly. Although a boost response is seen to a second dose, duration of protection will likely be an issue in this population [Siberry GK, et al.

Phase I/II, open-label trial of safety and immunogenicity of meningococcal polysaccharide diphtheria toxoid conjugate vaccine in human immunodeficiency virus-infected adolescents. PIDJl. 2010;29(5):391-396; Lujan-Zilbermann J, et al. Immunogenicity and safety of 1 vs 2 doses of quadrivalent meningococcal conjugate vaccine in youth infected with HIV. J Pediatr. 2012;161(4):676-681 e672; and Siberry GK, et al. Safety and immunogenicity of quadrivalent meningococcal conjugate vaccine in 2- to 10-year-old HIV-infected children. PIDJ. 2012;31(1):47-52].

In addition to the evidence of increased risk for meningococcal disease in HIV-infected persons and meningococcal vaccine response, the WG also discussed other programmatic considerations for use of meningococcal vaccines in HIV-infected persons. There are approximately 1 million persons living with HIV in the US[1]. An additional 40,000 new HIV infections are diagnosed each year[1]. Only about half of those diagnosed with HIV receive regular HIV care[2]. Of those retained in care, approximately 89% are prescribed antiretroviral therapy and 77% achieve viral suppression[2]. For HIV-infected persons in care, HIV clinics already may be administering other vaccines recommended for HIV-infected persons. HIV-infected persons in care may be more likely to have CD4 counts and viral loads favorable for immunogenicity [[1] Centers for Disease Control and Prevention. *HIV Surveillance Report, 2014*. www.cdc.gov/hiv/library/reports/surveillance; [2] www.cdc.gov/hiv/prevention/programs/pwp/linkage.html].

Risk for meningococcal disease among men who have sex with men (MSM) was discussed in detail during February's ACIP meeting. Of meningococcal disease cases among MSM for whom HIV status is known, the majority (59%) are HIV-infected. This has made disentangling the relative contributions of HIV and MSM status to the increase in risk for meningococcal disease challenging in MSM populations. However, vaccinating all HIV-infected persons offers an opportunity potentially to impact meningococcal disease risk among MSM.

In summary, a growing body of evidence supports an increased risk for meningococcal disease among HIV-infected persons. Several studies have demonstrated between a 5- to 24-fold increased risk for meningococcal disease in HIV-infected persons compared to HIV-uninfected persons. In HIV-infected persons, risk is due primarily to serogroups C, W, and Y. Suboptimal vaccine response and programmatic challenges may limit the impact of vaccination on disease burden in HIV-infected persons. However, because HIV-infected persons represent a relatively small, defined population who receive care in a specialized medical setting, implementation of a recommendation in this population may be less burdensome.

The current consideration is for use of MenACWY conjugate vaccines only because in HIV-infected persons, risk appears to be due primarily to serogroups C, W, and Y. No safety or immunogenicity data are available for the use of serogroup B meningococcal vaccines in HIV-infected persons. Because increased risk from HIV-infection is lifelong, routine booster doses would be recommended for HIV-infected persons similar to other groups at increased risk.

There was strong support in the WG for including HIV-infected persons in the groups at increased risk of meningococcal disease who are recommended MenACWY vaccination. The primary considerations for the WG included the evidence of increased risk of meningococcal disease in HIV-infected persons and the potential benefits of vaccination in this targeted group. However, the WG also recognized that suboptimal vaccine response and likely issues of duration of protection in HIV-infected persons may limit the impact of vaccination in this group. There were differing opinions in the WG about the age at which to begin vaccination of HIV-

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infected persons, with some favoring 2 months and others 11 years of age. However, the majority of the WG members supported vaccinating HIV-infected persons beginning at 2 months of age.

The pros and cons of including HIV-infected children 2 months through 10 years of age in the recommendation were discussed by the WG. In terms of the pros, harmonizing with the current ACIP recommendations for use of MenACWY vaccine in persons with functional or anatomic asplenia or complement component deficiencies. Because the number of HIV-infected children in the US is small, this likely would not be a burdensome or expensive recommendation. Biologically, it is unlikely that the increased risk of meningococcal disease in HIV-infected persons differs for children and adults. The hSBA titers following 1 or 2 doses of MenACWY vaccine in HIV-infected children 2 through 10 years are higher than in HIV-infected adolescents 11 through 24 years of age. Regarding the cons, depending upon the timing of doses for some children, the schedule may not fully harmonize with ACIP and AAPs recommendations for routine use of MenACWY vaccines in children 11 through 12 years of age. In addition, vaccination would require multiple doses over the child's lifetime. There are limitations in the current data available to document the burden of meningococcal disease in HIV-infected children in US.

Based on the discussions of the WG, the following two policy options for use of MenACWY vaccines in HIV-infected persons were proposed for a vote during this session:

> <u>Option 1</u>
> Human Immunodeficiency Virus (HIV)-infected persons aged ≥2 months should routinely receive MenACWY vaccine* (Category A)
>
> OR
>
> <u>Option 2</u>
> Human Immunodeficiency Virus (HIV)-infected persons aged ≥11 years should routinely receive MenACWY vaccine** (Category A)
>
> [*Includes MenACWY-D (Menactra®), MenACWY-CRM (Menveo®), and Hib-MenCY-TT (MenHibrix®); **Includes MenACWY-D (Menactra®) and MenACWY-CRM (Menveo®)].

Option 1 is consistent with the current recommendations for use of MenACWY vaccines in persons at increased risks for meningococcal disease, including persons with functional or anatomic asplenia or complement component deficiencies. Option 1 was supported by the majority of the WG.

In addition to the recommendation language, the following guidance would be provided for use of MenACWY vaccine in HIV-infected persons:

- ❑ In HIV-infected persons aged 2 years of age and older who have not been previously vaccinated, two doses of MenACWY vaccine should be administered 2 months apart. For children under 2 years of age, the schedules already require multiple doses, and additional doses would not be recommended as part of the primary series.

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- HIV-infected persons who previously received 1 dose of MenACWY vaccine would be recommended to receive a second dose at the earliest opportunity, and then would be recommended to receive boosters at the appropriate interval based on their age at the last MenACWY dose received.

Discussion Points

Dr. Romero did not believe that the statement about 50% of persons diagnosed with HIV receiving regular HIV care would apply to children. The diagnosis of HIV is made early among children, and he would surmise that about 80% are under HIV care. He also noted that children who acquire this disease perinatally comprise only 0.6% of the total 40,000.

Ms. MacNeil replied that those numbers were for people diagnosed with HIV overall, and probably were much more skewed toward adolescents and adults. While she did not have the exact numbers for children under 13 years of age in care, she agreed that it is probably much higher. In addition, she thought it was probably correct that children who acquire the disease perinatally comprise only 0.6% of the total 40,000.

Dr. Moore pointed out that although it was noted that biologically, there is no difference between children and adults, differences are observed in rates of meningococcal disease that may have been attributed to exposure to different strains of meningococcal bacteria over time which is why attention is focused on older teens and young adults. Based on that, there is a sensible argument for starting 11 years of age even though the biology of HIV is the same. The behavioral risk factors associated with meningococcal disease are different.

Ms. MacNeil confirmed that the highest incidence rates are among infants and young children. There is an increased incidence in children less than 5 years of age, so potentially some cases could be prevented in that age group.

Dr. Belongia asked what the justification was for the different intervals for the booster dose for children under 7 years of age at 3 years versus 5 years.

Dr. Cohn replied that this was based on waning immunity from the different schedules. The schedules differ in young infants in terms of the number of doses versus older adults. It is based on the 2-dose Menactra® waning immunity data, which was substantially faster than the waning immunity of a single dose in adolescents.

It seemed to Dr. Thompson (NVAC) that there is a strong correlation between CD4 and antibodies. With respect to waning, she wondered whether the WG considered the possibility of booster doses related to CD4 versus just an age criterion and if there are data to support that. In reality in the population, there is a distribution of people with different levels of progression of their HIV, CD4 counts, et cetera. At some level, waning may reflect what is occurring in that respect. CD4 counts are regularly monitored by clinicians.

Ms. MacNeil responded that the WG did not discuss boosters related to CD4 counts, but there was discussion about more frequent boosters every 3 years. The thought currently is to try to harmonize with the recommendations for other groups at increased risk, and to continue to monitor cases through surveillance. If an issue is observed, more frequent boosters could be administered.

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Dr. Kimberlin (AAP) expressed the AAP's appreciation for the diligence with which ACIP had approached this issue. AAP's Committee on Infectious Disease (COID) has engaged in many discussions as well. The focus that had been impressive to the AAP COID was listed as a con of dropping the age to 2 months, given the limited data to document burden of disease in HIV-infected children in the US. The AAP COID's interpretation is that there are no data to suggest that. Following that, without evidence of increased risk, their discussion was focused on 11 years of age and older.

Dr. Baker (IDSA) asked whether anyone could tell her the numbers of children in the US under 11 years of age who have functional or anatomic asplenia or complement component deficiencies.

Ms. MacNeil replied that the numbers are probably very small for both. In general for all ages, it is thought that about 1% of people have a complement component deficiency and overall about 1 million people in the US have asplenia.

Dr. Baker (IDSA) pointed out that the good news is that there is a small number of perinatally-infected children in the US. She thought the estimate would be that greater than 90% of HIV-infected children are in medical care. It is biologically implausible to her that children would have no increased risk under 11 years of age. While she hears people say that there is not a large disease burden or there are no data for children under 11 years of age, it seemed inconsistent with past and current policies to exclude a group. From a programmatic point-of-view, she thought there would be a lot of questions from the public about excluding this group at risk, including those at greatest risk for meningococcal disease—children less than 1 year of age plus HIV-infection. She indicated that the IDSA Public Health Committee favors Option 1.

Dr. Reingold was curious why one would make this recommendation for the ACWY-135 vaccine and not for the B vaccine. It seemed to him that serogroup B causes about a third of the cases in the US.

Dr. Cohn responded that the number of cases among persons with HIV are primarily serogroup C with some Y.

Ms. MacNeil indicated that about 80% of cases are C, W, and Y in HIV-infected persons, and this has been increasing recently. There are no safety or immunogenicity for MenB vaccines in HIV-infected people at this time.

Vote: Use of MenACWY Vaccines in HIV-Infected Persons

Dr. Rubin motioned to approve Policy Option 1. Dr. Stephens seconded the motion. The motion carried unanimously with 15 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

15 Favored:	Belongia, Bennett, Ezeanolue, Harriman, Harrison, Karron, Kempe, Moore, Pellegrini, Romero, Reingold, Riley, Rubin, Stephens, Walter
0 Opposed:	N/A
0 Abstained:	N/A

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VFC Resolution

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli indicated that the purpose of this revision was to update the eligible groups for the use of meningococcal conjugate vaccines to include children 2 months of age and older who are infected with HIV. Eligible groups would include the following, which reflects the addition of children infected with HIV:

- ❑ Children aged 2 months through 10 years who are at increased risk for meningococcal disease attributable to serogroups A, C, W, and Y, including:
    - → Children who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-C9, properdin, factor H, or factor D or taking eculizumab [Soliris®])
    - → Children who have anatomic or functional asplenia, including sickle cell disease
    - → Children infected with Human Immunodeficiency Virus (HIV)
    - → Children traveling to or residing in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with local population will be prolonged (MenACWY vaccines only)
    - → Children identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroups A, C, W, or Y
- ❑ All children aged 11 through 18 years of age.

No changes were recommended to the following sections of the resolution:

- ❑ Recommended Vaccination Schedule and Intervals
- ❑ Recommended dosage
- ❑ Contraindications and Precautions
- ❑ The Serogroup B Meningococcal Vaccine component of the resolution

The standard statement regarding updates based on published documents will be included:

> If an ACIP recommendation regarding meningococcal vaccination is published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL.

Discussion Points

Ms. Pellegrini requested clarification regarding whether the language on the booster doses would be incorporated by reference.

Dr. Santoli replied that she did not discuss the links included in this resolution that are not changed for the 2013 statement. All of the language is included through a link, and if there are

changes, those are updated by reference. Links in the resolution point to the booster language and other language about administration of the vaccine.

Vote: VFC Resolution for the Use of MenACWY Vaccines in HIV-Infected Persons

Dr. Rubin motioned to approve the VFC Resolution for Use of MenACWY Vaccines in HIV-Infected Persons. Dr. Harrison seconded the motion. The motion carried unanimously with 15 affirmative votes, 0 negative vote, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Belongia, Bennett, Ezeanolue, Harriman, Harrison, Karron, Kempe, Moore, Pellegrini, Romero, Reingold, Riley, Rubin, Stephens, Walter
0 Opposed: N/A
0 Abstained: N/A

Evidence-Based Recommendations Work Group Update

Arthur Reingold, MD
University of California, Berkeley
Chair, ACIP Evidence-Based Recommendations Work Group

Dr. Reingold indicated that the purpose of the Evidence-Based Recommendations WG is to provide a forum for discussion of best practices for the evidence-based recommendation process, including development and use of evidence tables and an evidence to recommendation framework to ensure consistency and enhance transparency in the development of ACIP recommendations, with the goal of developing a uniform approach to evaluation and use of the evidence base for ACIP recommendations.

The aims of the WG are potentially to modify and / or propose additional guidance for the ACIP evidence-based recommendation process, including GRADE and subsequent use of an evidence to recommendation framework, specifically to:

- Identify areas for improvement and harmonization regarding development and use of GRADE evidence tables among ACIP WGs
- Propose criteria that should be considered when determining whether GRADE evidence tables should be prepared for vaccine recommendations
- Develop a more transparent process outlining the formulation of recommendations that defines methods for the incorporation of additional factors that contribute to decision-making, as well as GRADE evidence tables generated by systematic review

The WG will develop the following:

- ❑ Guidance outlining proposed modifications and/or additions to the Evidence-Based Recommendations approach for consideration and approval by ACIP
- ❑ When developing the guidance, processes used by other nationally and internationally recognized groups also charged with formulating clinical and prevention policies will be considered
- ❑ A toolkit for use by ACIP Work Groups when formulating evidence-based recommendations
- ❑ A summary of any changes to the Evidence-Based Recommendations approach used by ACIP for publication (e.g., in *MMWR*)

Potential topics for the Evidence-Based Recommendations WG to address include the following:

- ❑ Quality Assessment of Evidence:
  - ➢ Determine the optimal way to consistently include the following data when evaluating the evidence using GRADE:
    - immunogenicity data
    - post-licensure safety and effectiveness assessments
    - data addressing the population-level impact of vaccine use
  - ➢ Evaluate methods to systematically and consistently evaluate burden of disease and outline how these data should be utilized during the process of recommendation development
- ❑ Recommendation Development:
  - ➢ Develop guidance providing additional structure for the evidence to recommendation process, including incorporation of the following:
    - population-level impact of vaccine use
    - values and preferences (audience, methods to elucidate such as provider surveys, et cetera)

Hepatitis Vaccines Update

Arthur Reingold, MD
University of California, Berkeley
Chair, ACIP Hepatitis Work Group

Dr. Reingold emphasized that ACIP believes it is very important to update recommendations on a regular basis. It has been almost 10 years since the last recommendation, although there have been updates in the interim. Hepatitis A recommendations were published in the *MMWR*

Recommendations and Reports in 2006 and Hepatitis B recommendations were published in *MMWR* Recommendations and Reports in 2005 and 2006. While there may not be a lot of new information or new vaccines available, the WG thinks it is important at least to update the statements and bring them current through 2016. The basic plan is for the WG to create two new documents, one on Hepatitis A and the other on Hepatitis B that will combine all of the information into single document that incorporates any new information.

As a reminder, the ACIP Hepatitis WG Term of Reference are as follows:

- ❑ Update ACIP recommendations for Hepatitis A vaccine
  - ➢ Current ACIP recommendations
    - ACIP Routine Recommendation for Hepatitis A Vaccine. *MMWR* 2006 May 19;55(RR-7):1-23.
    - Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the ACIP. *MMWR* 2007 Oct 19;56(41):1080-4.
    - FDA Approval of an Alternate Dosing Schedule for Twinrix®. *MMWR* 2007 Oct 12;56(40):1057.
    - Updated recommendations from the ACIP for use of hepatitis A vaccine in close contacts of newly arriving international adoptees. *MMWR* 2009 Sep 18;58(36):1006-7.

- ❑ Update ACIP recommendations for Hepatitis B vaccine
  - ➢ Current ACIP recommendations
    - ACIP Routine Recommendation for Hepatitis B Vaccine (Infants/Children). *MMWR* 2005 Dec 23;54(RR-16):1-33.
    - ACIP Routine Recommendation for Hepatitis B Vaccine (Adult). *MMWR* 2006 Dec 8;55(RR-16):1-33.
    - FDA Approval of an Alternate Dosing Schedule for Twinrix®. *MMWR* 2007 Oct 12;56(40):1057.
    - Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the ACIP. *MMWR* 2011 Dec 23;60(50):1709-11.
  - ➢ Current CDC Guidelines
    - CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. *MMWR* 2013 Dec 20;62(RR-10):1-19.
    - Update: Shortened Interval for Postvaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers. *MMWR* 2015 Oct 9;64(39):1118-20.

From May 2014 to April 2015, the WG considered Hepatitis A disease burden and population protection and catch-up vaccination for children / teens 2 through 18 years of age. From February 2016 to present, the WG has been considering immunogenicity and safety of HEPLISAV-B, a 2-Dose Hepatitis B Vaccine Series for Adults; and updating the ACIP recommendations for Hepatitis B vaccination. The ultimate goals is to develop the revised vaccine statements over the course of the next 6 to 12 months. They will then be presented to ACIP for evaluation and hopefully concurrence.

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Vaccine Supply

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Santoli presented an update on diphtheria, tetanus, and pertussis (DTaP)-containing vaccines Pentacel® and Pediarix®, and Merck vaccines in prefilled syringes.

In December 2015, Sanofi Pasteur announced a manufacturing delay with Pentacel® vaccine. As a result, Sanofi Pasteur is only able to meet approximately 70% of historical Pentacel® vaccine demand. At this time, sufficient supplies of the relevant individually administered vaccines DAPTACEL®, ActHIB®, and IPOL® are available to address the anticipated gap in Pentacel® supply. Sanofi Pasteur anticipates resolution of this Pentacel® delay during the second half of 2016.

GlaxoSmitnKline (GSK) is experiencing a delayed release of its Pediarix® vaccine. This delay is anticipated to resolve in late June to early July 2016. At this time, sufficient supplies of GSK's individually administered vaccines (DTaP and HepB) are available to address the gap in Pediarix® supply. In addition, Sanofi Pasteur has indicated it has sufficient supplies of IPV and / or Pentacel® vaccine to address the gap in Pediarix® supply.

The following prefilled syringes are currently unavailable:

- ❑ Gardasil 9 (HPV)
- ❑ Pediatric Recombivax (Hep B)
- ❑ Adult Recombivax (Hep B)
- ❑ Pediatric Vaqta (Hep A)

Merck anticipates return to availability in the second quarter of calendar year 2017. In the interim, Merck has sufficient supplies of the vial presentations for each of these vaccines to meet historical demand for both vial and prefilled syringe presentations.

CDC's Vaccine Supply/Shortage Webpage can be found at: www.cdc.gov/vaccines/vac-gen/shortages/default.htm

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Influenza

Introduction

Ruth Karron, MD
Chair, Influenza Work Group

Dr. Karron reported that since the February 2016 ACIP meeting, the Influenza WG has considered recent data pertaining to vaccine safety, FluLaval™ Quadrivalent vaccine evaluated in 6 through 36 months of age, the newly licensed Flucelvax Quadrivalent® vaccine, and vaccine effectiveness data for live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV). She indicated that the topics for this session would focus on vaccine safety for 2015-2016; FluLaval™ Quadrivalent; Flucelvax Quadrivalent®; vaccine effectiveness data for 2015-2016, including effectiveness of LAIV and IIV, from the US Influenza Vaccine Effectiveness (US Flu VE) Network and MedImmune; and proposed recommendations for use of influenza vaccines.

FluLaval™ Quadrivalent

Bruce L. Innis, MD, FIDSA
Research and Development Program for Influenza Vaccines
GSK Vaccines

Dr. Innis presented the immunogenicity and safety data for FluLaval™ Quadrivalent in children 6 through 35 months of age. He reminded everyone that original IIVs were administered to young children at a reduced dose to diminish their immunogencity[1-3]. Most contemporary split or subvirion vaccines are less reactogenic in young children, but have variable immune responses in the age group below 3 years[4-5].

In the US, Fluzone™ is the sole IIV licensed for children 6 through 35 months of age. Its approved dose is 0.25 mL containing 7.5 µg of purified hemagglutinin (HA) for each of the strains contained in the vaccine. This is half the dose that is approved for children 3 years of age and older. In this development program, GSK used a 0.5mL dose containing 15µg of purified HA per strain of FluLaval™ Quadrivalent in the anticipation that this would improve its immunogenicity [[1]Wright PF, Thompson J, Vaughn WK, et al. J Infect Dis 1977;136:S731-41; [2]Gross PA, Ennis FA, Gaerlan PF, et al. J Infect Dis 1977;136:623-32; [3]Gross PA. J Infect Dis 1977;136:S616-25; [4]Englund JA, Walter EB,Gbadebo A, et al. Pediatrics 2006;118:e579-85; [5]Walter EB, Rajagopal S, Zhu Y, et al. Vaccine 2010;28:4376-83l].

As a reminder, FluLaval™ Quadrivalent (Q-QIV) received FDA approval in August 2013 for use in persons 3 years of age and older. The vaccine is available in pre-filled syringes or a multi-dose vial. In January 2016, GSK submitted a Supplemental Biologics License Application (sBLA) to extend the indication to 6 through 35 months of age. The expected FDA action date is November 26, 2016. The dose will be 0.5mL and will contain 15µg HA from each of the recommended A/H1N1, A/H3N2, B-Victoria, and B-Yamagata strains. The proposed indication follows:

FLULAVAL™ QUADRIVALENT is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL™ QUADRIVALENT is approved for use in persons 6 months of age and older

The sBLA contained immunogenicity and safety data generated in three small Phase 1 or 2 studies and one very large Phase 3 trial. The development program began in 2010 and ran over a period of four immunization seasons. This allowed GSK to acquire safety and immunogenicity data on approximately 2000 subjects who were all actively monitored for safety for 6 months post-vaccination. Dr. Innis focused on the large pivotal Phase 3 study during this presentation, but emphasized that the relevance of the earlier studies is that they established that the profile of FluLaval™ immunogenicity and safety were consistent over multiple annual strain updates.

The Phase 3 study was an observer-blind randomized Fluzone™ QIV controlled trial conducted in 69 centers in the US and Mexico from October 2014 through June 2015. There were 2424 children 6 through 35 months of age enrolled who appear in the total vaccinated cohort (TVC). Children received one or two doses according to their vaccine priming status in accordance with the ACIP recommendation. The strain composition of both vaccines was identical, including:

- A/California/7/2009 (A/H1N1)
- A/Texas/50/2012 (A/H3N2)
- B/Massachusetts/2/2012 (B/Yamagata)
- B/Brisbane/60/2008 (B/Victoria)

Blood samples were collected pre-vaccination and 28 days after the last vaccine dose. Reactogenicity data, including body temperature that was assessed using a standard digital thermometer, were reported by parents on a diary card daily for 7 days after dosing. Additional safety data were collected by the investigators at each subsequent visit with the parent or guardian of the study subject.

The primary protocol objective was to evaluate the immunogenic non-inferiority of FluLaval™ QIV versus Fluzone™ QIV in terms of geometric mean titers (GMTs) and seroconversion rates (SCRs) as determined by a standardized and validated hemagglutination inhibition (HI) assay approximately 28 days after completion of dosing in children 6 through 35 months of age. The secondary objectives were to:

- Evaluate immunogenicity of FluLaval™ QIV based on Center for Biologics Evaluation and Research's (CBER's) acceptance criteria for seroconversion and seroprotection
- Describe safety and reactogenicity
- Describe immunogenicity
- Describe relative risk of fever for FluLaval™ QIV compared to Fluzone™ QIV within 2 days post-vaccination

There were no notable demographic differences in terms of age, gender, ethnicity, or vaccination priming status. The average age was 19.5 months. There were slightly more males than females. Most of the subjects were of non-Hispanic ancestry. There were approximately 200 participants from Mexico, while the rest were from the US. There was baseline medical history indicating the presence of at least one risk factor that could predispose a subject to complications of influenza infection in 6.8% and 6.2% of subjects respectively for Fluzone™

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versus the comparator. The most frequent risk factor was chronic pulmonary disease, mostly asthma. There were 102 subjects in the younger age stratum of 6 through 17 months of age, and 1,422 in the older stratum. Of the subjects, 1,110 were vaccine unprimed.

While pre-vaccination titers were low and similar between the groups for all strains, the vaccine response for the double dose FluLaval™ treatment appeared to be slightly higher for the two B strains included in the vaccine. The primary confirmatory objective was to demonstrate the immunogenic non-inferiority of FluLaval™ QIV compared to the comparator, which was met. The success criteria included a GMT ratio of ≤ 1.5 for each strain and an SCR of ≤ 10% for each strain. The GMT ratios were < 1 for all strains in favour of the double dose treatment, although more so for the B strains than for the A strains. The SCR was < 6% in favour of the double dose FluLaval™ treatment, again notably more so for the B versus the A strain. Conformance with the CBER acceptance criterion for inactivated vaccines was assessed and was exceeded by both treatment groups, but more so for FluLaval™. The CBER acceptability criterion for seroprotection was 70% of subjects who met or exceeded a titer of 1:40 by HI test following immunization. Both products met this criterion for 3 of the 4 strains, but neither met the criterion for B Victoria. The pre-immunization titers were quite low, with less than 5% of this cohort having a titer of 1:40 or greater. While this is presumably the explanation, Dr. Innis believes that the response to this strain also illustrates the potential benefits of having a double dose in the vaccine for this age group, because the difference is particularly notable when baseline titers are low.

The higher titers observed in the double dose FluLaval™ group relative to the standard of care prompted the investigators to perform a post-hoc analysis comparing the immune response elicited by the vaccine in all children and then according to age group and according to priming status. The post-hoc superiority analysis was performed of FluLaval™ over Fluzone™ using a conventional superiority criterion articulated by CBER; that is, superiority was indicated when the lower bound of the 95% confidence interval was > 1.5. Two important subgroups' influenza B responses were superior in the double-dose FluLaval™ group: 1) children 6 through 17 years of age, regardless of their vaccine priming status; and 2) all children under 3 years of age who were not previously vaccinated. In terms of the SCR difference, in this case the superiority criterion for superior immunogenicity was that the lower limit of the 95% confidence interval was >10%. That was met again in these same two groups for the response to the influenza B components of the vaccine. The comparative immunogenicity data acted as a surrogate for vaccine efficacy.

In terms of reactogenicity data, in terms of incidence rates per subject over 7 days following vaccination, there were no notable differences between the treatments (any symptoms, injection symptoms, general symptoms) for all symptoms or Grade 3 symptoms. In addition, there were no notable differences between all pain, redness, and swelling and Grade 3 pain, redness, and swelling between the treatments. With regard to solicited general AEs for All versus Grade 3, because the children were young they were monitored for drowsiness, fever, irritability, and loss of appetite. Again, there were no notable differences. The rates of unsolicited AEs, shown in the following table, were equal among the treatment groups as expected and this supports the excellent safety profile of the new vaccine relative to what has been the standard of care for the last 16 years:

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	FluLaval™ QIV	Fluzone™ QIV
[follow up period]	N = 1207	N = 1217
Any unsolicited AEs, n (%) [28 days after vaccination]	549 (45.5%)	537 (44.1%)
Medically attended AEs, n (%) [entire study]	727 (60.2%)	719 (59.1%)
Potential immune mediated disease, n (%) [entire study]	1 (0.1%)	1 (0.1%)
Any SAEs, n (%) [n related] [entire study]	22 (1.8%) [0]	21 1.7%) [0]

With respect to relative risk of fever, rates were similar between groups and the relative risk of fever ≥38°C was 0.97.

In conclusion, the primary objective was met. Immunogenic non-inferiority of FluLaval™ QIV to Fluzone™ QIV was demonstrated for all four strains in terms of GMTs and SCR. The use of 0.5mL dose (15µg per strain) of FluLaval™ QIV was not only immunogenically non-inferior to the standard of care, but also it elicited superior immune responses to both influenza B strains in children 6 through 17 months of age or in children 6 through 35 months of age who had not been vaccinated previously. Despite its double dose and injection volume, the FluLaval™ QIV reactogenicity and safety profile was equal to that of Fluzone™ QIV. As HI antibody titer post-vaccination is positively correlated with protection from influenza illness, GSK believes that double-dose FluLaval™ QIV may improve protection against influenza B, which is a potentially serious and life-threatening illness in young children. At the same time, the use of a 0.5mL dose (15µg per strain) FluLaval™ QIV will reduce complexity and cost in mounting the annual immunization campaign by allowing the same vaccine dose to be used for all persons who are eligible regardless of their age.

Discussion Points

Regarding fever, Dr. Walter inquired as to whether any of the children received other vaccines simultaneously and whether the investigators specifically assessed pneumococcal conjugate vaccine (PCV13).

Dr. Innis responded that simultaneous vaccination was permitted. Though this study did not assess PCV13, GSK has evaluated PCV13 in the past for Fluarix® and FluLaval™. The risk of fever is increased with these products and PCV, but not remarkably so. This is an acceptable combination.

Referring to Slide 18, Dr. Kempe noted that there was a relative risk of high fever of almost almost 6 and almost 3. She wondered whether the reason that was not significant was because there were small numbers of cases. She also inquired about the total N.

Dr. Innis replied that there were very small numbers of cases. For the relative risk of 6, there were 4 cases in the FluLaval™ group and 1 case in the Fluzone™ group. The total N is approximately 1200 subjects per group.

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Flucelvax Quadrivalent® (ccIIV4)

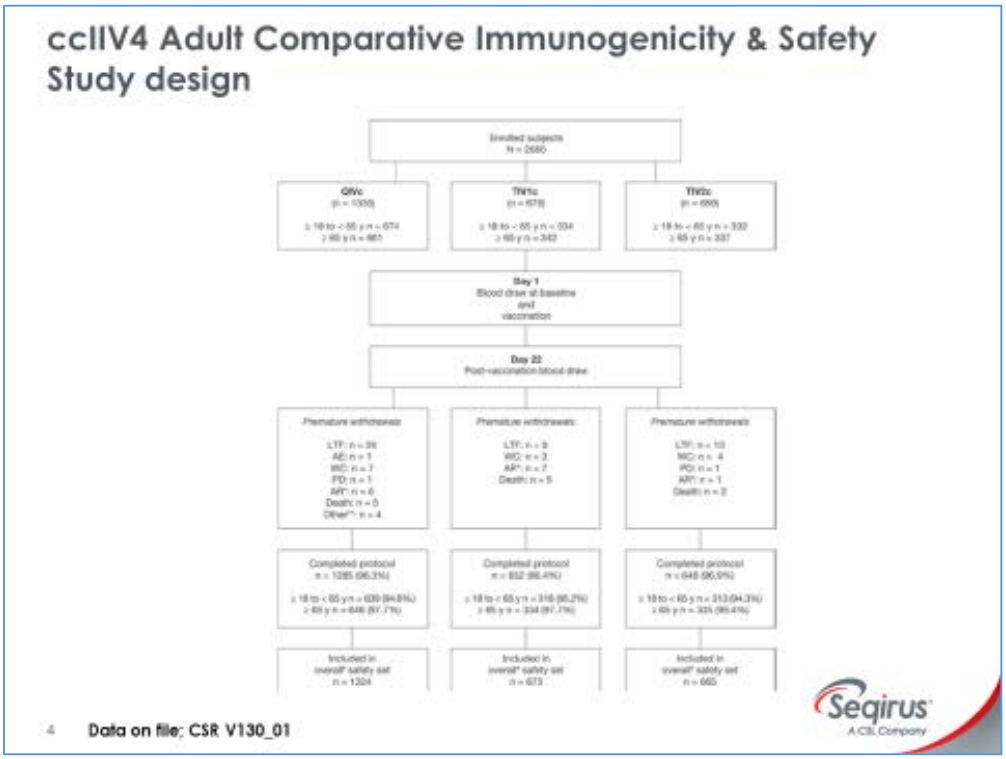
Dr. James Mansi
Seqirus™ A CSL Company

Dr. Mansi provided an update on Flucelvax Quadrivalent® (ccIIV4), the Seqirus™ quadrivalent inactivated cell culture influenza vaccine. This is Seqirus's™ first influenza quadrivalent influenza vaccine. Flucelvax Quadrivalent® was approved by the FDA on May 23, 2016 for individuals 4 years of age and older.

Using the cell-based technology or culture platform as the Seqirus™ currently licensed Flucelvax Trivalent® cell culture vaccine; whereby, influenza virus is propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line. This platform provides an alternative to traditional influenza vaccine passage through eggs, and allows for a flexible high volume process without reliance on eggs. Moreover, given that the process is closed and semi-automated, the risk is reduced for external contamination.

The licensure of Flucelvax Quadrivalent® was based on the immunogenicity, safety, and tolerability results from two pivotal Phase III trials, both of which were conducted in the United States (US) during the 2013-2014 Northern Hemisphere Influenza season. The first study evaluated ccIIV4 in adults 18 years of age and older, while the second study evaluated ccIIV4 in children 4 through 17 years of age. Across both studies, ccIIV4 was shown to be immunogenic against all four influenza strains and demonstrated a safety profile similar to the trivalent cell culture vaccine, while being equally well-tolerated.

The following diagram represents the study design and subject dispensation for the adult study:



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Approximately 2600 adults 18 years of age and older were stratified into two age groups, either 18 through 65 years of age or 65 years of age and older. They were randomized in a 2:1:1 fashion to receive either ccIIV4 or one of two ccIIV3 vaccines, the first having all three of the World Health Organization (WHO)-recommended strains for that season and the second having the two recommend A strains with the alternate B strain, B/Victoria. Baseline blood specimens were drawn at Visit 1 and again 3 weeks following immunization.

The preliminary objective of the study was to demonstrate non-inferiority of the antibody response from ccIIV4 compared to both ccIIV3 vaccines by the GMT ratios as well as the seroconversion rates. The secondary objective was to evaluate the immunologic response of ccIIV4 and to demonstrate superiority of the ccIIV4 on the alternate B strain. Safety data was collected through 6 months post-immunization.

With respect to the immune response, non-inferiority across all four vaccine strains was met by both seroconversion rates, whereby the upper bound of the 95% confidence interval did not exceed the pre-defined non-inferiority margin of 10. Similarly, for the GMT ratios, the upper bounds of the 95% confidence interval of each of the four strains did not exceed the pre-defined non-inferiority margin of 1.5. All of this confirms that the addition of the fourth influenza strain to the trivalent formulation did not negatively impact the immune response or the antibody response of the three other strains. Additionally, ccIIV4 demonstrated superiority to the alternate B strain compared to ccIIV3.

In terms of the antibody response, overall the immune response was similar between ccIIV4 and ccIIV3, with the antibody response being more robust in the younger age group of 18 through 65 years as compared to the older age group of 65 years and older. This can be attributed to age-related immunosenescence. The Center for Biologics Evaluation and Research (CBER) immunogenicity criteria were met against all strains for both HI titers >40 and the percent of subjects achieving sero-protective levels in the adult population of 18 through 65 year olds. In the adult population 65 years of age older, the CBER immunogencity criteria were met for all four strains for HI titers. The criteria was met for seroconversion only for the H1N1 strain. The lower antibody response has been observed previously in older adults in other influenza vaccine studies.

With respect to safety and the tolerability profile of ccIIV4 in the adult population, a similar percentage of subjects reported solicited AEs across all three of the vaccine groups. Overall, the solicited AEs were reported in a lower percentage of older adults 65 years of age and older as compared to the younger cohort of adults 18 through 65 years of age. The most common local AE was pain at the injection site, while the most common systemic AE was headaches. Across the entire study group, the percentage of subjects reporting unsolicited AE were few, with similar rates across each of the three vaccine groups. SAEs were reported in about 1% of subjects, with none found to be related to the vaccine. Thus, the reactogenicity and safety profile of Flucelvax Quadrivalent® were consistent with those of the Seqirus™ trivalent cell culture vaccine in the adult population, and similar to what is observed in other influenza vaccines in this adult population.

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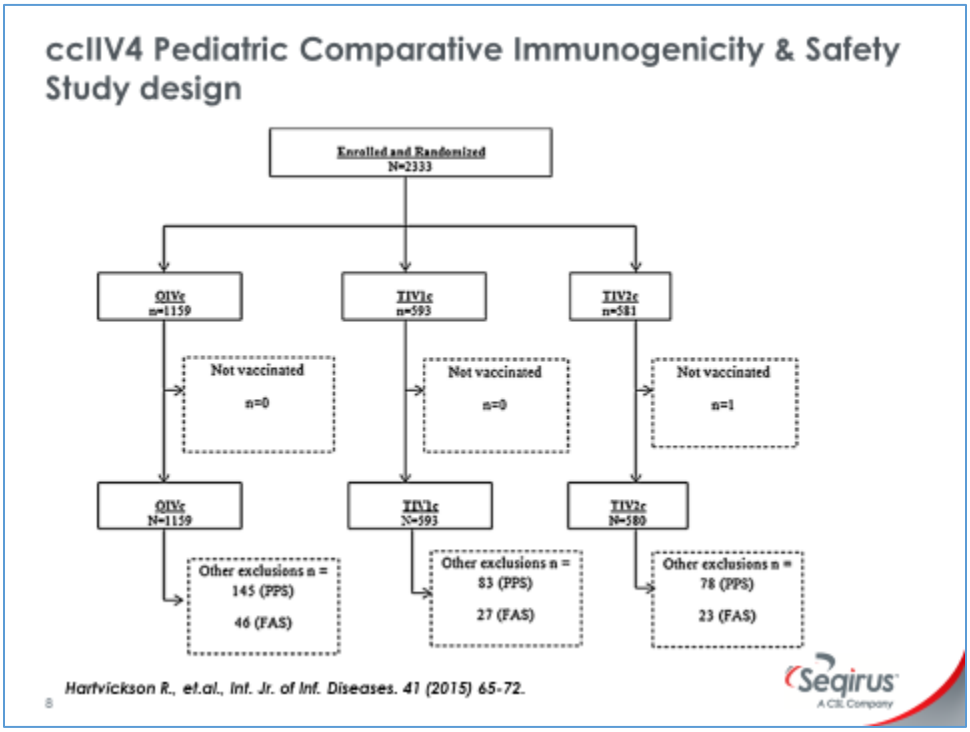
The pediatric study included approximately 2300 children 4 through 17 years of age who were stratified into two age groups, children 4 through 8 years of age and children 9 through 17 years of age shown in the diagram below:



Within these strata, subjects were randomized to receive vaccine in a 2:1:1 fashion to receive either ccIIV4 or one of two ccIIV3 vaccines, the first having all three of the WHO-recommended strains for that season and the second having the two recommend A strains with the alternate B strain, B/Victoria. Previously vaccinated children received one dose; whereas, influenza vaccine naïve children received two doses one month apart. Baseline blood samples were taken at Visit 1 and again 1 month following the last dose of study vaccine. Similar to the adult study, a primary objective of this study was to demonstrate non-inferiority of ccIIV4 against the GMT ratio and seroconversion rates compared to ccIIV3. The secondary objectives included the antibody response of ccIIV4 compared to ccIIV3 according to CBER and the Committee for Medicinal Products for Human Use (CHMP) criteria, and demonstration of superiority of ccIIV4 to the alternate B strain. Once again, safety was followed up through 6 months following the last dose of study vaccine.

The immune response to the cell culture vaccine was shown to be non-inferior for both the seroconversion rates, where the confidence intervals for each of the four influenza strains were below the pre-defined non-inferiority margin of 10. For GMT ratios, all four of the vaccine strains were shown to be non-inferior below the pre-defined non-inferiority margin of 1.5. Once again, superiority of ccIIV4 was demonstrated in the population of children 4 through 18 years of age against the alternate B strain in the vaccine. In terms of the antibody response, overall the immune responses were similar between ccIIV4 and each of the trivalent cell culture vaccines. The CBER criteria for immunogenicity based on seroconversion and HI titers >40 were met in children 4 through 18 years of age for all four of the influenza strains in the vaccine. The European CHMP criteria were equally met for seroconversion and HI titers.

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With respect to safety and tolerability of ccIIV4 in this pediatric population, overall the safety profile was similar to that of the comparator trivalent cell culture vaccines and to what has been observed in other influenza non-cell culture vaccines, including similar reactogenicity profiles. The reported solicited AEs were generally mild to moderate in nature and of a limited duration, resolving in less than 7 days. The most common local AEs reported were tenderness and injection site pain across all of the vaccine groups in equal proportions. The most common systemic AEs reported were sleepiness, fatigue, and headache across all three of the vaccine groups. Unsolicited AEs were reported in about 24 percent of subjects equally across each of the three vaccine groups. None of those were judged by the investigators as possibly related to any of the vaccines, and were comparable across all three. SAEs were reported in about 1% of all subjects and were equally distributed across each of the three vaccine groups, and none were judged by the investigators as vaccine-related.

In conclusion, the cell culture-based platform represents an alternative to traditional egg-based vaccine platforms, allowing for a flexible, high-volume process without relying on eggs. Given that it is a closed, semi-automated process, risk for external contamination is limited. What has been shown in the clinical trials for ccIIV4 is that from an immune perspective, ccIIV4 was able to illicit an immune response that was non-inferior to the comparator ccIIV3 and provided a superior immune response to the alternate B vaccine. The safety profile of MDCK cell-derived QIV was similar to that of TIVc vaccines, including a similar reactogenicity profile. No unexpected safety signals or concerns occurred throughout the study across the various ages.

Discussion Points

Dr. Gorman (NIH) requested an estimation of the time advantage over egg-based manufacturing processes in terms of a pandemic, and an estimation of Seqirus™ production capacity.

Dr. Mansi replied that the cell-based platform allows for more flexible and rapid production of influenza vaccine, particularly in a pandemic. They have run estimates on pandemic readiness, which he indicated he would share with ACIP. In terms of production capacity, Seqirus™ is able to meet current demands.

Dr. Belongia said he thought it was important to acknowledge that although manufacturing occurs in cell culture, it begins with egg-adapted viruses as a source and does not eliminate the problem of using eggs completely. Mutations can occur during egg adaptation. For the adult study, he wondered whether Dr. Mansi had any data on the proportion of participants who received vaccine the previous year and if so, whether there was a distribution of some people who were and were not vaccinated in the prior year.

Dr. Mansi noted that the full potential of the cell-based platform would be reached once they reach the starting point with the virus in the cell basing. The majority of adults were previously vaccinated, so a high number of adults had seroprotective levels at baseline, particularly in the older adult population that was equally distributed among the three vaccine groups.

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Vaccine Safety Update

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention

Dr. Shimabukuro shared the following table depicting the influenza vaccine products utilized during the past season, pointing out that IIV is commonly used when speaking of inactivated products collectively or some group of inactivated products, while all LAIV is quadrivalent.

Vaccine	Abbreviation
Trivalent inactivated influenza vaccine	IIV3
Quadrivalent inactivated influenza vaccine	IIV4
Quadrivalent live attenuated influenza vaccine	LAIV4
High-dose trivalent inactivated influenza vaccine	IIV3-HD
Intradermal trivalent and quadrivalent inactivated influenza vaccines	IIV3-ID IIV4-ID
Cell culture-based trivalent inactivated influenza vaccine	ccIIV3
Recombinant trivalent inactivated influenza vaccine	RIV3

He reminded everyone that the Vaccine Adverse Event Reporting System (VAERS) is a passive reporting system that is administered by the CDC and FDA. The strengths are that it includes national data, is good for rapid signal detection, and can detect rare AEs. The limitations are the limitations inherent to passive surveillance in general, including reporting bias, inconsistent data quality and completeness, lack of unvaccinated comparison group. Because of this, whether a vaccine caused an AE generally cannot be assessed from VAERS data.

Included for this season were US influenza vaccine reports received in VAERS through May 27, 2016 for individuals vaccinated July 1, 2015 through May 6, 2016. Signs, symptoms, and diagnoses are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terms. Clinical review of reports, which includes review of medical records when available, were performed for the following:

- All serious reports after IIV4, IIV4-ID, LAIV4, ccIIV3, RIV3
- All anaphylaxis reports in persons with a history of egg allergy
- Pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies, and serious pregnancy reports

Empirical Bayesian data mining was also conducted. Serious reports are based on the Code of Federal Regulations and include death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability.

Following IIV3, IIV4, LAIV4, and IIV3-HD in 2015-2016, serious reports were 5% to 6% and non-serious reports were 94% to 95%. Keeping in mind that VAERS is a passive system, the percentage of serious reports is the percentage of all reports that met the regulatory definition for "serious" that were submitted to VAERS. It is not the rate of SAEs after influenza vaccination, which is very low based upon the clinical trials. These percentages of breakdowns for serious and non-serious events are similar to other vaccines in the VAERS database. Guillain-Barré Syndrome (GBS) reports comprised a very small percentage of total reports from 0.5% to 1% for these products. That is similar to what was observed last year. Anaphylaxis reports are rare in VAERS, ranging from 0.3% to 0.6%. There were two reports of anaphylaxis following LAIV4 in persons with a history of egg allergy. One was in an adult who received LAIV4 alone, while the other was in a child who received multiple other vaccines during the same visit. There were no data mining findings for GBS or anaphylaxis. Following ccIIV3, RIV3, IIV3-ID, and IIV4-ID overall similar observations were made. There were no data mining findings for GBS or anaphylaxis for these influenza products either.

There was a total of 58 reports of pregnancy in VAERS for the season following IIV3 or IIV4. The median maternal age was 32 years, with a range of 14 through 44 years of age. Gestational age was reported in 17 (29%) cases. The median gestational age was 20 weeks, with a range of 4 to 38 weeks. The breakdown for the 17 reports was approximately one-third for each trimester. Of the 58 reports, 8 included pregnancy-specific outcomes or 14% of the total reports. There were 5 spontaneous abortions, 1 stillbirth, and 2 cases of vaginal bleeding. The overwhelming majority of reports either were non-pregnancy specific such as injection site reactions and other non-pregnancy specific events, or no AE report. There was a total of 7 LAIV4 reports, none of which included any pregnancy-specific events. In fact, 5 of the 7 had no AE.

In summary of VAERS surveillance for the 2015-2016 influenza season, no new safety concerns were detected for IIVs, LAIV4, ccIIV3, or RIV3. Surveillance for the 2016-2017 influenza season will include enhanced safety monitoring for the following:

- ❑ Adjuvanted influenza vaccine (Fluad®)
- ❑ IIV4-ID (Fluzone® Intradermal Quadrivalent)
- ❑ Pregnancy reports
- ❑ Anaphylaxis reports in persons with a history of egg allergy

Turning to FDA near real-time surveillance, for GBS following influenza vaccination in Medicare beneficiaries for the 2015-2016 influenza season,

FDA conducts near real-time surveillance for GBS following influenza vaccination every influenza season in collaboration with CMS.
Weekly statistical testing compares GBS rates in the current season with rates in the prior three seasons in the Medicare database. During 2015-2016 season, there were 15.4 million IIV administrations. This includes all IIV products combined comprised primarily of standard dose IIV3, IIV4, and High-Dose IIV.

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FDA's 2015-2016 season surveillance showed a GBS rate increase following IIV of small magnitude, with 7.25 cases/million IIV vaccinees in comparison to an average of 5.45 cases/million IIV vaccinees for the past three seasons. The limitations of surveillance include the fact that it was a comparison of current to historical data, this is a claims-based analysis, there was a change from ICD-9 in the previous seasons to ICD-10 in the 2015-2016 season, and there was no control for confounders. End-of-season analysis using self-controlled designs has been initiated.

As a reminder, the Vaccine Safety Datalink (VSD) was established in 1990 and is a collaboration between CDC and 9 integrated healthcare plans. VSD collects data on over 9 million persons per year, which is approximately 3% of the US population. VSD links vaccination data to health outcome data. VSD includes vaccination records; health outcomes from hospitalizations, emergency department (ED) visits, and outpatient encounters; and information on patient characteristics. These are all linked by unique identifiers into a large linked database that CDC uses for surveillance and epidemiologic studies.

The outcomes assessed for the end-of-season analysis for 2015-2016, which are the same as assessed last season, are shown in the following table:

Pre-Specified Outcome	Age Group	Risk Window (days)	Control Window* (days)
Anaphylaxis	**≥6 mos**	**0-2**	**7-9**
Bell's palsy	**≥6 mos to <18 yrs 18-49 yrs ≥50 yrs**	**1-42**	**-56 to -15**
Encephalitis	**≥6 mos**	**1-21**	**-56 to -15**
Guillain-Barré syndrome	**≥6 mos**	**1-42**	**43-84**
Seizures	**6-23 mos 24-59 mos**	**0-1 for IIV 0-14 for LAIV**	**14-20 for IIV 15-29 for LAIV**
Transverse myelitis	**≥6 mos**	**1-21**	**-56 to -15**

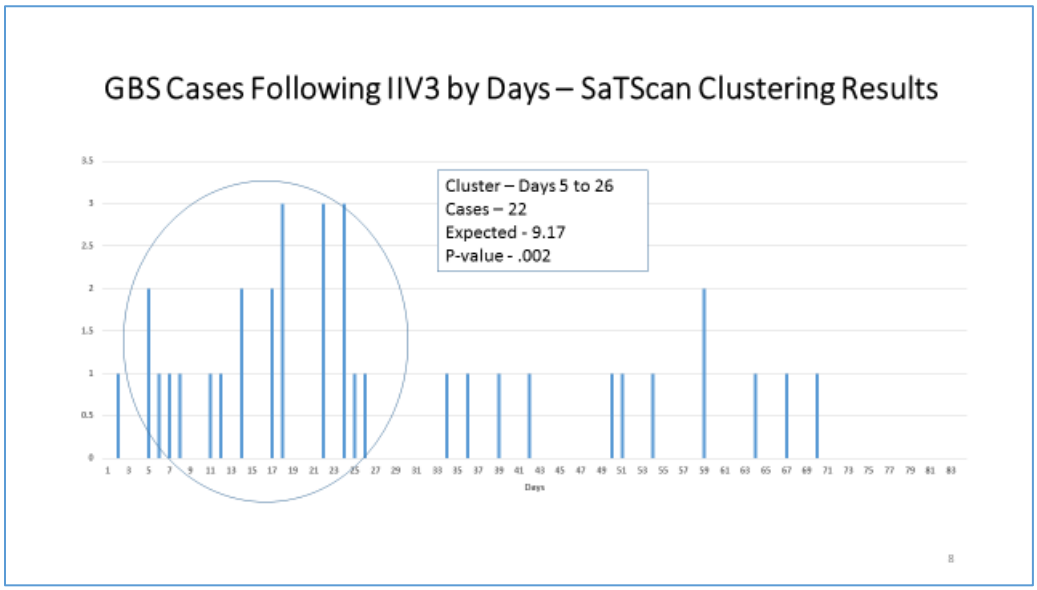
In terms of the number of Dose 1 doses administered in the VSD for this season, there were roughly 3.2 million IIV doses and relatively small amounts of vaccine doses administered for the other products. Because of this, the end-of-season focused on IIV3. There is not enough data on the other products to achieve meaningful results.

Because of the transition from ICD-9 to ICD-10 in 2015, VSD analysis was limited to analysis of ICD-10 data, specifically IIV3 doses administered after October 1, 2015. A self-controlled risk interval (SCRI) analysis was conducted. There was a concern about the transition from ICD-9 to ICD-10 and how that might impact the analysis, so the decision was made to assess ICD-10 data only for the current season using an SCRI design, which avoids the problems of the current versus historical ICD-10 versus ICD-9 issues. GBS was the signaling outcome in the 2015-2016 season. The risk window for GBS in this analysis was Days 1 through 42 (the biologically plausible risk interval) and the comparison window was days 43 through 84. The incident definition was "first occurrence in a year." The SCRI design assesses vaccinated cases only,

each patient serves as his or her own control, and the goal is to look for events in the risk window and events in the comparison window.

For those greater than 6 months of age, there were 27 cases in the risk window and 4 in the comparison window. That is a relative risk of 3.38, which is statistically significant. In those less than 65 years of age (6 months through 64 years of age), there were 14 cases in the risk window and 4 cases in the comparison window. That is a relative risk of 3.5, which is statistically significant. In individuals 65 or more years of age, there were 13 cases in the risk window and 4 cases in the comparison window. That is a relative risk of 3.25, which is statistically significant. The next model assessed inpatient or ED encounters for all individuals greater than 6 months of age. There were 18 cases in the risk window and 6 in the comparison window. The relative risk is 3, which is statistically significant. A quick chart review was performed for inpatient or ED encounters in those greater than 6 months of age. The quick chart review included an electronic medical record review to confirm a case as an incidence case, with a diagnosis by a neurologist. The relative risk was 3.67, which was statistically significant. In terms of the general results from the 2014-2015 season for all ages, there were 18 cases in the risk window and 13 in the comparison window. The relative risk was 1.38, which was statistically significant. The take-home message is that, for the current season assessing the risk of GBS associated with IIV using various models with different ages and different settings and conducting a quick chart review, a statistically significant relative risk is consistently being observed of 3 to 3.6 in this preliminary analysis.

The following chart reflects the GBS SaTScan™ clustering results in the VSD using automated data for the 2015-2016 influenza season:



In summary, VSD identified a significantly elevated relative risk of 3.67 (95% CI: 1.02, 13.14) using the SCRI method in the quick chart review analysis. The corresponding attributable risk for GBS following IIV3 is approximately 2.6 additional GBS cases per million doses administered. VSD will continue to further evaluate the association by conducting chart reviews of all GBS cases (inpatient, emergency department and outpatient), and by conducting a case-centered analysis that adjusts for seasonality of both IIV3 administration and of GBS and other potential confounders.

To summarize influenza safety monitoring for the 2015-2016 season, no new safety concerns were detected in VAERS surveillance. FDA surveillance for GBS following influenza vaccination in Medicare beneficiaries showed a GBS rate following IIV of 7.25 cases per million compared to an average of 5.45 for the prior three seasons. Further assessment using self-controlled methods is in progress. For CDC VSD end-of-season analysis, a signal was identified for GBS following IIV3 in the SCRI design. Estimated attributable risk is 2.6 GBS cases per million IIV3 doses administered. Signal assessment using detailed chart review and case-centered analysis is in progress. The preliminary GBS risk estimate appears consistent with that observed in some previous influenza seasons.

In conclusion, the association between IIV and GBS is not new. This has been observed in the past. The data have been variable across seasons. If there is an increased risk, it is small on the order of 1 to 2 additional cases per 1 million doses administered. The preliminary risk estimates observed for this season is similar to what has been observed in some past seasons. The CDC and FDA need to perform additional assessments on these signals. The findings need to be placed in the context of the known benefits of influenza vaccination in preventing disease and complications from influenza. Influenza disease is actually a risk factor for GBS.

Discussion Points

Noting that introduction of newer vaccines such as the quadrivalent high-dose might have some safety implications, Dr. Kempe asked what percent of the FDA data included quadrivalent or high-dose.

Dr. Shimabukuro responded that CDC monitors those vaccines, but the data are so sparse there are not meaningful results. He did not have the breakdown of that information for the FDA, but indicated that he could follow up with them.

Dr. Karron asked for a reminder of the risk associated with GBS as associated with influenza infection.

Dr. Shimabukuro said that while he did not have exact numbers, there are pretty well-established risk factors for GBS, including upper respiratory illnesses, of which influenza is one; gastroenteritis, specifically campylobacter; surgery; age; pregnancy; and others.

Dr. Bennett asked if there was an estimation of what percentage of GBS cases might be associated with influenza vaccine.

Dr. Shimabukuro said that while he did not know specifically, when studies have controlled for influenza disease, it has basically lowered the risk. The risk went away.

Dr. Stephens asked whether the question with ICD-9 and ICD-10 was a sensitivity issue.

Dr. Shimabukuro responded that his understanding was that it is a one-to-one, or a single outcome compared to a single outcome. The ICD-9 diagnosis was acute infective polyneuritis, while the ICD-10 diagnosis is GBS. If anything, the ICD-10 should be a better code. Based on the preliminary work done, this does not seem to be impacting the surveillance. CDC has work underway to assess the impact in general of the ICD-9 to ICD-10 transition.

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Dr. Moore said that from work done in her state and others, in efforts to correlate claims data with actual medical records, there is not good correlation between the diagnosis according to the claims data and the medical record review. She noted with pleasure that the final results involve actual record reviews to confirm the diagnosis of GBS in doing these assessments. Obviously, with such small numbers over millions of doses administered, it can swing one way or the other very easily. She asked when those data would be available.

Dr. Shimabukuro replied that he was uncertain when the results would be available. He will have to follow-up with FDA. CDC is in the process of reviewing the cases, but he did not have a specific hard date on when the reviews and the case-centered analysis would be completed.

Dr. Walters asked whether the years in which the association had been seen happened to track with any predominant strains circulating that year. He wondered whether it pertained to circulating disease or the vaccine strain.

Dr. Shimabukuro responded that the last time an increased risk was observed was during the pandemic, which was with monovalent H1N1. However, it was not observed in seasonal vaccine that year. This is the first time since the pandemic that an increased risk has been observed for GBS. It is the first time an increased risk has been observed with H1N1-containing seasonal vaccines. Therefore, options are being explored to determine how to further assess multiple years of data. There was a strain change in the past season. It was the same for the two prior seasons. There was a strain change in the As and one of the Bs for this season. The vaccine changes year-to-year, and it is not unreasonable to think that there may be differences in reactogenicity based on changes in the vaccine. However, it is not clear whether these findings could be attributed to any strain change.

Dr. Gorman (NIH) noted that the increased number of cases in the 2009 monovalent was approximately 1 case per million doses, so about half. Recognizing all of the confounders already mentioned, he thought that they were in the same range for monovalent.

Dr. Shimabukuro responded that several studies showed increased risk. In the meta-analysis, it was 1.6 and this is 2.6. If there is an increased risk, it is on the order of 1 to 2 additional cases per million doses administered.

Dr. Gorman (NIH) asked when the diagnosis of GBS is made—the day the symptoms start or the day the diagnosis is made for attributing the diagnosis.

Dr. Shimabukuro replied that there are automated analysis and chart confirmed analysis. For automated analysis, it is really based on the dates in the administrative database. When a chart confirmation is done, an effort is made to pinpoint symptom onset to determine if that is an incident case.

Dr. Gorman (NIH) pointed out that GBS, like most diseases, has a distribution of seriousness. He asked whether Dr. Shimabukuro had any sense of whether GBS after influenza vaccination is more or less severe than GBS in general.

Dr. Shimabukuro responded that there is not a difference in the severity of course regardless of whether it occurs after vaccination or is a spontaneous case.

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Dr. Middleman (SAHM) thought there was a similar issue of GBS that was initially associated with meningococcal vaccination, and then it was found that the campylobacter season was playing a role. She asked whether Dr. Shimabukuro felt that by using self-controlled analysis this is a potential risk in that vaccination was probably given during that same kind of season and that by using self-controls, they may have left the campylobacter season.

Dr. Shimabukuro replied that there is seasonality to GBS. One reason CDC is conducting the case-centered analysis is because that controls for seasonality of GBS. It is possible that seasonality is a confounder, but that is part of the assessment.

Dr. Thompson (NVAC) asked how reports are made to the VSD and whether there is a potential that things that happen later in the context of a patient's time since the vaccine might have less likelihood of being reported, or whether there was no concern about reporting bias to the VSD.

Dr. Shimabukuro responded that VAERS is a spontaneous reporting system that depends upon people to send in reports. VSD is a large linked database that utilizes electronic health records, so no one is actually reporting into VSD. These data are captured in the health systems administering people's health insurance programs. While there may be biases to VSD data. Reporting bias should not be one of them.

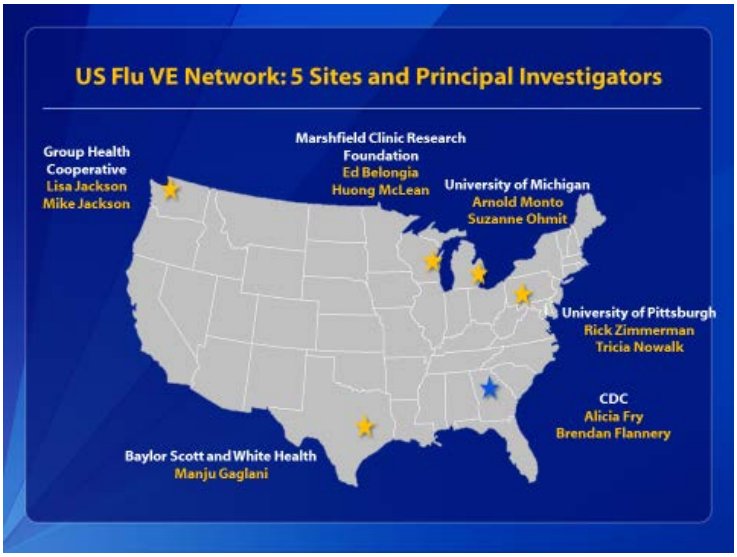
Vaccine Effectiveness Update

Dr. Brendan Flannery
Influenza Division
Centers for Disease Control and Prevention

Dr. Flannery reviewed end-of-season estimates of influenza vaccine effectiveness for the 2015-16 season from the US Flu VE Network, and presented data comparing LAIV and IIV effectiveness among children and adolescents aged 2 through 17 years during the season.

In terms of the end-of-season estimates, the percentage of visits for influenza-like illness (ILI) by week from the Influenza-Like Illness Surveillance Network (ILINet) over the past 6 seasons since the 2009-2010 season shows the late increase in ILI activity observed in the 2015-2016 season, with peak ILI activity occurring in March. This is one of the few seasons that has had a peaked in March. Influenza A/H1N1pdm09 virus predominated with circulation of both B virus lineages.

The US Flu VE Network, funded by CDC, conducts annual studies of influenza vaccine effectiveness at five sites within the US, shown in on the following map along with the Principal Investigators (PIs) at each site:



Of note, the same sites have participated in the US Flu VE network over the past 5 influenza seasons. To briefly review methods for the VE estimates presented during this session, US Flu VE network sites enroll outpatients 6 months of age and older who present with an acute respiratory illness with cough of 7 or fewer days duration. This analysis includes patients enrolled from November 2, 2015 through April 15, 2016. All enrolled patients are tested for influenza by reverse transcription-polymerase chain reaction (RT-PCR). VE estimates are based on the test-negative design, comparing vaccination odds among influenza PCR-positive cases versus PCR-negative patients as the control group. For this analysis, vaccination is defined as receipt of at least one dose of any 2015-2016 influenza vaccine and includes partially vaccinated children. Vaccination status was determined from medical records, immunization registries, or self-report with plausible timing and location of immunization, referred to as plausible self-report, for patients aged 9 years and older. VE is estimated as 1 minus the adjusted odds ratio times 100%. Odds ratios were adjusted for study site, age, self-rated general health status, race/Hispanic ethnicity, interval (days) from onset to enrollment, and calendar time.

A total of 7,563 patients were enrolled during the season, of whom 82% were influenza negative (controls) and 18% were influenza positive. The predominant influenza virus among enrolled patients was A/H1N1pdm09, with cases due to both B lineages and only 6% of confirmed cases due to A/H3N2, the predominant virus during the 2014-2015 season. All viruses from enrolled patients that were antigenically characterized were similar to vaccine reference viruses, with limited genetic variability among H1N1pdm09 or B viruses, and mixed circulation of two clades of H3N2 viruses, all characterized as vaccine-like.

The overall adjusted VE estimate for all vaccines was 47% with 95% confidence interval from 39% 53%. VE estimates were statistically significant for patients of all ages with the exception of adults aged 50 through 64 years. Restricting to inactivated vaccines only, adjusted VE was 49%, very similar to the estimate for all vaccines. The adjusted VE against illness associated with A/H1N1pdm09 virus was 41%, with 95% confidence interval from 31% to 51%. Again, VE was statistically significant for all ages except adults aged 50 through 64 years. Restricting to inactivated vaccines, adjusted VE was 44%. For all ages combined, adjusted VE against A/H3N2-related illness was 45% with confidence intervals from 9% to 66%. For B Yamagata viruses, adjusted VE was 55% with confidence intervals from 41% to 66%, and for B Victoria

lineage viruses, adjusted VE was 55% with confidence intervals from 38% to 68%. Estimates restricted to inactivated vaccines were similar to overall estimates.

Over 2000 children were included in the analysis of LAIV and IIV effectiveness among children 2 through 17 years of age by influenza virus type and subtype. Of these, 18% were influenza positive and almost half of the influenza cases were H1N1pdm09, with somewhat higher numbers of B/Victoria lineage viruses than B/Yamagata. Regarding the methods for this analysis, vaccination was defined as at least one dose, including partially vaccinated children. Only documented doses were considered for children 2 through 8 years of age. Documented doses and plausible report of vaccination were considered vaccinated for those 9 through 17 years of age. Vaccine type was determined from medical record or parent report if the record had no information. Odds ratios were adjusted for study site, age, and listed variables, including calendar time in biweekly intervals. Of note is that because of the importance of this analysis this season, all analyses were independently confirmed by Jessica Pruszynski at Baylor Scott & White Health. A total of 154 enrolled children were excluded from this analysis, primarily because their illness onset occurred prior to confirmed influenza circulation at that site, or illness onset occurred within 14 days of vaccination.

In terms of adjusted VE estimates for LAIV and IIV among children 2 through 17 years of age against any influenza A or B and for A/H1N1pdm09-related illness and by B lineage, estimated LAIV effectiveness against any influenza was 3% with confidence intervals including zero. Estimated IIV effectiveness was 63% with a confidence interval from 52% to 72%. Estimates for LAIV effectiveness against A/H1N1pdm09 and B viruses were not statistically significant, while estimates for IIV were similar to the VE estimate against any influenza. Among children 2 through 8 years of age, no significant VE was demonstrated against any influenza, A/H1N1pdm09 or influenza B. The lowest point estimates were observed against A/H1N1pdm09 viruses. Similarly, estimates of LAIV effectiveness were not significant among patients 9 through 17 years of age, although the point estimate for VE against A/H1N1pdm09 was higher than among children 2 through 8 years of age. The adjusted odds of influenza was also estimated of influenza among LAIV versus IIV vaccinated children similar to an analysis or relative effectiveness, excluding unvaccinated children. In this analysis, children who received LAIV had significantly higher odds of influenza due to any virus type or due to A/H1N1pdm09 compared to IIV vaccinated children. Odds ratios greater than 1 favor IIV. The result for influenza B was not statistically significant.

In addition to US Flu VE data, data also were received from the Department of Defense (DoD) laboratory-based influenza surveillance system. These data include military dependents 2 through 17 years of age who presented to participating facilities during the 2015-2016 season with ILI. Laboratory testing by clinical indication was by RT-PCR or culture, and the study used a test-negative design with RT-PCR negative controls. Vaccination status was determined from electronic medical records. The estimates were adjusted for two age groups and 3 time periods during the season. Regarding adjusted VE estimates for military dependents 2 through 17 years of from the DoD laboratory-based influenza surveillance system, estimated VE against A/H1N1pdm09 associated illness for LAIV was 15% with confidence intervals including zero. Estimated VE for IIV against A/H1N1 was 68% and was statistically significant. Numbers of influenza positive cases among vaccinated children were small for A/H3N2 and B, but estimated VE against influenza B was statistically significant for both LAIV and IIV in this system [Lt. Col. Susan Federinko, US Air Force].

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This analysis is subject to limitations. First, the final end-of-season analyses are pending, since prior season vaccination status is pending for one site and chronic conditions were not included in adjusted estimates. However, data were received from all five sites for prior end-of-season vaccination and chronic conditions. Those will be included in updated analyses, which have been run already and did not change the results presented during this session. In previous seasons, final analyses have been similar to preliminary end-of-season results. Secondly, there is limited precision for some VE estimates due to small numbers of influenza cases in some strata.

In summary, the 2015-2016 influenza season was a late season, with peak enrollment at US Flu VE network sites in March and mixed circulation of A/H1N1pdm09 and B viruses. Overall vaccine effectiveness for any vaccination was 47% against influenza A and B. Point estimates were 41% for A/H1N1pdm09 and 55% for B viruses. Vaccine effectiveness for LAIV was significantly lower than IIV among children 2 through 17 years of age. No significant LAIV effectiveness was observed against A/H1N1pdm09 or B viruses. Relative effectiveness significantly favored IIV over LAIV against A/H1N1pdm09-associated illness.

2015-16 US Influenza Vaccine Effectiveness
Influenza Clinical Investigation for Children (ICICLE) Study

Chris Ambrose, MD
Vice President, Infectious Disease
US Medical Affairs, MedImmune

The Influenza Clinical Investigation for Children (ICICLE) VE study demonstrated significant overall VE for LAIV4 and IIV in US children 2 through 17 years of age in 2015-2016. For LAIV4, VE was 46% (95% CI: 7, 69) and for IIV VE was 65% (95% CI: 48, 76). Supporting those results are similar results in a 2015-2016 in a test-negative VE study in the United Kingdom (UK) and a large cohort study in Finland. Including the DoD study just presented, these LAIV4 VE estimates are similar to VE observed with IIV in children in recent seasons (e.g., 2011-2012 and 2012-13)[1-3]

Reduced effectiveness has been observed this last season relative to IIV vaccine for LAIV. But the range of the point estimates in these studies is within the range observed in other seasons. There is no explanation at present for the difference between these studies compared to the CDC LAIV4 VE estimate, particularly because the CDC and ICICLE study methods are very similar and in past seasons have reached similar estimates of effectiveness. The differences may relate to a limited sample size (less than 150 children have received LAIV), statistical power, or limitations of observational study design [[1]Ohmit et al, CID 2013; [2]McLean et al, JID, 2014; [3]Flannery B. ACIP presentations. 2014]. Similar to the CDC VE study, ICICLE is an observational, test-negative design. Community-dwelling children 2 through 17 years of age were enrolled at the following US sites:

- ❑ Marshfield Clinic, Wisconsin (Edward Belongia)*
- ❑ Baylor Scott & White Health, Texas (Manjusha Gaglani)*
- ❑ Vanderbilt University, Tennessee (Marie Griffin)
- ❑ Wake Forest University, North Carolina (Katherine Poehling)
- ❑ Akron Children's Hospital, Ohio (Blaise Congeni)
- ❑ HealthPartners Como Clinic, Minnesota (Poornina Kavathekar)
- ❑ Kaiser Permanente, Oregon (Allison Naleway)

- University of Florida, Gainesville (Kathleen Ryan)

Children are enrolled who are seeking outpatient care for febrile acute respiratory illness with onset <5 days. Like the CDC study, subjects are excluded who were vaccinated <14 days before symptom onset. Nasal swabs are tested by PCR using a respiratory viral panel. This is a subtle difference from the CDC study in that MedImmune knows the outcome for influenza and other respiratory viruses, which allows them to perform an important secondary analysis comparing cases being influenza positive to controls being positive with another respiratory virus. That was in addition to the study requested by the FDA, because this is an FDA post-marketing commitment study. Sites are monitored up to 3 times per season to confirm data accuracy. That is important to ensure good clinical practice and because it is an FDA post-marketing commitment. Like the CDC study, the Medimmune study results were independently analyzed [*Also participate in CDC VE study but at different clinic sites, so the same patients are not being enrolled].

The ICICLE study enrolled 1,238 children from November 30, 2015 to April 15, 2016. Of these, 226 were excluded from analysis for the following reasons:

- Enrolled before or after influenza circulation: n=215
- Vaccination <14 days before illness: n=7
- Missing documentation of vaccination date and/or type: n=3
- Lack of signed consent: n=1

This resulted in 1,012 subjects being retained for analysis. Of these, 594 were unvaccinated children, 101 were LAIV4 recipients, and 317 were IIV recipients.

The 2015-2016 ICICLE population characteristics by vaccine group are delineated in the following table:

	No Vaccination (n=594)	**LAIV4 (n=101)**	**IIV (n=317)**
2 to 4 years 5 to 8 years 9 to 17 years	28% 36% 36%	33% 47% 20%	36% 36% 28%
Privately insured	45%	56%	53%
Chronic condition	16%	6%	26%
Prior vaccination in 2014-2015	32%	73%	77%

This is an observational study, so there are differences in the children who were unvaccinated versus those whose parents elected to receive LAIV4 versus those who elected to receive IIV. Some of the greatest differences are illustrated in the table in terms of age, insurance status, chronic conditions, and prior vaccination.

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In terms of the overall adjusted estimates of effectiveness for the two vaccines, overall effectiveness of LAIV4 was 46% with similar estimates for H1N1 A and B. Over 60% of isolates detected were H1N1, so there would not have been an overall statistically significant effectiveness if there was not a trend of effectiveness for H1N1. For IIV, the estimates were 65%, 71% for H1N1, and 56% for B. With the greater sample size, the IIV estimates are much more precise. For children receiving any vaccine or at least one dose of vaccine, secondary analyses confirmed that the results are similar for those fully vaccinated, excluding those negative for any respiratory virus, and excluding those with high-risk conditions. The point estimates are all the same. When those with high-risk conditions are excluded, for LAIV the estimate of H1N1 VE is statistically significant.

Regarding overall VE for LAIV4 and IIV by calendar time, an interim analysis was performed at the end of February that showed an estimate of high effectiveness. As time went on and more subjects were enrolled and more cases were identified, the point estimate of VE decreased to 46%. Waning immunity is a possibility, or it could just be gaining additional precision as more subjects are enrolled and more cases are identified.

Clearly, the ICICLE results differ from CDC's results for LAIV. Supporting the ICICLE results is a 2015-2016 VE study by Public Health England (PHE). The PHE study is a test-negative VE study in UK children 2 through 17 years of age (N=279). 2015-2016 is the third year of the UK vaccination program. LAIV4 is the predominant vaccine used in UK children without contraindications. Vaccine uptake has been achieved in each of the three years of approximately 40%. The estimated overall LAIV4 VE was 57.6% (25.1, 76), which was statistically significant [Public Health England statement, June 22, 2016 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/530756/Influenza_vaccine_effectiveness_in_primary_care_in_children.pdf]. The UK is aware of the data from the US and Finland, and is proceeding with their program for the upcoming season.

A 2015-16 VE study by the Finland National Institute for Health and Welfare (THL) was presented at the Nordic Vaccine Meeting in April 2016. This is a cohort study in Finland of 58,857 children 24 through 35 months of age. They are using the comprehensive healthcare utilization and administrative databases that exist in Finland to comprehensively track outpatient visits, influenza positive tests, and vaccinations. Like the US and UK, the predominant A strains were H1N1. The overall unadjusted VE of LAIV was 46% (22, 63) and was statistically significant, and IIV was 60% (27, 78). Most of the cases were A strains, and the estimates were similar for LAIV at 48% and 78% for IIV.

The PI was consulted because these were unadjusted early estimates. However, the initial adjustments have been made and the estimates are very similar, changing by only a single percentage point and still being statistically significant. Finland routinely vaccinates children 6 through 35 months of age, up to 60% of the LAIV recipients were previously vaccinated [Nohynek et al., Nordic Vaccine Meeting, April 2016. Confirmed by personal communication June 21, 2016]. The overall VE for all three studies is statistically significant with the estimates being 46% for US ICICLE, 58% PHE, and 46% Finland THL.

Based on data from recent seasons for LAIV and IIV across the different subtypes, highly variable results have been observed for H1N1pd09 for both vaccines, but especially for LAIV. In 2009, CDC described the high effectiveness of LAIV, albeit on a very small sample, and low effectiveness of IIV. In 2010-2011 with the trivalent formulation and 2013-2014 quadrivalent formulation, the reverse was observed in the CDC and ICICLE studies. Interestingly, in Canada

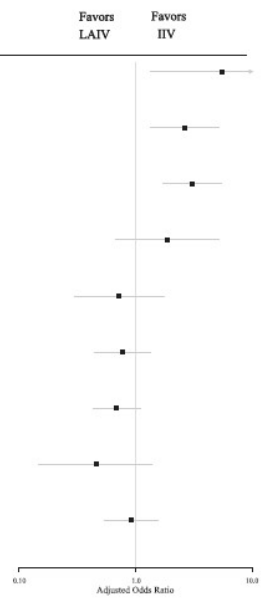
in 2013-2014, there was high effectiveness of LAIV that was confirmed by a cluster randomized study conducted there in elementary school-aged children. Clearly, there have been highly variable results for the LAIV H1N1pdm09 strains. All of these studies were conducted with the A/California strain.

These variable results led to the investigations of the stability of that strain, which was found to be heat unstable. It was confirmed in the laboratory that real-world exposures that were confirmed to have occurred could negatively impact the potency of the vaccine upon administration. This led to the replacement of that strain with a more heat-stable H1N1pdm09 LAIV strain, the A/Bolivia strain that was used in the 2015-2016 vaccines. In light of the recent data, there is clearly still a biological phenomenon that is reducing the effectiveness of the H1N1 LAIV strains.

Significant research is underway to better understand the biology of the strains so that they can be further optimized in the future. For 2010-2013 VE of IIV and LAIV against Matched H3N2 in children, there was comparable effectiveness of LAIV and IIV with something of a trend toward higher effectiveness with LAIV perhaps. The 2010-2015 VE of IIV and LAIV against influenza B in children was very comparable.

Data from a CDC evaluation of seasonal effectiveness of LAIV and IIV in children 2 through 17 years of age were summarized in a publication and are shown here:

Influenza Type/ Subtype	Influenza Season	Vaccine Type	Total	No. (%) Positive	aOR
A/H1N1pdm09	2010–2011	LAIV	102	7 (9)	5.53
		IIV	420	9 (2)	REF
	2013–2014	LAIV	154	24 (16)	2.65
		IIV	459	27 (6)	REF
	Combined*	LAIV	256	31 (12)	3.08
		IIV	879	36 (4)	REF
A/H3N2	2010–2011	LAIV	103	8 (8)	1.89
		IIV	431	20 (5)	REF
	2011–2012	LAIV	150	10 (7)	0.73
		IIV	490	42 (9)	REF
	2012–2013	LAIV	171	27 (16)	0.77
		IIV	523	99 (19)	REF
	Combined*	LAIV	321	37 (12)	0.69
		IIV	1013	141 (14)	REF
B	2010–2011	LAIV	100	5 (5)	0.46
		IIV	448	37 (8)	REF
	2012–2013	LAIV	174	30 (17)	0.93
		IIV	520	96 (18)	REF



Consistent with what Dr. Ambrose presented, the trend of favoring IIV for H1N1pdm09, but in some cases trending toward favoring LAIV for H3N2 and B [Chung et al, Pediatrics, 2015].

Any presentation of these studies requires a presentation of the limitations. There is a potential for bias in observational studies because the treatment is not being randomly assigned. Also, VE estimates can be imprecise and vulnerable to random effects. This is particularly true in this season where there is a small number of recipients in all of the studies (<150) in the CDC and ICICLE study, which makes it vulnerable to random effects. In addition to what is expected from

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cohort studies and others, multiple assumptions must be met to ensure study validity of the case-control approach. Those are well-summarized by Jackson et al in *Vaccine*. These are hard to check, but are the underlying assumptions for the framework of these studies providing valid estimates [Jackson et al., Vaccine. 2013].

In conclusion, three studies (four if the DoD study is included) demonstrated similar, statistically significant overall VE of LAIV4 in 2015-2016 in children 2 through 17 years of age of 46% to 58%. These estimates are similar to VE observed with IIV in children in recent seasons[1-3], although in the last season, lower effectiveness is being observed with LAIV compared to IIV. The differences from these four estimates compared to the CDC VE LAIV4 estimate may be due to limited sample, statistical power, and limitations of observational study design. MedImmune agrees that healthcare providers (HCP) should be made aware of these data so they can make informed decisions and have informed discussions with their patients in the upcoming season. AstraZeneca/MedImmune will share available 2015-2016 VE data with US HCPs to inform discussions of 2016-2017 vaccine options with patients. Research is underway to improve LAIV A/H1N1pdm09 strains in future seasons [[1]Ohmit et al, CID 2013; [2]McLean et al, JID, 2014; [3]Flannery B. ACIP presentation. December 2014].

<u>LAIV Versus IIV Effectiveness: Summary of Evidence Since 2009</u>

Dr. Brendan Flannery
Influenza Division
Centers for Disease Control and Prevention

As background for discussion, Dr. Flannery presented a brief review of LAIV and IIV effectiveness data in children and adults since 2009. To summarize the two presentations during this session for the 2015-2016 season:

1) Data from the US Flu VE network indicate no LAIV effectiveness against A/H1N1pdm09 but significant VE for IIV
2) Data from the US Department of Defense test-negative study indicate no LAIV effectiveness against A/H1N1pdm09 but significant VE for IIV
3) In a Medimmune presentation of data from the ICICLE test-negative study, the VE estimate against A/H1N1pdm09 was not significant despite a higher point estimate, but this study also identified significant VE for IIV.
4) All studies reported higher VE for IIV than LAIV although point estimates varied

CDC received information from researchers from other countries where LAIV is used. All countries used quadrivalent LAIV this season. From a test-negative VE study in the UK, preliminary data indicate significant adjusted VE for LAIV against any influenza A or B among children 2 through 17 years of age. A national observational cohort study conducted in Finland reported significant unadjusted estimates of LAIV effectiveness against influenza A, mainly H1N1pdm09, among 2-year olds. Point estimates were higher for IIV, but confidence intervals overlapped. There was no estimate of LAIV effectiveness in children from the Canadian test-negative study this season, nor was there an estimate from Israel where LAIV was not available this season.

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For each of the last three seasons, the US Flu VE Network has identified no significant effectiveness of LAIV against medically attended influenza. In two of these seasons, the predominant influenza virus was A/H1N1pdm09 and in one season, antigenically drifted A/H3N2 viruses predominated. In the first three seasons, LAIV was trivalent. Quadrivalent LAIV replaced LAIV3 in 2013-2014. It was not possible to separate any effects of quadrivalent vaccine during the last three seasons from factors related to the circulating viruses during those seasons. In the US Flu VE network, three seasons since 2009 had enough A/H1N1pdm09 circulation to estimate LAIV and IIV effectiveness. None of the estimates for LAIV were significant, and relative effectiveness significantly favored IIV in all three of these seasons. In three seasons since 2009, LAIV and IIV showed similar effectiveness against influenza A/H3N2, and in 2014-2015, as previously mentioned, neither LAIV nor IIV provided significant protection against the predominantly drifted H3N2 viruses. Against influenza B viruses, estimates of LAIV and IIV effectiveness were similar during three seasons since 2009. For the 2015-2016 season, the estimate for LAIV effectiveness against influenza B viruses was not statistically significant, while significant effectiveness was found for IIV. The relative effectiveness analysis did not find a significant difference between IIV and LAIV against influenza B viruses in 2015-2016.

For the 2013-2014 season, all LAIV in the US was quadrivalent and all LAIV outside the US was trivalent. There were three observational VE studies conducted in the US during 2013-2014: US Flu VE study, MedImmune's ICICLE post-marketing study, and the DoD-led study among military dependents. None of the three studies identified significant VE for quadrivalent LAIV against the predominant H1N1pdm09 virus, while all found significant VE for trivalent inactivated vaccine against H1N1pdm09. These data led to a change in the LAIV H1N1pdm09 HA component from A/California to A/Bolivia. The 2015-2016 season is the first season in which LAIV contains the updated H1N1pdm09 construct. Finally, there was one CDC-funded household cohort study conducted by the University of Michigan that found a high point estimate of 82% for LAIV effectiveness, but did not find significant VE for either LAIV or IIV due to small numbers of influenza cases in the cohort.

During 2013-2014, CDC began conducting a relative effectiveness analysis of US Flu VE data as part of the GRADE consideration for the preferential recommendation of LAIV. The analysis is modeled after the LAIV-IIV comparative efficacy studies conducted before 2009, comparing odds of influenza in vaccinated children. Relative effectiveness against H1N1pdm09 significantly favored IIV in two seasons, 2010-2011 and 2013-2014. There were no significant differences in LAIV versus IIV against A/H3N2 or B viruses in the seasons indicated.

During 2013-2014, several studies of trivalent LAIV were conducted outside of the US. Two observational studies conducted outside the US during the 2013-2014 seasons, one in the UK, and one in Canada, did not find statistically significant effectiveness of trivalent LAIV despite high point estimates in the observational VE study in Canada. Of note, although the UK study did not find effectiveness for trivalent LAIV against the A/H1N1pdm09 virus, an ecologic analysis observed a trend toward reduced influenza incidence in LAIV pilot areas in which about 50% of school children in the target age range received LAIV. In addition, in a cluster-randomized trial of trivalent LAIV compared to trivalent IIV, influenza incidence was significantly lower in LAIV vaccinated students and their contacts compared to students vaccinated with IIV and their contacts during the 2013-2014 season when H1N1pdm09 predominated.

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In terms of data comparing LAIV and IIV effectiveness in adults from the DoD Global Laboratory-based Influenza Surveillance System, these data are from published estimates of LAIV and IIV effectiveness among active military aged 18 years and older for 2010-2011 through 2013-2014. Estimates for 2011-2012 include dependents and children. The VE estimates are from test-negative studies using the laboratory-based surveillance system, and are against all influenza types A or B. Nonsignificant estimates were reported for LAIV effectiveness against any influenza in the 2010-2011 and 2013-2014 seasons, and for IIV in 2013-2014. Adjusted estimates were similar for LAIV and IIV during 2011-2012 and 2012-2013 [Eick-Cost 2012; MacIntosh 2013; Eick-Cost 2013; Cost 2014].

Finally, there are limited data on the serologic response to the A/H1N1pdm09 LAIV vaccine component or shedding of vaccine virus. One small Norwegian study of 38 children vaccinated with trivalent LAIV showed reduced antibody response measured by HI titer increase to the H1N1pdm09 component compared to H3N2. Serologic studies by US Flu VE network sites have shown limited increase in H1N1pdm09 titers following quadrivalent LAIV vaccination even among children with low pre-vaccine baseline HI titers. Another small study demonstrated that shedding of A/H1N1pdm09 vaccine virus following LAIV was reduced after repeat LAIV vaccination, but found no influence of pre-vaccination serum antibody titer on H1N1 vaccine virus shedding. Unfortunately, serologic and viral shedding data may provide little information to identify problems with the A/H1N1pdm09 vaccine component without a better understanding of correlates of protection for LAIV [[1] Mohn, JID 2014; [2]US Flu VE network (unpublished); [3]Ilyushina, JID 2014].

To summarize the available data for LAIV effectiveness since 2009, preliminary US Flu VE Network data for 2015-2016 indicated that quadrivalent LAIV offered no significant protection against influenza A (H1N1)pdm09 in children aged 2 through 17. Poor VE for quadrivalent LAIV was observed during two preceding flu seasons in children aged 2 through 17:

- 2013-2014: No significant VE for LAIV4 against A(H1N1)pdm09
- 2014-2015: No significant VE for LAIV4 or IIV3/4 against drifted A(H3N2) viruses

During previous seasons, most evidence demonstrated that LAIV3 worked as well as IIV3 against A(H3N2) and B viruses in children aged 2 through 17. There was poor VE for LAIV3/4 against A(H1N1)pdm09 in active military.

The reason for poorer overall performance of LAIV compared to IIV, particularly with regard to the A(H1N1)pdm09, over the last few seasons is not well-understood and is a subject for further study. How well the influenza vaccine works can vary by season, virus type/subtype, the vaccine, and age and other host factors of the people being vaccinated. While the causes of the low estimate of 2015-2016 VE in the US VE Network studies are not clear, some possibilities include:

- Suboptimal performance of the A/Bolivia/559/2013 (H1N1) HA vaccine strain.
- Potential interference among viruses in the quadrivalent vaccine [i.e., additional B vaccine component effects viral replication of A(H1N1)pdm09 virus].
- Reduced immunogenicity of LAIV (or replication in nasal passages?) resulting from a more highly vaccinated population in recent years; compared with populations of earlier studies, in which it is likely that a higher proportion of children were vaccine-naïve.

Discussion Points

Dr. Stanley Plotkin (Audience Member) noted that while they had heard a great deal of epidemiologic data, what struck him was the lack of immunologic data. LAIV is more complicated than IIV in the sense that one needs to assess serum responses intranasal, IgA secretory responses, and even cellular responses that have all been associated as correlates of protection. He asked whether there were any data on the recent vaccine.

Dr. Ambrose replied that he was not aware of any data on the 2015-2016 vaccine, including the A/Bolivia strain, in terms of cellular or antibody responses. As Dr. Flannery summarized, there are studies with the A/California H1N1pdm09 strain and a few others that generally show that there is shedding, antibody responses, or T-cell responses. But, they are lower than what is generally seen for other strains. It is very difficult with IIV to pinpoint an exact correlate. It is consistent with the more moderate effectiveness in that the responses are more in the moderate range.

Dr. Karron thought it had been quite challenging to find a correlate of protection for LAIV, and it is not for lack of looking. In many of the studies, there was a lot of effort to look at correlates of protection. In fact, vaccine shedding is probably a better correlate. She wondered what data exist, if any, about the relative shedding of various components. Regarding licensure of LAIV and related to Dr. Plotkin's question, at the time it was licensed it was based on immunogenicity equivalents. But, the serum antibody responses to the trivalent and the quadrivalent vaccine were very modest. At that time, the FDA specifically called for effectiveness studies to look at this issue of effectiveness of the quadrivalent preparation. Given these data about effectiveness, she wondered what the FDA's plans were.

Regarding shedding, Dr. Ambrose said that when they reviewed the comprehensive data following the 2013-2014 data, it was mixed. One study of the trivalent formulation showed relatively high shedding of the H1N1pdm09 A/California strain close to 60%. In a subsequent quadrivalent study, it was lower in the 10% to 20% range. Frustrating about that study was that the first sample was on Day 4 to 7 post-vaccination, which is after the peak shedding would occur.

Dr. Sun (FDA) said that the data are obviously of concern to the FDA. FDA has been working with CDC and MedImmune since the 2013-2014 findings. They also recognize that influenza is a very complex disease and that there are occasional surprises. The FDA always approaches these types of matters with deliberateness, especially given the fact that all of the study results have not been fully reviewed. He thought it was fair to say that the studies are not completely consistent. It is also important to recognize that the LAIV approach has offered advantages in the past for influenza over IIV, especially among certain age groups. LAIV continues to be an important alternative in the armamentarium against influenza. As part of the evolutionary process, changes have been made in order to try to address this problem. Obviously, more work needs to be done. There are additional studies that FDA would like to see from MedImmune and others. At this point, FDA is not ready to undertake a requirement for changing the prescriber's information. FDA wants to continue to work with MedImmune to find out the root cause of this phenomenon. They are also engaged in internal discussions about what else can be done.

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Dr. Harriman noted that the ICICLE study was in US children while the UK and Finland studies were in different populations. She wondered if there was any thought that those two are more likely to be influenza vaccine naïve.

Dr. Flannery responded that the ICICLE, MedImmune, and US Flu VE studies, the percentages of previous vaccination are very similar as would be expected in the US population at between 70% and 80%. They do not have the actual numbers from the UK and Finland. The sense is that the UK has had uptake in several years of a pilot program that has been expanded, so there has been relatively less exposure in that population. In the Finnish study, about 60% of the children have received vaccine. Finland does not have a universal infant vaccination program, so the LAIV and IIV program beginning in 2 year olds, a lot of those children are receiving vaccines early on in the schedule, but this is the beginning of their vaccination program. For that cohort, if they were 2 year olds and received prior vaccination, they would not have been expected to see more than just that one prior vaccination.

Dr. Bresee (SME) asked whether Dr. Ambrose knew what the VE against the H1 strain specifically is.

Dr. Ambrose responded that in the Finland study, the predominant strains were A strains and H1N1 strains. This is where there was 47% for LAIV that was statistically significant, and 78% for IIV that was statistically significant. In the UK program, he had only the overall vaccine effectiveness. His understanding was that their epidemiology last year was very similar to the US in which the predominant strain was H1N1 and they had B/Victoria strain circulating as well.

Dr. Gorman (NIH) asked whether the study in Canada was conducted on naïve children or if children had been previously vaccinated with LAIV.

Dr. Flannery responded that there was a very low vaccination rate in that cohort, so they conducted a trial. 2013-2014 was the second season, so some children were vaccinated over the two seasons. In one group, it is school vaccinations.

Dr. Romero noted that the Influenza VE Net and ICICLE studies had overlapping centers: Marshfield and Baylor Scott & White. The two sites in the ICICLE study account for one quarter of the sites, while Flu VE Net is one third of the sites. He wondered whether any comparison had been done of the VE at both of these sites, and if the analyses for the differences in VE hold up when that group alone was assessed.

Dr. Ambrose responded that for the two sites in the ICICLE study, the estimates of VE were very similar, almost identical, to the overall vaccine effectiveness observed in the entire study.

Dr. Flannery indicated that there was an extra slide, 33, in the slide set that may be helpful in terms of answering the questions related to what the differences are in the studies and at the sites. The two sites contributed LAIV-vaccinated children, but they did not have a large number. CDC's data for those two sites are very similar to the MedImmune data overall. The other sites contributed LAIV vaccinated children as well as H1N1 cases or failures in LAIV children. There were about 150 total LAIV recipients versus about 753 children enrolled who had received inactivated vaccine. CDC is not comfortable breaking down the LAIV data by site. There is some site-to-site variability, but CDC sees the overall estimate as a reflection of the whole. There are more similarities than differences in the two studies. An effect modification has not been observed of prior season vaccination. There is no explanation for prior vaccine as an

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effect modifier of what is seen as low VE for LAIV. The MedImmune study enrolls children with an ILI definition of fever specifically. Overall estimates do not change when children are restricted to those who have cough and fever and / or sore throat. If patients are restricted who are enrolled within 5 days of illness onset, very similar estimates are observed.

Dr. Kempe noted that there was a percentage that relied on report, which might differ between getting a shot or inhaled vaccine. She heard that in the CDC presentation not the others. She asked what percent that was and if that issued had been studied.

Dr. Flannery responded that about two thirds of their children are two to eight year olds, all of which is by document. There is no self-report. For a small number of children, there was parent-report of vaccination that was outside of the health system that provided the documents. So, it is plausible because they were able to provide a location outside the system and a date, but that really is a small number of children. If the analysis is limited to documented vaccination only for both of those age groups, the overall estimates are still the same for LAIV and IIV.

Proposed Recommendations Summary / Vote

Lisa Grohskopf, MD
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf reminded everyone that what was discussed and approved during the February 2016 meeting was reiteration of the core recommendations that annual influenza vaccination is recommended for all persons 6 months of age and older. There was a minor change in timing of vaccination language and changes to the egg allergy recommendations allowing use of LAIV and removing the 30-minute post-vaccination waiting period that had been recommended previously. There was also some additional specific language about the specific case of individuals with a history of severe egg allergy.

New Licensures that that will be listed in the Available Products table include: 1) Fluad®, the MF59-adjuvanted inactivated influenza vaccine trivalent from Seqirus™, which is for persons 65 years of age and older; and 2) Flucelvax Quadrivalent®, which is the cell-culture-based inactivated influenza vaccine, which has been available previously as trivalent and now will be available as quadrivalent for persons years of age and older. ACIP has had the opportunity to hear presentations on these. Potential upcoming licensures, which also have been presented at ACIP, which will not be in the table as they are not yet licensed, but will be acceptable options to existing products for appropriate age groups if licensed: 1) Flublok Quadrivalent®, which is a recombinant quadrivalent influenza vaccine for persons 18 years of age and older; and 2) Flulaval Quadrivalent®, which is an inactivated influenza vaccine for persons 6 months of age and older. Again, those will not be in the table but will be mentioned as potential upcoming licensures and will be viable options for existing products in the relevant age groups once licensed.

In terms of LAIV efficacy, the WG had the opportunity to hear presentations of the data heard during this session and an opportunity to discuss it. One of the considerations that went into the discussion was the importance of ensuring that policy reflects understanding of the latest VE data, which in this case indicates that at least in the US data, IIV is more effective than LAIV against influenza A(H1N1)pdm09, which was the predominant circulating virus this year. There

is also an understanding that there is an uncertainty about LAIV4 effectiveness against A(H3N2) and B viruses, which has been available since the 2013-2014 season. Most notably, there has not yet been an opportunity to see how well the quadrivalent performs against A(H3N2) in a season where there is good match. 2014-2015 was an H3N2 predominant season, but there was drift of H3, so there was poor match and the inactivated vaccine did not perform well either. There is a conviction that policy should encourage use of the most effective vaccines available, and a conclusion in general that LAIV should not be used in routine practice though there was not consensus regarding the exact language surrounding that. There was also discussion that there is a need to specify that changes in the recommendations are interim, if there are changes, for the 2016-2017 season, as data may be different in future seasons.

There was discussion of a number of programmatic implications should the recommendations change. There was a lot of discussion regarding the potential impact on vaccine supply if LAIV is not recommended for use. It is projected that there should be a maximum produced 171 to 176 million total maximum doses projected for all influenza vaccines. This information was presented at the Adult Influenza Vaccination Summit in May. Among these doses, about 14 million are projected LAIV doses, which is about 8% of the total. There was recognition that providers may have difficulty purchasing other products and also understanding of the fact that not all products are licensed for all age groups. There are other vaccines, inactivated and otherwise, which are not licensed for children for example. CDC has contacted manufacturers regarding the likelihood of mitigating any potential shortages. A second concern raised was that this may impact school-based programs, many of which primarily use LAIV. One recent publication indicates that this is not a large number of children. In recent seasons, an estimated 5% of children were vaccinated at school, 55% of whom received LAIV according to that study.

If LAIV were not to be used, there would be no alternative for those who refuse injectable vaccine if LAIV is not recommended for use. This may impact vaccine coverage. Communicating to providers and parents the rationale for the policy change was felt to be critical to maintaining a strong influenza vaccine program. There was also concern that any change in the LAIV recommendations may potentially result in decreasing LAIV use, which may in turn preclude evaluation of LAIV effectiveness in future seasons because there will not be the same numbers witnessed in recent seasons. With that in mind, two basic options were raised:

Option A:

- **LAIV should not be used in any setting**
  - More definitive response to the available data
  - May be more clear to communicate message

Option B:

- **LAIV may be used in settings where otherwise an individual may not be vaccinated**
  - Leaves flexibility in the program for certain situations
  - Iterative step, may be easier to transition back to LAIV if the vaccine is reformulated
  - May limit the programmatic impact of change

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The potential language posed for each option follows:

Option A: Interim Recommendation That LAIV Should Not Be Used

> "In light of the evidence for poor effectiveness of LAIV in the U.S. over the last three influenza seasons (2013-14 through 2015-16), for the 2016-17 season, ACIP makes the interim recommendation that LAIV should not be used."

Option B: Interim Recommendation for Limited Use of LAIV

> "In light of the evidence for poor effectiveness of LAIV in the U.S. over the last three influenza seasons (2013-14 through 2015-16), for the 2016-17 season, ACIP makes the interim recommendation that LAIV should not be routinely used. Use of LAIV may be considered in certain circumstances."

Examples may include (clinical guidance to be developed by CDC):

- ❑ Refusal of injectable vaccine
- ❑ Shortage of age-appropriate IIV or RIV
- ❑ School based programs with no alternative vaccine

<u>Discussion Points</u>

Regarding the WG's thoughts about this information, Dr. Karron indicated that this was very much a rapidly evolving situation so some of the language shown differed from what the WG saw. In the initial discussion with the WG, there was also the option of not making any change to the recommendation, for which there was no enthusiasm. The WG was very clear that some change was needed. There was division as to whether it should be a recommendation that LAIV should not be used, or should be used under certain circumstances. For those who felt that perhaps it should be used under certain circumstances, most of the concerns were programmatic in nature and related to implementation.

Dr. Moore pointed out that the way the language was written, it implied that LAIV was particularly bad for the last three seasons. Given that no formulations had good effectiveness in the 2014-2015 season, it might be fairer to state something to reflect that the problems were different during that season and that it was not the fault of any vaccines.

Dr. Reingold asked whether the current statement was preferential for IIV and if not, whether any consideration had been given to a statement that would state a preference for IIV.

Dr. Karron replied that the existing statement has no preference for one over the other. The statement considered in the WG regarded stating a preference for IIV. She invited the WG to comment. The original statement the WG considered was a reverse preferential recommendation in favor of IIV, but the WG was divided on this.

Ms. Pellegrini requested further information regarding why the full membership was seeing such different recommendations from the ones the WG originally considered as the IIV preference.

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Dr. Bresee (SME) said he thought what the WG was commenting on demonstration of data that indicated a lack of effectiveness of one of the choices, so the word “preference” seemed to connote the difference between a good vaccine and a better vaccine. The wording that it had “limited use” seemed more aligned with what the data are showing.

Dr. Kimberlin (AAP) extended gratitude to the Influenza WG and to MedImmune for responding quickly to a rapid developing and changing sequence. This has a major impact on pediatric practices. A number of emergency calls have been conducted that assessed the pediatric practice equivalence of programmatic changes and impacts. However, everything kept circling back to the science for the AAP. The science simply shows that one product has not worked for the last three years; whereas, IIV has. Thus, AAP prefers Option A for that reason.

Dr. Savoy (AAFP) pointed out that many people have likely ordered their vaccine for the upcoming year, and it is probably too late to change that. If she were to see this recommendation, she would want to know explicitly whether ACIP was telling her not to give that vaccine or that she should give it but should know that it might not work as well. People are going to need to make some practical decisions about this.

Dr. Wharton responded that this would depend upon what ACIP recommended as well as the clinical guidance developed subsequently. If language like Option B were used, she thought it would suggest that if some amount of LAIV had been purchased, it might be appropriate to use in limited circumstances but not the way it was used last year. Regarding the issue of supply, the manufacturers could make statements about what vaccine remained available. However, even if all the numbers were reassuring, there still is likely to be some difficulty for individual providers if they did need to obtain influenza vaccine to identify vaccines that might be age-appropriate for their patients. This might require a higher level of efforts, and all providers may not be prepared to do this. The end result is that some providers might not end up with influenza vaccine for their patients.

Dr. Gorman (NIH) asked whether the determination regarding the poor effectiveness was driven primarily by the A strains and the H1N1 strains.

Dr. Karron said she thought the data were clear for H1N1 and the data for other strains were less clear, but concerning. Certainly, there was poor effectiveness of the vaccine last year with a mismatched year. In prior years with H3N2 and mismatching, there has been variation in efficacy or effectiveness. She wondered if they had ever seen zero or negative even if there was a very bad mismatch. That certainly was a concern in the WG.

Dr. Ambrose showed the following graphic of the three observational, test-negative studies conducted in 2014-2015 for LAIV4 and IIV. The CDC study on the left efficacy was 17% for IIV and -8% for LAIV4. The ICICLE study was 40% for IIV that was significant, and 30% for LAIV4 that was not significant. The UK PHE results were very similar. The additional data available were from a randomized placebo controlled study conducted in Japan in children 7 through 18 years of age. Many of these children were previously vaccinated with inactivated vaccine. In that study, efficacy was 23% against completely mismatched strains and that was statistically significant; whereas, in the UK and US observational studies some matched strains were circulating. There was evidence that LAIV was working, albeit at a low level against those mismatched strains, which was not detected by the CDC study but would be consistent with what was observed in the ICICLE and UK PHE study. In terms of how this relates to past data, in the original Belshe study in 1997-1998 demonstrated 86% against mismatched strains.

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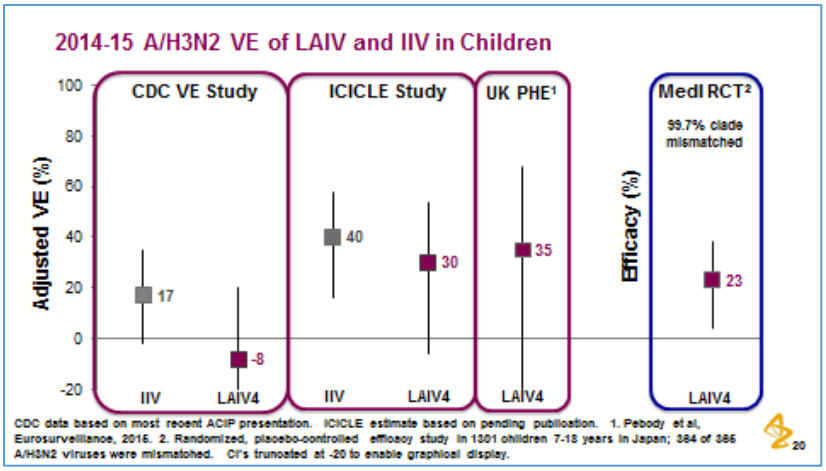
According to CDC classification, those were four-fold different. Similar high relative efficacy was seen compared to inactivated vaccine when there were four- to eight-fold different viruses in 2004-2005. But there was an 8- to 16-fold difference in 2014-2015, the absolute efficacy estimates were in the 20% to 30% range. Essentially, the randomized trial and much of the observational data, at least from ICICLE and PHE, were consistent with what has been observed before with the trivalent formulation against severely mismatched by a 16-fold difference in H3N2. Statements being made that no effectiveness is demonstrated are not correct. This is the classic "absence of evidence is not evidence of absence." There is no evidence of zero percent effectiveness of LAIV. There is just evidence of low effectiveness that is not significant.



Dr. Messonnier thanked the ACIP membership, recognizing the complexity of this discussion. As everyone must have gathered, Dr. Frieden saw these data before joining them earlier in the morning. He tried to focus on the need to make decisions based on imperfect data. As a science-driven group, ACIP must make a decision about whether they have actionable data. Her understanding from the WG deliberations was that despite the fact that there are discrepancies in the data, the WG felt strongly that these data are actionable. Where they fell out of consensus regarded whether it was absolute that the vaccine should not be used, as AAP supports, or whether because of some of the programmatic issues, which AAFP pointed out, there should be some space such that if clinicians had no other option, it would be better to give LAIV versus nothing. She asked the group to deliberate these issues, remember that someone ultimately will have to offer clinical guidance to individuals, clinicians, and parents faced with this decision.

Dr. Lett (CSTE) thought it would be helpful to know more about how binding pre-books would be in the private and public sectors.

Dr. Wharton responded that on the public sector side, CDC would take their cue from and would implement what ACIP advised. In terms of the private sector, individual providers are likely to have various purchase agreements which they would have to deal with themselves.

As a member of the WG, Dr. Zahn (NACCHO) commented that for Option B, the discussion was that LAIV would be given if the option of IIV was not available. While he appreciated Dr. Bresee's point that they did not want it to appear preferential, having multiple bullet points about various situations felt more preferential than simply stating to give IIV unless there was no other

choice as a provider than to give LAIV. There was some conversation among the WG members about avoiding saying too much to providers, because providers have many other issues with which they must deal.

Dr. Bennett said she thought the changing in wording from the use of the word “preference” to the use of “should not be routinely used” and “may be considered in certain circumstances” addressed what Dr. Zahn was saying.

Dr. Moore said that as an Immunization Manager and member of the committee, what struck her as important pertained to who H1N1 disproportionately affects with more severe disease. Younger adults and children tend to have more severe disease with H1N1, which also happens to be the group for whom LAIV is targeted. Knowing that it will not work against H1N1 or that there is no evidence of effectiveness, she would not feel comfortable giving a child that vaccine because if it is an H1N1 year, it would leave them vulnerable. Programmatically, LAIV comprises 8% of the total supply available. This can be figured out. However, she worried also about sending the message that whomever receives LAIV has gotten an inferior product. That has another layer of communication complications. The public looks to ACIP to make recommendations for the best possible vaccines.

Not being a member of the WG, Ms. Pellegrini found this to be a lot of information to absorb on short notice and about which to make a very important decision. She said she was struggling with the differences in effectiveness data among the strains, and among the strains from year-to-year. She found the difference among the results in different countries to be particularly confounding. She wondered what it was about the US that the vaccine did not work, while the same vaccine seemed to work in other places. Setting aside 2014-2015 as a season of mismatch, they were looking at two different vaccines because the A strains were California and Bolivia. It is still H1N1, but is a slightly different vaccine. Also setting aside 2014-2015, she felt like there were two data points. A couple of years ago, ACIP preferentially recommended LAIV based on one really strong data point and they regretted that. She was not much happier dealing with what felt like to her to be two data points to make the opposite recommendation. On the basis of all of this, she said she would like the committee to consider postponing a vote until the next morning to give the members time to review and process the information.

Dr. Karron said she felt Ms. Pellegrini’s pain in terms of the data. She clarified that the GRADE analysis performed for a preferential recommendation of LAIV was not based on a single data point. It was based on several RCTs. Unfortunately, those were for a different vaccine essentially—the trivalent vaccine. She found the fact that the H1N1 components had been changed but the results were the same to be especially disturbing and concerning in terms of the efficacy of this vaccine against H1N1. There may be issues of viral interference. There may be issues connected to the fact that the US has a more highly immunized pediatric population against influenza than anywhere else in the world, which may contribute to differences observed in the US versus other populations. Less is known about H3N2 and B, but she thought that the data for H1N1 were quite compelling.

Dr. Messonnier acknowledged that ACIP was being rushed. Unfortunately, CDC felt a great sense of urgency to make some sort of recommendation. Putting it off until the morning might mean that other things could not proceed. No decision would basically be a decision, so no vote would not be helpful.

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Echoing Dr. Karron and responding to Dr. Messonnier, Dr. Schaffner (NFID) suggested that this issue should not depend at all on programmatic issues. ACIP should decide whether LAIV is an ineffective or insufficiently effective vaccine. If that was the decision, Option A was clear. He suggested that Option A was the clear choice.

Dr. Baker (IDSA) thought this was great because CDC is filled with very capable people who can interpret data without an advisory committee. However, this is why CDC has an ACIP. She appreciated Dr. Messonnier bringing them back to Dr. Frieden's comment. Things change. The one thing she has learned about influenza is that it changes all of the time—the virus, the policy, et cetera. She thought that the science made this actionable, and that they did not have a choice. She said she had great sympathy for doing something with Option B in terms of all of the programmatic issues, but the science suggested that Option A was correct. She was not sure whether overnight would be helpful, but she thought a decision must be made.

Dr. O'Leary (PIDS) indicated that the Pediatric Infectious Disease Society (PIDS) would like to support Option A for many of the reasons articulated. Moreover, there are good data to show that IIV is effective though it varies from year-to-year. However, there were enough unanswered questions about LAIV that he did not think they could recommend in good conscience its use in children.

Dr. Gorman (NIH) pointed out that if Option A was approved and the recommendation went to Dr. Frieden and he agreed, he wondered whether insurances would be freed of their responsibility of paying if providers administered an FDA-approved vaccine to those children.

Dr. Bennett requested input from Dr. Wharton, pointing out that this was also why the VFC vote had been tabled. There are a number of financial implications that must be better understood.

Dr. Wharton responded that it is difficult to predict what exactly insurers would do. In general, it is not expected that insurance coverage would change immediately following an ACIP recommendation. Generally changes are phased in over time.

Dr. Bennett added that it usually takes a year from the time ACIP makes a recommendation.

Having been a private practitioner for 20 years, Dr. Gorman (NIH) noted that it took a year to start paying. He did not think it would take a year to stop paying.

Vote: Influenza Vaccine Recommendations

Dr. Harrison motioned to approve Option A. Dr. Walter seconded the motion. The motion carried with 13 affirmative votes, 1 negative vote, and 1 abstention. The disposition of the vote was as follows:

13 Favored:	Bennett, Ezeanolue, Harriman, Harrison, Karron, Kempe, Moore, Romero, Reingold, Riley, Rubin, Stephens, Walter
1 Opposed:	Pellegrini (due to insufficient time to review the data)
1 Abstained:	Belongia (due to conflict of interest)

Although they voted "yes," many ACIP members expressed regret. Dr. Bennett lamented that it was a very sad day for the influenza vaccination program. However, she stressed that "if you've

seen one influenza year, you've seen one influenza year" and that they might be back next year reaching a very different conclusion.

VFC Vote: Influenza Recommendation

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli indicated that the purpose of this resolution was to update the resolution to remove LAIV from the VFC program. No changes were proposed to the IIV component of the resolution.

The other sections of this component of VFC resolution will not be changed. The following statement will be included regarding updates based on published documents:

> If an ACIP recommendation regarding influenza vaccination is published within 6 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the URL.

Discussion Points

Dr. Thompson requested clarification regarding the implications of approving this resolution in terms of payment for physicians for VFC-ordered vaccines if they have already ordered / paid for them. She also asked for clarification of the implications of the timing of the resolution in terms of current influenza season vaccinations.

Dr. Santoli responded that providers receive VFC vaccines at no charge. CDC provides contracts and makes doses available to states for the VFC program. This indicates that CDC will make vaccines available for children who are covered by the VFC program, and those are the vaccines to which providers of the VFC program will have access and will be able to administer. They do not bill for these vaccines, although they do bill for the administration fee. That will occur as normal, but the resolution will limit the formulary for influenza vaccines that CDC will make available through the VFC program this year.

Vote: VFC Influenza Vaccine Recommendation

Dr. Kempe motioned to approve the VFC Influenza Vaccine Recommendation. Dr. Rubin seconded the motion. The motion carried with 13 affirmative votes, 1 negative vote, and 1 abstention. The disposition of the vote was as follows:

13 Favored:	Bennett, Ezeanolue, Harriman, Harrison, Karron, Kempe, Moore, Romero, Reingold, Riley, Rubin, Stephens, Walter
1 Opposed:	Pellegrini (due to insufficient time to review the data)
1 Abstained:	Belongia (due to conflict of interest)

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Day 1: Public Comment

No public comments were offered during this session.

Respiratory Syncytial Virus Vaccine

Introduction

Ruth Karron, MD
Chair, Respiratory Syncytial Virus Vaccine Work Group

Dr. Karron said that she was delighted to introduce the Respiratory Syncytial Virus (RSV) WG, both because RSV is such an important pathogen in young children and the elderly and also because so much has been accomplished in terms of vaccine development; therefore, it is time to constitute an ACIP WG.

RSV was discovered almost 60 years ago in 1957. It is a major cause of lower respiratory tract illness (LRTI) in infants, young children, and older adults. In the US, there are approximately 150,000 hospitalizations each year in US infants and children and approximately 180,000 hospitalizations in US elderly. In the US, these represent the “tip of the iceberg,” and there is a substantial outpatient disease burden in both populations. RSV is a global pathogen and it is a leading cause of hospitalization and serious LRTI in children throughout the world. Despite having been recognized as a human pathogen 59 years ago, a vaccine does not exist. There is a monoclonal antibody (mAb) called palivizumab, but that is given as a monthly injection, is quite expensive, and is recommended for only a subset of high-risk infants.

The following graphic represents the RSV vaccine landscape in 2003, with just a couple of companies and NIH involved in developing vaccines:

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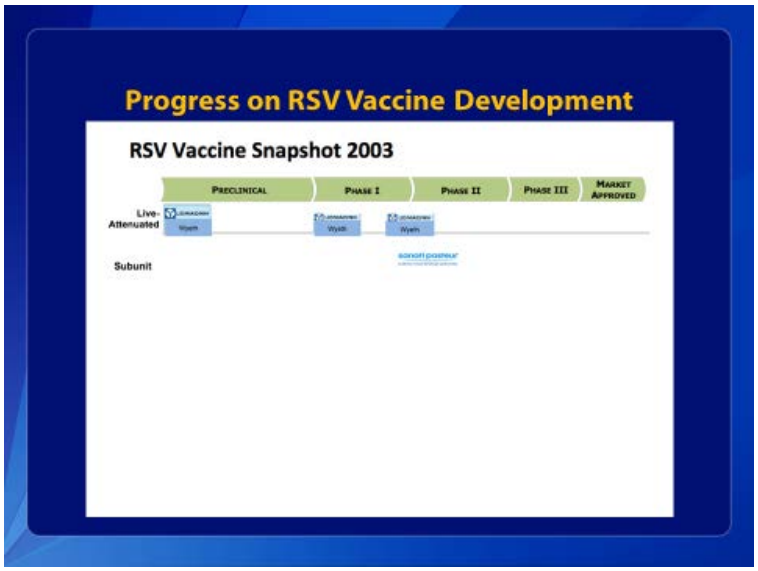
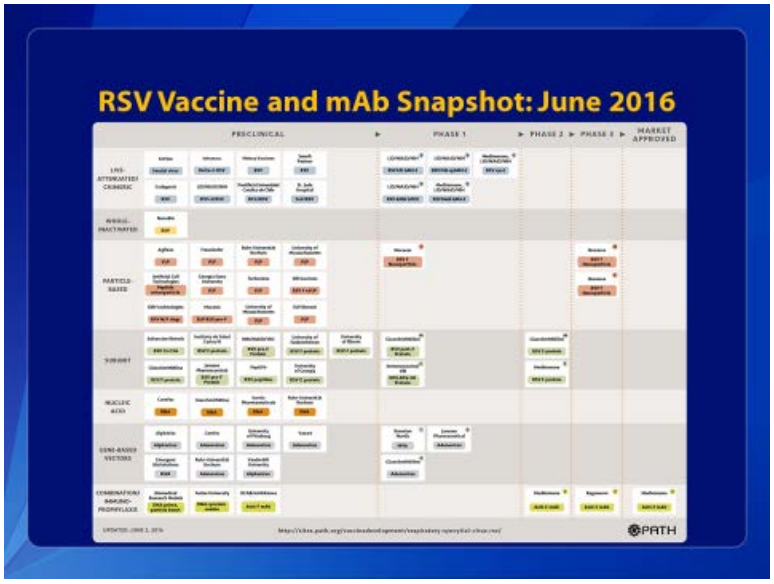


Contrast that with the current state of affairs shown in the following graphic of 2016 mAb and RSV vaccine development:



There are approximately 60 products in development, of which 3 are in Phase 3 development. Two of the vaccines in Phase 3 development are manufactured by Novavax. One is currently being evaluated in mothers for maternal immunization to protect young infants, and one has completed enrollment in the elderly. There are a number of other products, but the products in particular that are meant for the elderly are further along in clinical development than the products meant to protect young children, either through maternal immunization or through active immunization of the infant.

For that reason, at this time, the WG was constituted to focus primarily on the elderly because it is anticipated that a vaccine could be licensed as early as 2017-2018. The current terms of reference for this WG are to consider recommendations for the use of RSV vaccine in adults 60

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years of age and older and in adults with underlying medical conditions. The current tasks of the WG are to:

- ❑ Review the epidemiology of RSV infection and burden of RSV disease in older adults;
- ❑ Review efficacy, immunogenicity, safety, and cost-effectiveness of RSV vaccine(s) in older adults and adults with underlying medical conditions as these data become available;
- ❑ Provide evidence-based recommendations regarding use of RSV vaccine(s) in older adults; and
- ❑ Identify areas in need of further research for informing potential future vaccine recommendations.

Because it is anticipated that over time, there also will be vaccines to consider for protection of infants and children, the terms of reference and the membership of the WG may evolve over time to accommodate these additional needs. With the exception of the liaison members, the WG initially was constituted with the focus on elderly adults in mind.

This session included an overview of RSV and RSV vaccines with regard to obstacles and progress in RSV vaccine development, targeted vaccine populations, and considerations for RSV vaccine use. Future presentations will include presentations on burden of RSV in older adults, clinical trial results, and cost-effectiveness.

Overview of RSV Vaccines

Lindsay Kim, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Kim began by acknowledging Dr. Karron's mentorship and leadership in the standing up of this ACIP WG. She explained that RSV is a common cause of acute respiratory infections (ARI) in infants and young children. By the first year of life, 50% are infected, with virtually all children infected with RSV by 2 years of age. RSV is the most common cause of LRTI among infants, and it frequently manifests as bronchiolitis or pneumonia. It can present with apnea in infants less than 6 weeks of age. There is a questionable relationship between RSV infection during early childhood and subsequent development of reactive airway disease and wheezing.

In adults, RSV can cause repeat infections after being exposed and infected during infancy and early childhood. It most often causes upper respiratory tract illnesses, but sometimes can be asymptomatic. When it does cause symptoms, they are more severe than the common cold with less fever and fewer systemic symptoms compared to influenza. LRTI also can occur, especially among the immunocompromised, those with underlying cardiopulmonary disease, and the elderly. Frequently, RSV can also manifest as exacerbations of chronic medical conditions such as chronic obstructive pulmonary disease (COPD), asthma, and congestive heart failure. In some case series of immunocompromised persons, RSV can manifest as pneumonia and sinusitis, with mortality rates of 50% or more reported.

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This table shows frequency of symptoms among adults aged 65 years and older:

Table 6. Frequency of Symptoms Among Single Virus Infections (Viruses Detected in at Least 30 Cases)

No. of Episodes (N)	RSV (N = 39)		Influenza A (N = 98)		Metapneumovirus (N = 31)		Rhinovirus/ Enterovirus (N = 75)		Coronavirus (N = 30)	
Symptom	n[a]	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Nasal congestion	28	71.8 (55.1–85.0)	76	77.6 (68.0–85.4)	23	74.2 (55.4–88.1)	58	77.3 (66.2–86.2)	28	93.3 (77.9–99.2)
Sore throat	25	64.1 (47.2–78.8)	63	64.3 (54.0–73.7)	20	64.5 (45.4–80.8)	58	77.3 (66.2–86.2)	22	73.3 (54.1–87.7)
New or worsening cough	36	92.3 (79.1–98.4)	87	88.8 (80.8–94.3)	28	90.3 (74.2–98.0)	61	81.3 (70.7–89.4)	27	90.0 (73.5–97.9)
New or worsening dyspnea	20	51.3 (34.8–67.6)	32	32.7 (23.5–42.9)	8	25.8 (11.9–44.6)	26	34.7 (24.0–46.5)	9	30.0 (14.7–49.4)
New or worsening sputum production	27	69.2 (52.4–83.0)	49	50.0 (39.7–60.3)	14	45.2 (27.3–64.0)	33	44.0 (32.5–55.9)	12	40.0 (22.7–59.4)
New or worsening wheezing	18	46.2 (30.1–62.8)	30	30.6 (21.7–40.7)	3	9.7 (2.0–25.8)	11	14.7 (7.6–24.7)	8	26.7 (12.3–45.9)
Fever	22	56.4 (39.6–72.2)	71	72.4 (62.5–81.0)	17	54.8 (36.0–72.7)	30	40.0 (28.9–52.0)	15	50.0 (31.3–68.7)
Headache	32	82.1 (66.5–92.5)	72	73.5 (63.6–81.9)	25	80.6 (62.5–92.5)	57	76.0 (64.7–85.1)	26	86.7 (69.3–96.2)
Fatigue	31	79.5 (63.5–90.7)	75	76.5 (66.9–84.5)	21	67.7 (48.6–83.3)	59	78.7 (67.7–87.3)	20	66.7 (47.2–82.7)
Myalgia	25	64.1 (47.2–78.8)	69	70.4 (60.3–79.2)	19	61.3 (42.2–78.2)	51	68.0 (56.2–78.3)	23	76.7 (57.7–90.1)
Feverishness	18	46.2 (30.1–62.8)	58	59.2 (48.8–69.0)	18	58.1 (39.1–75.5)	36	48.0 (36.3–59.8)	17	56.7 (37.4–74.5)

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

[a] n, number of subjects in a given category.

The most frequent symptoms reported by persons with RSV infection were new or worsening cough (92%), headache (82%), fatigue (80%), and nasal congestion (72%). RSV and influenza often are thought of commonly as similar pathogens, but they do have different symptomologies. As seen in the above slide, fever is reported more frequently in influenza A-infected persons at 72% versus 56% in RSV in adults.

In terms of the burden of RSV in older US adults, the importance of RSV infections in adults was first recognized as a result of outbreaks in long-term healthcare facilities in the 1970s. One population based study estimated that RSV infection causes 177,000 hospitalizations and 14,000 deaths annually[1]. Another study found that the average annual RSV hospitalization rate was 15 per 10,000 residents[2]. What was striking was that the investigators also found a similar rate of hospitalization for influenza. Another study published in 2014 found that there were 154 medically attended RSV episodes per 10,000 persons in adults 50 years and older with increasing incidence with age. This was a prospective study over 4 respiratory seasons in community-dwelling older adults who were seeking care for ARI[3]. For a higher risk group of adults 65 years and older, another study found that RSV caused approximately 18 hospitalizations per 1000 persons and 5 deaths per 1000 persons with chronic lung disease using retrospective data from the Tennessee Medicaid database[4] [[1]Falsey 2005; [2]Widmer 2012; [3]McClure 2014; [4]Griffin 2003]. So, there is a burden of RSV in older US adults.

In terms of the virus itself, RSV is an enveloped ribonucleic acid (RNA) Paramyxoviridae virus with 2 major subgroups, A and B, which are based on the surface proteins. The viral genome consists of 10 genes that encode 11 proteins, two of which are named F and G. The Fusion (F) and attachment (G) surface glycoproteins are the most important in their ability to induce neutralizing antibodies. The F protein is highly conserved between the RSV subgroups, making it a promising vaccine target. Humans are the only source of transmission, and RSV is spread by direct or close contact through large droplets or fomites on objects and surfaces. These can last from 30 minutes to 6 hours. The incubation period is 4 to 6 days, with a range of 2 to 8 days. Viral shedding can occur for 3 to 8 days, but can last up to 4 weeks.

There are several methods for testing for RSV or diagnosing it. Laboratory diagnosis of RSV can be done by rapid tests of respiratory specimens (midturbinate, nasal swab, or wash). These include antigen assays, which are highly sensitive in young children, with reports of 80%

to 95% sensitivity. However, they have much lower sensitivity in adults of about 14% to 39% due to low virus shedding. Therefore, this is not the optimal way to diagnose RSV in adults. Reverse transcriptase polymerase chain reaction (RT-PCR) assays are now more widely available and have a much higher sensitivity in adults, with some reports approaching over 90%. Viral isolation from respiratory specimens in cell culture can also be performed to diagnose RSV; however it can take 1 to 5 days, is more expensive, and is less sensitive than current methods of RT-PCR. Sensitivity can also be affected by which laboratory is performing that method. Serology is used mainly for seroprevalence studies and not for patient care; however, the added benefit of serology is that it can add to case finding in adults as studies that use both PCR and serology can detect more RSV than virus isolation or PCR alone.

The goal for RSV vaccine development is to safely induce sufficient immunity to protect against serious RSV infections like LRTI and possibly apnea in infants. The induction of sterilizing immunity is not required and actually might not be feasible. In the late 1960s, a formalin inactivated vaccine underwent clinical trials in children 2 months to 7 years of age. Unfortunately, there were some devastating results that impacted the development of RSV vaccines for several decades. The trials ended when seronegative vaccine recipients had more severe RSV-associated LRTIs than non-recipients when they acquired natural infection during the subsequent RSV season. Of vaccine recipients, 80% required hospitalization compared to 5% of controls who never received vaccine. There were 2 deaths in the vaccine recipient group.

Data assessing vaccine recipients with serious outcomes from this trial and rodent models found that the vaccine caused a vaccine-enhanced disease syndrome in RSV-naïve infants or those who had not yet had primary infection. This was due to two main reasons. First, the vaccine did not induce enough neutralizing antibody, and second, it induced a Th2- and CD4-biased immune response leading to more inflammation, more cytokine release, and more obstruction and worse outcomes in infants and children. There are many implications of the formalin-inactivated vaccine trial, including the fact that vaccine development / production slowed down due to the need to know more about the immunology of RSV disease and immune responses. Because of the enhanced disease seen during the vaccine trials, non-replicating vaccines are unlikely to be used in RSV-naïve infants. Therefore, different vaccines types are now being used for different target populations. These include replicating or vectored vaccines for active immunization of RSV-naïve infants and children, subunit vaccines with or without adjuvant for maternal immunization to protect the very youngest infants, and subunit vaccines with or without adjuvant to protect the elderly and boost their already-existing immunity.

Recently, there has been quite some movement in RSV vaccine development as shown on the graphic earlier by Dr. Karron. There are more than 60 different products in development by several manufacturers. There are different types of vaccines ranging from live-attenuated to subunit to those with gene-based vectors. The furthest along is the RSV Fusion protein vaccine using recombinant nanoparticle technology developed by Novavax, which will be the first vaccine that the ACIP will consider. This vaccine recently completed Phase 3 clinical trials.

There are four RSV vaccine priority groups, which are comprised of the populations at risk of severe disease:

- ❑ Neonates and Young Infants
- ❑ Older Infants and Children
- ❑ Pregnant Women
- ❑ Older Adults

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Neonates and young infants have the greatest potential benefit due to having the highest burden of disease and mortality among all age groups; however, there are a couple of obstacles to think about when developing a vaccine for this age group. They have immature immune systems and the presence of pre-existing maternal antibody can make active immunization in this age group challenging. Therefore, the most promising strategy for the youngest infants is maternal vaccination or administration of an extended half-life monoclonal antibody.

Older infants and children face similar issues to young infants, but have more mature immune systems and lower levels of maternally acquired antibodies. This should lead to better responses to vaccines. Currently, development is focusing on live-attenuated virus and vectored vaccines with several candidates in Phase 1 clinical trials.

Pregnant women are also a high risk population. The use of a vaccine for pregnant women has several objectives including protecting the young infant by inducing high levels of neutralizing antibodies that are transferred to the fetus, preventing maternal to infant transmission of infection, and protecting the pregnant woman herself from infection. Pregnant women would not be at risk for enhanced disease, given that as infants / children they were already naturally exposed and infected. RSV F subunit vaccines are in development, and these candidates are in Phase 1, 2, and 3 clinical trials.

Lastly, older adults have a substantial disease burden. However, immunosenscence might be a challenge to overcome. Several subunit vaccines are currently in development. Vaccine candidates are in Phase 1, 2, and 3 trials. The RSV F subunit nanoparticle vaccine will be the first RSV vaccine to be considered for FDA licensure and use, and it is the focus of the current ACIP RSV WG.

In August 2015, news media reported early indications of vaccine efficacy of the Novavax vaccine targeted for older adults. Early indications show it to be efficacious for RSV in older adults. More data will be forthcoming as Phase 2 and 3 trial results become available, and these will be presented to ACIP.

As ACIP deliberates the use of an RSV vaccine in older adults, several issues will be considered including disease burden, appropriate outcome measures, immunogenicity and correlates of protection, duration of protection, the cost-effectiveness of the vaccine, implementation issues, and education of stakeholders (particularly among family practitioners and other providers who would be administering the vaccine, and the public who would be receiving the vaccine). The proposed ACIP timeline will include a review of the epidemiology and burden of RSV in older adults in 2016; vaccine manufacturer presentations on clinical trial results in 2017; discussions regarding correlates of protection, immunogenicity, and cost-effectiveness in 2017; and implementation considerations, the GRADE evidence, and a potential vote in 2018.

Safety of Maternal Tetanus, Diphtheria, Acellular Pertussis (Tdap) Immunization

Introduction and Enhanced Surveillance of Tdap Vaccine Safety in Pregnancy in VAERS

Pedro L. Moro, MD, MPH

Dr. Moro reminded everyone that there were two recent ACIP recommendations. The first was in 2011, which indicated that unvaccinated pregnant women should receive a dose of Tdap to provide infants with maternal transplacental passive antibody protection against pertussis during the early postnatal months[1]. The next recommendation was a year later, in 2012, to administer Tdap during every pregnancy, irrespective of prior history of receiving Tdap [2]. The optimal timing for administration is between 27 to 36 weeks gestation. At the time of the recommendations, limited data were available on the safety of Tdap vaccination in pregnancy [[1]CDC. *MMWR*. October 21, 2011 / 60(41); 1424-1426. Available at www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm; and [2]CDC. *MMWR*. February 22, 2013 / 62(07);131-135. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm.

During the 2012 deliberations, ACIP expressed the need for enhanced monitoring and safety studies of Tdap in pregnancy. The CDC Immunization Safety Office (ISO) implemented a comprehensive vaccine safety monitoring effort for maternal Tdap safety[1]. That included enhanced surveillance in VAERS, a clinical review of all Tdap pregnancy reports, epidemiologic studies in the VSD, and clinical research in the Clinical Immunization Safety Assessment (CISA) Project. In 2015, Tdap vaccination coverage during pregnancy among women who had a live birth was 42.1% versus 27% in 2014[2] [[1]Moro et al. Hum Vaccin Immunother. 2015;11(12):2872-9; and [2]Pregnant Women and Tdap Vaccination, Internet Panel Surveys, United States, April 2014 and April 2015 (unpublished data)].

In terms of the safety of Tdap in pregnancy in VAERS, surveillance in VAERS from October 2011 through June 2015 showed no new or unexpected vaccine safety concerns among pregnant women who received Tdap or their infants. These findings were presented at the February 2014 ACIP meeting and have been published [Moro PL, et al. Vaccine. 2016 Apr 29;34(20):2349-53].

There were three studies in the VSD on Tdap in pregnancy, which are reflected in the following table, along with the safety data:

Safety of Tdap in pregnancy in VSD

Period	Sample size	Safety data
2010-2012 [a]	26,224 vaccinated 97,265 unvaccinated	▪ No increased risk of preterm birth, small for gestational age or hypertensive disorders ▪ Slight increased in risk of chorioamnionitis
2007-2013 [b]	29,155 vaccinated with Tdap (varying intervals from prior tetanus-containing vaccinations)	▪ No increased risk of acute adverse events (fever, allergy, and local reactions) or adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight) for women who had a previous tetanus vaccination regardless of timing since prior tetanus containing vaccine
2007-2013 [c]	36,844 vaccinated 8,464 Tdap and IIV on same day 28,380 sequentially	▪ No statistically significant increased risk of fever or any medically attended acute adverse event in pregnant women concomitantly compared with sequentially ▪ No differences in both groups in pregnancy outcomes (e.g., Small for gestational age, low birth weight, preterm delivery)

[a] Kharbanda EO, et al. JAMA 2014;312:1897–904
[b] Sukumaran L, et al. JAMA. 2015;314(15):1581-1587
[c] Sukumaran L, et al. ObGyn. 2015;126(5): 1069–1074

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Dr. Moro reminded everyone that VAERS is a passive reporting system that is administered by the CDC and FDA. The strengths are that it is capable of rapid signal detection, can detect rare AEs, generates hypotheses, encourages reports from healthcare providers and accepts reports from patients and others, and makes data available to the public. The limitations include reporting bias, inconsistent data quality and completeness, inability to assess whether a vaccine caused an AE, lack of an unvaccinated comparison group, and no field for pregnancy status, making it difficult to search for reports. Because there is no denominator, it is not possible to calculate the incidence or prevalence of an AE or to estimate the risk of an AE.

Surveillance was initiated on November 26, 2012. The VAERS database was searched for reports of pregnant women after administration of Tdap vaccinated from 10/11/2011 through 5/6/2016. Medical records were requested and reviewed for all pregnancy reports associated with Tdap. The reporter / patient was also queried for prior administration of tetanus-containing vaccine.

VAERS received a total of 464 pregnancy reports after Tdap. In 54% of reports, the manufacturer was the reporter. The majority (85%) of Tdap doses were give alone. There were 26 (5.6%) reports of repeat doses. For a majority of the reports (80%), Tdap was given during the third trimester. In terms of pregnancy-specific AEs, the two most commonly reported conditions were premature delivery (< 37 weeks) and stillbirth. Regarding fetal or infant AEs, one neonatal demise was reported to VAERS. Four major birth defects were reported: ectopic kidney in newborn, hypoplastic left heart syndrome, Trisomy 12, and clubbed foot. The predominant non-pregnancy specific AEs included injection site reactions and systemic reactions. Regarding reports of repeat Tdap doses among pregnant women, 26 were reported to have received a previous dose of Tdap. The interval between current and previous Tdap was 7 days to 9.4 years, with a median of 1.8 years. Thirteen reports did not describe an AE. AEs in 13 reports included:

- 4 reports of injection site or arm pain
- 2 reports each of oligohydramnios, intrauterine growth restriction / poor fetal growth, and elevated blood pressure / abdominal pain
- 1 report each of stillbirth with trisomy 12, maternal urinary tract infection, and maternal systemic reactions (e.g., fever, chills)

In conclusion, in VAERS no new unexpected vaccine safety concerns were noted among pregnant women who received Tdap or their infants. A limited number of pregnancy reports with repeat Tdap doses were received by VAERS. CDC will continue to monitor the safety of Tdap vaccine during pregnancy.

Discussion Points

Dr. Hayes (ACNM) asked what the rate of GBS is in the general population who received Tdap compared to the maternal vaccination group.

Dr. DeStefano (SME) responded that he did not think they had those specific rates. Pregnancy is a risk factor for GBS, but there are no data to suggest that maternal receipt of Tdap vaccination is associated with GBS.

Maternal Pertussis Vaccination and Structural Birth Defects in Offspring

Lakshmi Sukumaran, MD, MPH
Immunization Safety Office
Centers for Disease Control and Prevention

Dr. Sukumaran indicated that she would be presenting the VSD study on behalf of the Health Partners Institute VSD team. Tdap vaccine has been recommended for routine use in pregnant women not previously vaccinated since 2010 in California and since 2011 across the US. In the fall of 2012, ACIP recommended that Tdap be administered during every pregnancy, with a preference for it to be given between 27 through 36 weeks gestation. Many other countries also have implemented maternal Tdap vaccination programs.

The objective of the Health Partners Institute VSD team study was to examine risks for structural birth defects following maternal Tdap vaccination within the VSD. The study outcomes were any birth defect, major structural defects, and microcephaly. Microcephaly in particular was chosen as an outcome because in Brazil, there is a maternal Tdap immunization program and there was some speculation initially that increases in microcephaly were due to maternal Tdap vaccine and not Zika virus.

The 7 VSD sites that contributed data to the study on Tdap in pregnancy included the following:

- Group Health Cooperative
- Northwest Kaiser Permanente
- Kaiser Permanente Northern CA
- Kaiser Permanente Southern CA
- Kaiser Permanente Colorado
- HealthPartners
- Marshfield Clinic

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In a study of coverage data on maternal Tdap vaccination in live births between 2007 and 2013 within the VSD that was published earlier this year, there was a steady background rate of first trimester vaccinations during the study period. This usually represents women who did not realize that they were pregnant at the time of vaccination. However, it is an important for this study because most birth defects occur in the first trimester. There was a large increase in vaccinations in 2010 related to the California vaccine recommendations and in 2013 following the ACIP recommendations [Kharbanda et al. Vaccine 2016].

An observational cohort study was conducted of pregnant women and their infants from the 7 VSD sites. Pregnancies ending in a live birth between January 1, 2007 and September 1, 2013 were studied. Pregnancies were identified through a validated algorithm based on administrative electronic health record and birth certificate data [Naleway et al. Vaccine. 2013]. Pregnant women were included who had continuous insurance enrollment from 6 months prior to their last menstrual period (LMP) through 6 weeks postpartum, with at least 1 outpatient visit during pregnancy. Infants were required to have birth weight and gestational age available. If they survived to 12 months of age, they were required to have 4 months of insurance enrollment, with 1 outpatient visit during the first year of life. For infants who died during the first year of life, these insurance and health utilization criteria were not applied.

Exclusions were identified from International Classification of Diseases (ICD)-9 codes and pharmacy files. Multiple gestation births and live births with a known exposure increasing their risk for a structural birth defect were excluded, including receipt of a live virus vaccine during pregnancy, pre-existing diabetes, use of a teratogenic medication, infant congenital TORCH infections (toxoplasmosis, other, rubella, cytomegalovirus, and Herpes simplex), and infant chromosomal abnormalities. Maternal Tdap administrations were identified using claims and EHR data found in standardized VSD files. Three exposure windows were assessed:

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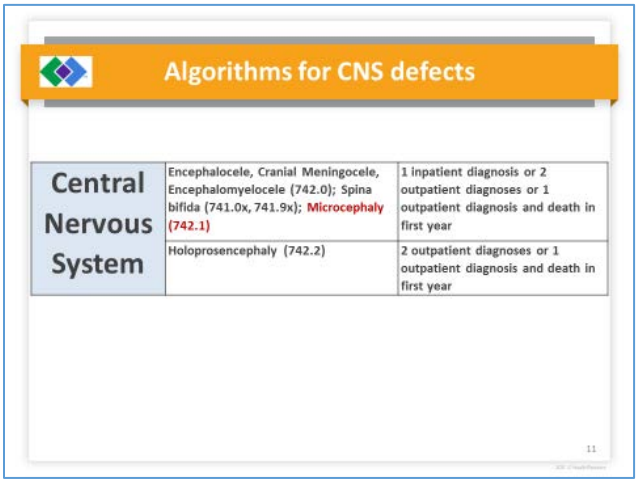
- First trimester, defined as <14 weeks gestation, which is the most biologically plausible time period for a birth defect to occur
- 27 to 36 weeks gestation, which is consistent with current ACIP recommendations for optimal timing of maternal Tdap administration
- Any week during pregnancy, since Tdap can be given at any time during pregnancy

Three neonatal outcomes were examined that were identified from inpatient, outpatient, or emergency visits during an infant's first year of life. "Any structural birth defect" was defined by the presence of 2 or more ICD-9 codes from 740.0–759.9. For selected major structural defects, there was a list of over 50 defects that affect an infant's life expectancy, health status, or physical or social functioning. The major structural birth defects were selected *a priori* based on outcomes monitored in US and European birth defect surveillance systems, and outcome-specific algorithms were developed and applied to increase the specificity for identification of major structural defects: For microcephaly, there was also a specific algorithm, which Dr. Sukumaran showed an example of as follows:



In general, for major structural birth defects there was a specific code with different outpatient and inpatient diagnoses required based on validation work that was done. For microcephaly, the code 742.1 would be required with 1 inpatient diagnosis or 2 outpatient diagnoses or 1 outpatient diagnosis and death in the first year.

For the statistical analysis, baseline characteristics between vaccinated and unvaccinated women were compared. Logistic regression was used to estimate aggregate propensity scores to adjust for multiple risk factors. The propensity scores included maternal demographic factors, healthcare utilization during pregnancy, and maternal comorbidities. Prevalence differences were estimated using Poisson distribution with identity link and robust variance. Prevalence ratios were estimated using generalized linear models with Poisson distribution.

After applying exclusion criteria, 324,463 pregnancies were included. Of these, 13% were Tdap-exposed and 87% were Tdap-unexposed. Over 3,000 women were vaccinated before 14 weeks gestation and over 20,000 women were vaccinated between 27 and 36 weeks gestation. In terms of baseline characteristics of the cohort, maternal age, race, and ethnicity were similar

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between the groups. Most vaccinated women were 15 through 24 years old. A slightly higher percentage of vaccinated women received adequate prenatal care and Tdap vaccinated women were more likely to receive another vaccine during pregnancy. Rates of smoking and hypertension were similar between the groups.

Regarding the results of the analysis for any structural birth defect following maternal Tdap, when Tdap vaccine was given before 14 weeks gestation, the rate of any structural birth defect was 6.3% compared to 6.2% in unexposed women. For 27 through 36 weeks gestation, 7% of Tdap-exposed and Tdap-unexposed had a structural birth defect. For Tdap at any time during pregnancy, 6.8% compared to 6.2% of unexposed had a structural birth defect. These differences were not statistically significant.

For major structural birth defects, when Tdap was given before 14 weeks gestation, the rate was 1.8% compared to 1.6% in unexposed women. For Tdap between 27 through 36 weeks gestation, the rate was 1.7% compared to 1.6% in unexposed women. For Tdap at any time during pregnancy, the rate was 1.7% compared to 1.6% in unexposed women. These differences are not statistically significant.

For microcephaly, when Tdap was given before 14 weeks gestation, the rate was 12/10,000 in Tdap-exposed and 12/10,000 in Tdap-unexposed. For Tdap administered at 27 through 36 weeks gestation, the rate was 10/10,000 in Tdap-exposed compared to 12/10,000 in Tdap-unexposed. For Tdap at any time in pregnancy, the rate was 9/10,000 in Tdap-exposed compared to 12/10,000 in Tdap-unexposed. These differences were not statistically significant.

There are some limitations to the study. Birth defects were identified through diagnostic codes using the outcome-specific algorithms rather than clinical exam or direct review of charts. There is a potential for missing diagnoses in children if they had lapses in their insurance coverage. Also, the study was limited to live births. Therefore, it was not possible to study stillbirths, elective terminations, and spontaneous abortions.

In summary, maternal Tdap vaccination during pregnancy was not associated with increased risk for birth defects, including microcephaly, among live birth offspring. These results support the safety of maternal Tdap vaccination for the infant outcomes evaluated.

Discussion Points

Dr. Harrison inquired as to why a record review was not done for at least a subset of the ICD-9 codes.

Dr. Sukumaran replied that a record review was done when the algorithms were being developed for identifying the birth defects to make sure that the codes were valid, and to make sure that the background rates in the VSD were similar to national background rates. That algorithm was then applied to the larger dataset.

Dr. Reingold was curious as to why the investigators did not assess the effect of giving vaccine in the interval between 15 through 26 weeks. Given that ACIP is considering the potential for recommending the vaccine earlier in pregnancy, it might be of interest to do that calculation and show it.

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Dr. Sukumaran responded that this group was included in the "Tdap given at any time during pregnancy" group. If the recommendation changes for the timing of administration, this group can be assessed more carefully.

Given the furor in the discussion about the 2011-2012 recommendations by many ACIP members and liaisons at that time, Dr. Baker (IDSA) congratulated the investigators on performing this study. The second trimester will be assessed and evaluated, and that information will be needed moving forward. She found these data to be beautiful and very reassuring.

Dr. Sukumaran responded that they do have the data on the second trimester, so it is possible to evaluate this closely as well.

Reactogenicity and Immunogenicity of Tdap Vaccine in Pregnant Women

Kathryn Edwards, MD
Vanderbilt University School of Medicine

Dr. Edwards provided an overview of the clinical study of Tdap safety during pregnancy, and preliminary results from the reactogenicity and immunogenicity analyses. ACIP has recommended that providers administer a dose of Tdap during each pregnancy, with the optimal timing being 27 to 36 weeks gestation. Available data support the safety of Tdap in pregnant women, but data on the safety of repeat Tdap doses are limited. As part of a comprehensive monitoring to evaluate the safety of Tdap in pregnant women, a clinical study was implemented in the CDC CISA Project. The primary study aim was to compare rates of injection-site and systemic reactions after Tdap in pregnant women versus non-pregnant women. The secondary study aim was to explore differences in injection-site and systemic reactions in pregnant women who received Tdap before the current pregnancy versus pregnant women receiving their first Tdap dose. There also were two exploratory aims funded by a Bill and Melinda Gates Foundation grant to Vanderbilt, which were to:

- Measure antibody levels to pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbria (FIM) and diphtheria and tetanus toxoids prior to and one month after administration of Tdap vaccine in both pregnant and non-pregnant women; and

- Compare levels of cytokines in women (pregnant and non-pregnant) with severe local or systemic reactions after Tdap with those without reactions, using measurements of cytokines before, during, and after the reactions.

There are additional studies in progress to:

- Assess the rates of preterm and small for gestational age (SGA) births in women who received Tdap during pregnancy;

- Assess the rates of additional obstetrical and infant outcomes in pregnant women receiving Tdap (e.g., pregnancy related hypertension); and

- Describe the health outcomes and growth parameters through 6 months of life among infants born to women who received Tdap during pregnancy.

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In terms of the methods, this is a prospective observational study of women 18 through 45 years of age receiving Tdap as first or repeat doses at Vanderbilt and Duke University clinics. Pregnant women ≥ 20 and ≤ 34 weeks gestation were enrolled in the study. These women received Tdap as part of their routine care. The goal of this part of the study was to enroll 375 pregnant women. Non-pregnant women receiving Tdap for usual care or as part of a research procedure and followed through 1 month after vaccination also were enrolled. The goal was to enroll 225 non-pregnant women. Prior Tdap, Td, or TT history was assessed by subject report, medical record review, or state registry to document vaccine receipt. Rates of local and systemic reactions were assessed during Days 0 through 7 after Tdap using memory aid with severity scales. Blood was collected on Days 0 and 28 after Tdap. Pertussis serology studies were performed at Vanderbilt, while the diphtheria/tetanus toxoid serologies were performed at Duke. Blood was collected in women with severe local and systemic reactions and in controls without the reactions for cytokine analysis on Day 0, the day of the reaction, and Day 28. Pregnancy outcomes were assessed via chart review, and infant outcomes were assessed by phone interview and chart review at 3 and 6 months of life.

The major statistical analysis was directed at non-inferiority analysis for reactogenicity because the study was really looking at the safety of the vaccines. For this purpose, comparisons were made of the proportions with moderate to severe and severe reactions during 0 to 7 days post-vaccination between pregnant women and non-pregnant women receiving Tdap, and between pregnant women who received prior Tdap and those with no prior Tdap receipt. The primary hypothesis was that the rates of moderate to severe reactions in pregnant women receiving Tdap would be non-inferior to non-pregnant women receiving Tdap. One sided statistical tests were used, with a non-inferiority margin of 10% for moderate to severe and 5% for severe reactions.

The mean age, gestational age, and gestational weeks at delivery at both study sites were comparable and the same as seen in other studies presented during the morning. There was also prior Tdap receipt in about 50% of the pregnant women at Vanderbilt, about 65% at Duke, and indeed a higher percentage had received prior Tdap, Td, or TT. In addition, because of vaccine availability at pharmacies, almost all vaccine administered was Sanofi Pasteur's Adacel® vaccine. A small proportion received Boostrix® vaccine. By and large, these women had participated in other vaccine studies and received other vaccines prior to the Tdap vaccine. For the non-pregnant women at the study sites, the mean age was very similar. Prior Tdap receipt was 60% at Vanderbilt and almost 80% at Duke. The non-pregnant women often were under the care of healthcare providers, which may explain their higher rate of prior Tdap receipt. Tdap, Td, and TT receipt was also very high in this group. All of the women in the non-pregnant group at Vanderbilt received Adacel® and about two-thirds at Duke did as well. Again, many of these women had received influenza vaccine the previous year.

Regarding local reactions within the 7 days after vaccination in pregnant versus non-pregnant women, the following definitions were used:

- ❑ Moderate: Induration and erythema: 10-34 mm; Pain/tenderness: Interferes with activity but did not necessitate medical visit or absenteeism

- ❑ Severe: Induration and erythema: >=35 mm; Pain/tenderness: Prevents daily activity and resulted in medical visit or absenteeism

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- ❑ Non-inferiority criteria met for moderate/severe and severe local reactions in pregnant vs. non-pregnant women, except moderate/severe pain

The rates of pain were greater in the pregnant women. The rates of tenderness, swelling, and redness did not differ between the pregnant and non-pregnant groups. Very few severe reactions were observed in the pregnant or non-pregnant women, and did not differ in their rates.

Comparing the proportion difference between pregnant and non-pregnant women, moderate to severe pain did reach the 10% or higher level in pregnant women. The biology that would explain this is not clear. In terms of systemic symptoms after vaccination, moderate fever was defined as ≥ 100.4 to < 102.2° F and other symptoms that interfered with activity but did not necessitate medical visit or absenteeism. Severe fever was defined as ≥ 102.2° F and other symptoms that prevented daily activity and resulted in medical visit or absenteeism. The rates of moderate to severe systemic reactions were comparable in the pregnant and non-pregnant groups for fever, feverishness, malaise, body aches, and headaches.

All comparisons for moderate to severe or severe reactions met non-inferiority criteria among pregnant women with and without prior Tdap receipt. There were no significant differences, and no indication that prior Tdap vaccination would predispose one to more reactions. For systemic and local reactions, when women are compared who had Tdap before to those who did not, there were no significant differences in any of the reactions at the 10% for moderate or severe reactions. It is reassuring that repeated Tdap does not appear to program one for more severe local or systemic responses. No women sought medical care for a vaccine reaction, and no SAEs were reported.

In terms of the serologic studies, for each of the pertussis antigens in both the pregnant and non-pregnant women, the antibody responses were significantly higher post-vaccination for all of the antigens. When the ratio of the pre and post-vaccination antibody titers (non-pregnant: pregnant women) was compared for all the pertussis antigens, some differences were shown. The ratio was significantly > 1.0 for PT and FHA titers post-vaccination and for FIM and PRN pre-vaccination. This means that non-pregnant women had significantly higher antibody titers at 28 days after vaccinations for PT and FIM and had significantly higher antibody titers at Day 0 for FIM and PRN when compared to pregnant women. The non-pregnant women had higher rates of prior immunizations and may have explained why they had higher pre-vaccination titers for FIM and PRN. Why they had higher post-vaccination titers for PT and FIM is not clear.

Comparing the ratio of those antibody titers to those who had not received Tdap before and those who had, for all of the pre-antibody titers, the no Tdap before had a lower ratio, meaning that the antibody titers in no Tdap before for pre-titers were all significantly less. Again, this may have reflected the higher titers in the women who received Tdap before reflected in their pre-titers. What is interesting, however, is that for the FIM and PRN, the antibody titers were higher in those who had not had prior Tdap. It is not clear whether that reflects immune suppression or is a statistical fluke. But again, all of them had antibody rises.

Regarding the cytokine study, 6 subjects had severe reactions. They were seen at the time of the severe reactions. They were matched to 6 controls who did not have severe reactions who were seen at that same time, and were matched by pregnancy status. There were 5 cases at Vanderbilt, 2 of whom were pregnant and 3 of whom were not. There was 1 non-pregnant case at Duke. They were matched for their pregnancy status. For each of the cytokine levels at each

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of the determinations, there were no significant differences between the cases and the controls. Also, there were no differences in the cases before and after vaccination or the time of local or systemic reactions for IL-6, IL-8, IL-10, TNF-α, and IL-5.

In conclusion, Tdap was well-tolerated in both pregnant and non-pregnant women. Moderate and severe injection-site pain occurred more frequently among pregnant women, but rates were consistent with clinically reported rates for the Tdap vaccine (16% per Adacel® package insert) and did not lead to medical visits. Of the pregnant women, 53% received a prior Tdap vaccine and rates of moderate and severe reactions were similar in pregnant women receiving the first or repeat Tdap vaccine. Both pregnant and non-pregnant women had significantly higher antibody titers to all antigens after vaccination. Obstetric and fetal outcome data are being collected.

Discussion Points

Dr. Karron wondered whether the antibody responses had been analyzed by gestational age.

Dr. Edwards responded that they did assess this. Unfortunately, they were so adherent to the study criteria, there was little variability in when women received the vaccine. Therefore, this cannot be addressed adequately.

Dr. Reingold asked whether there were any women in the study for whom it was a third pregnancy and who were receiving a third dose of Tdap.

Dr. Edwards replied that they did not have these data.

Dr. Baker (IDSA) asked whether Dr. Edwards could comment on the possibility of differences in circulating pertussis in the community among the two groups, and whether the study was performed at a time when pertussis activity was high, medium, or low.

Dr. Edwards responded that at the time of the study, the investigators did not appreciate that the issues regarding circulation of pertussis were occurring at either site. They did not have ongoing serologic studies that might have evaluated that. They have not assessed duration of antibody in this particular study, although they are in the process of analyzing data funded by NIH in which antibody titers were assessed over two years in women who were vaccinated post-partum. The antibody titers drop off very fast, which is very curious because for tetanus and diphtheria they do not. This is very interesting. Even in those patients, at two years there were still some antibody titers for some of the antigens. Some of these women were vaccinated within a year or so in the non-pregnant group. It is hard to say, but the investigators do not believe that there was natural transmission. Pertussis is a complicated problem.

Ms. Stinchfield (NAPNAP) noted that Dr. Edwards had used the words “reaction” and “response.” When vaccinating pregnant women and they get local redness and swelling, a pregnant woman might hear “a vaccine reaction equals I can’t have another one in the future.” To turn that to a positive, that is a robust immune response.

Dr. Edwards said that for many years, an attempt has been made to determine whether having a more vigorous local immune response translates to a better serologic response. That is not always consistently seen with all antigens. It would be difficult to say whether having a better response means having higher antibody. The most reassuring thing she could say about this

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would pertain to cytokine data. Only 6 people had severe reactions, which is very reassuring. Even at the time of the peak local reactions, there were not systemic cytokine responses that were elevated. This is very reassuring. It is not clear exactly what will happen in terms of repeated Tdap. They did conduct a study a number of years ago that also was funded by the CISA Project in which children were assessed at 4 to 6 years who had large local reactions after their fourth dose of DTaP at 18 to 24 months, and in general those children did have slightly more local responses after their fifth dose than they did at the fourth. However, it was not remarkable and there were no severe reactions and no inhibition of activities.

Dr. Sun (FDA) wondered whether anything was found in the assessments of infants at 3 and 6 months by telephone and chart review.

Dr. Edwards indicated that those are still in the process of being analyzed. All of the patients have not reached that mark, but these data should be available soon. Empirically speaking, there were no AEs of note.

Pertussis Vaccines WG Update

Art Reingold, MD
Chair, ACIP Pertussis Vaccine Work Group

Dr. Reingold reminded everyone that the Pertussis Vaccine WG was originally formed in April 2009. Since then, there have been some changes to the composition of the WG. As of June 2015, the WG had completed all but one remaining term of reference:

> *Review existing statements on infants and young children (1997), adolescents (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate into a single statement.*

This consolidated statement was drafted, has been reviewed by WG members, and is making its way through CDC clearance.

Since 2013, the ACIP recommendation for pregnant women has been as follows:

> *Health-care personnel should administer a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap.*

The guidance for use states the following:

> *To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation.*

Since then, several studies from other countries have looked at the immunogenicity of vaccinating pregnant women primarily from 27 through 36 weeks gestation. But one study prompted the request by CDC to reconvene the WG.

Three recently published studies with relevant data show equal or higher antibody concentrations among infants whose mothers were vaccinated in the second trimester compared to those whose mothers were vaccinated in third trimester[1]; higher PT antibody levels in mothers vaccinated at 28 through 32 weeks compared to those vaccinated 33 through 36

weeks[2]; and no differences in titers of neonatal antibodies between mothers vaccinated in the late second trimester and during the third trimester[3] [[1]Eberhardt CS, et. al. Clin Infect Dis. 2016 Jan 20.; [2]Naidu MA, et al. Am J Obstet Gynecol. 2016 Mar 9. [Epub ahead of print]; and [3]Vilajeliu A, et. al. Vaccine. 2015 Feb 18;33(8):1056-62].

The UK Joint Committee on Vaccination and Immunization changed its recommendation in February 2016 such that they now recommend that women receive the vaccine as early as 16 weeks of gestation, but after the mid-pregnancy ultrasound. Presumably then if there are any abnormalities, they cannot be blamed on a dose of Tdap that has recently been given.

The next steps for the WG are to review new data related to Tdap in pregnancy regarding timing of vaccination during pregnancy, Tdap effectiveness of preventing pertussis in infants, safety, and programmatic considerations. The plan for the October 2016 ACIP meeting is to present the consolidated ACIP statement and have additional discussion regarding the timing of maternal Tdap vaccination, summarizing the existing data and receiving suggestions from ACIP about keeping the timing the same or changing it in the US.

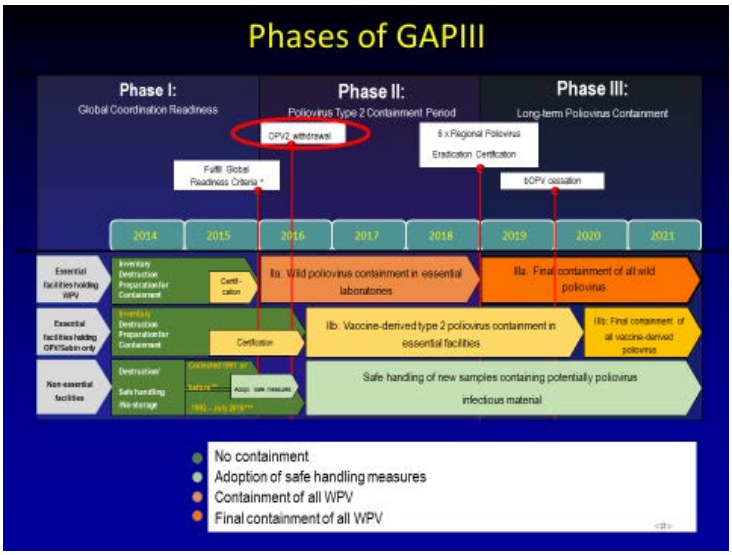
Laboratory Containment of Poliovirus Type 2

Olen Kew, PhD
National Poliovirus Containment Coordinator (NPCC)

Dr. Kew presented a status report on Poliovirus Type 2 containment in the US. The last wild poliovirus (WPV2) in the US was eradicated before 1965, WPV3 around 1968, and WPV1 around 1970. Globally, WPV2 was last detected in October 1999. Although vaccine strains of Type 2 have been detected through the present, indigenous WPV has not been detected since that time. Globally, it appears that WPV3 also has been eradicated though WHO is not prepared to declare that yet. The last case was in 2012 in Nigeria. WPV1 is barely hanging on. Thus far in 2016, there have been about as many cases as occurred in 30 minutes when this program began. As of 14 September 2016, there have been 25 cases in only three endemic countries: Pakistan has reported 14 cases, with the most recent being 27 July; Afghanistan has reported 8 cases, with the most recent occurring 8 August; and Nigeria has reported 3 cases, with the most recent detected in 6 August.

The goal of the WHO Global Action Plan on Poliovirus Containment, Third Edition (GAPIII) is to minimize poliovirus facility-associated risk after type-specific eradication of WPVs and sequential, type-specific cessation of oral poliovirus vaccine (OPV) use. The original hope was to eradicate all three serotypes in such a close time span that there could be a coordinated, concurrent containment of all three poliovirus serotypes. However, because of the long lag after the eradication of Type 2 and the occurrence of repeated outbreaks associated with Type 2 circulating vaccine-derived polioviruses, it became clear that Type 2 had to be contained specifically. Therefore, implementation is in three phases. Phase I was Global Coordination and Readiness, Phase II is Poliovirus Type 2 Containment by 2016, and Phase III is Complete Poliovirus Containment (all three serotypes) at least three years after the last WPV case/infection. The date for completion of Phase III depends on the timeline of WPV eradication in the remaining endemic countries. All “infectious” and “potentially infectious” poliovirus materials were requested to be inventoried by the end of 2015, although this was not accomplished. Not only WPV and OPV/Sabin of all three serotypes, but also vaccine-derived

polioviruses (which are phenotypically indistinguishable from WPVs). Some vaccine-derived polioviruses have circulated in communities for as long as 10 years. The objective is to reduce the number of facilities handling poliovirus to a minimum. The following graphic depicts the phases of GAPIII.



One of the key events was the withdrawal of OPV Type 2 from the vaccine by May 2016. The last dose of trivalent OPV was given before mid-May 2016, and a shift was made to a bivalent Type 1 and 3 vaccine. That poses a biological imperative to containing Type 2 in the US, and particularly in developing countries. The long-term plan is to cease the use of bivalent OPV as well and shift to IPV. Within that, WPV and vaccine-derived Type 2 poliovirus must be contained in what are known as “Poliovirus Essential Facilities” in 2016. An approach is being used that will phase in the strategy. “Containment” means to act on three options: 1)destroy and document destruction of all unneeded poliovirus infectious or potentially infectious materials, 2) transfer important materials to a Poliovirus Essential Facility, or 3) become a Poliovirus Essential Facility by implementing facility and personnel performance standards required by GAPIII.

In terms of the US role in global containment, Dr. Walter Dowdle initiated a survey in 2002–2003 that showed that 34% of all facilities worldwide storing WPV infectious or potentially infectious materials were in the US. CDC has the largest WHO Global Polio Reference Laboratory. The US is home to many leading poliovirus research institutions. There is no polio vaccine production in the US, but there is ongoing vaccine testing. While the risks of facility-associated poliovirus infections in the community in the US are low, they are not zero. The risks are much higher in developing country settings. The US has a responsibility to take a leading role and set a good example. The US National Poliovirus Containment Coordinator (NPCC) reports to the US National Certification Committee (NCC), the NCC reports to a Regional Certification Commission (RCC), and the RCC reports to the Global Certification Commission (GCC). The GCC ultimately will declare the eradication of polio worldwide, as was done previously with smallpox.

The NCC Task Force for Global Health in Decatur, Georgia is the Secretariat for the NCC, which is constituted by the eminent experts in their fields:

- Chair: Kenneth I. Berns, MD, PhD, Distinguished Professor Emeritus, Molecular Genetics and Microbiology, University of Florida
- Charles Brokopp, DrPH, Laboratory Director, Wisconsin State Laboratory of Hygiene
- Megan Davies, MD, Acting State Health Director, State Epidemiologist and Chief, North Carolina Division of Public Health
- Joseph Kanabrocki, PhD, CBSP, Associate Vice President for Research Safety, University of Chicago
- Ruth Lynfield, MD, State Epidemiologist and Medical Director, Minnesota Department of Health
- José Romero, MD, FAAP, Chief, Pediatric Infectious Diseases; Director, Clinical Trials Research, Arkansas Children's Hospital Research Institute
- Dominica (Dee) Zimmerman, University of Texas Medical Branch, Environmental Health and Safety

The 2002–2003 survey was implemented among 105,356 individual laboratories in 32,429 institutions. Only 180 laboratories reported storage of WPV infectious or potentially infectious materials. The survey did not ask about serotype. This included 12 CDC laboratories. The 2002–2003 polio survey came in wake of the Select Agent Act and had a very high response rate, which may not have been coincidental. The survey queried only about WPV materials, not OPV/Sabin strains. There was no differentiation by serotype. The findings from the 2002–2003 survey were the starting point for a 2015–2016 survey conducted by the Office of the NPCC based at CDC, which reports to CDC, NCIRD, NCC, and the Office of Assistant Secretary of Health (OASH) through National Vaccine Program Office (NVPO), directed by Dr. Bruce Gellin. CDC developed a web-based survey instrument that was modified from the original WHO/PAHO (Pan American Health Organization) template. The initial contact is by email. Two surveys were distributed, one of which was an internal CDC survey that was launched 14 December 2015 in an effort to comply with the 12 November request from the Director General of WHO to have this job completed by the end of 2015. The second was an external survey that was launched serially with the first launch 22 December 2015 among federal facilities, academic institutions, state and local health departments, industrial facilities, commercial diagnostic laboratories, and hospitals. The initial response rate was not very high, but has now risen to 82%.

NPCC's approach to containment was distribution of the survey by prioritization of the estimated risk. Phase IIa was containment of WPV2 and VDPV2 infectious materials. The top priority was academic laboratories that had been working with WPV2 and VDPV2 recently. The second priority was containment of potentially infectious materials. Phase IIb included the third priority of containment of OPV2/Sabin 2 infectious materials, and the fourth priority is OPV/Sabin potentially infectious materials. The priority categories frequently overlap, which was clear from the responses received. This was an opportunity to contain all PV and be removed from the list for the facility. Potentially infectious materials have been prioritized by risk, assigning the highest risk to stool specimens.

Surveys have been launched in successive waves, prioritizing by estimated risks. The highest priority has been assigned to WPV2 strains and enteric specimens, while the lowest priority has been assigned to domestic respiratory specimens and nucleic acids. Containment is an ongoing process. The immediate goal is PV2 containment in 2016. The overall goal is full

poliovirus containment, potentially as early as 2019. The survey results are used to guide the priorities for subsequent survey rounds. A collaborative approach to laboratories has been taken. The NPCC office has been assisted greatly by Biosafety Officers for coordination and further follow-up. NVPO assistance will be sought for chronic non-responders.

In terms of the internal CDC survey, CDC is the largest facility storing poliovirus infectious and potentially infectious materials. Containment receives strong institutional support. The CDC Polio Laboratory is the major WHO Global Polio Reference Laboratory, and contains the largest poliovirus collection in the world. It is the only CDC laboratory with WPV2/VDPV2 infectious materials. All WPV2/VDPV2 were moved to a containment laboratory and 189,763 vials of poliovirus infectious or potentially infectious materials in the CDC Polio Laboratory were autoclaved by 24 May 2016. Other CDC laboratories store poliovirus potentially infectious materials comprised of historical US and international specimens. All 149 CDC laboratories were contacted and completed the survey by 15 March 2016.

The external survey was launched in successive waves, with the first launch in December 2015. The survey was distributed to 113 laboratories identified in a 2002–2003 survey as storing WPV materials (other facilities identified in 2002–2003 were no longer operating). Special attention was given to laboratories known to be performing current research / testing with WPV2. There was a re-launch to first-round non-responders as well as subsequent launches to newly identified laboratories, state and large municipal health laboratories, other non-polio enteric virology laboratories (rotavirus, norovirus, astrovirus, Hepatitis A virus, Hepatitis E virus, et cetera) and enteric bacteriology laboratories. There is less concern about enteric bacteriology and parasitology laboratories, given that they do not normally store original stool specimens after isolation of infectious agents. However, enteric microbiome/metagenomics laboratories do retain specimens for reinvestigation as methods improve. There has been a significant amount of assistance from Biosafety Officers of large institutions to help fill any remaining gaps. There were 178 responses to the internal survey as of September 6, 2016. The major academic laboratories responded early. Most of the laboratories that responded later have worked with reference strains or have stored reference strains primarily for serology. More laboratories work with Type 1. Type 2 is not the favorite one for most research laboratories. The same is true with the Sabin strains.

There are a number of challenges. Some interpretations at WHO headquarters of GAPIII requirements are very prescriptive, and they are becoming an impediment to compliance. High-risk infectious materials and low-risk potentially infectious materials such as respiratory specimens and nucleic acids are grouped together for containment in GAPIII, without any real appreciation of the great differences in potential risk. WHO is aware of these challenges and has empaneled a Containment Advisory Group to help guide the way forward. Absence of statutory authority could limit compliance outside of federal government facilities. While this has the potential to limit compliance, that has not been the experience. The process for issuing certificates to Poliovirus Essential Facilities is incompletely defined. Potentially infectious materials, especially of OPV/Sabin variety, present challenges for outreach. Respiratory virology / microbiology laboratories have particular concerns about how poliovirus containment might adversely impact their vital work. Academic laboratories, with frequent student turnover, present special challenges to specimen management and containment. Non-poliovirus and non-virus laboratories are not generally aware of poliovirus containment. Some may store potentially infectious materials. Absolute poliovirus containment is not feasible. Undetected vaccine-derived excretion is likely to continue. For example, a patient in the UK has been excreting for nearly 30 years, and one chronically-infected patient went undetected for 13 years

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in the US. That is likely to continue. Poliovirus can be easily prepared by synthetic biology, fortunately and unfortunately. GenBank® sequence data exists in perpetuity. The goal must be major reduction of risk, which is feasible provided that colleagues are constructively engaged.

In terms of an example of the impact of Type 2 containment on US vaccination policy, the general recommendations for children with low or questionable documentation of vaccination are to take an alternative approach rather than just giving IPV, which would be the preferred approach. That would be serologic testing for neutralizing antibody to all three serotypes. This can be obtained commercially and at certain state health department laboratories, although there is limited availability. Persons with protective titers against all three types do not need to repeat doses, but should complete the schedule as age-appropriate. The alternative approach may no longer be feasible because commercial facilities are no longer working with Type 2, so they suspended Type 2 antibody in response to the request for them to contain their Type 2 strains [This information courtesy Mona Marin and Manisha Patel DVD/NCIRD/CDC].

Discussion Points

Dr. Ezeanolue asked whether consideration had been given to anticipated uptake in terms of moving from OPV to IPV, especially in countries like Nigeria.

Dr. Kew responded that this has been part of the plan for some time. There has been difficulty in Nigeria even administering OPV. While he did not know the acceptance rate precisely, enormous effort has been invested in each country to raise coverage rates to as high as possible. The weaknesses in the overall strategy is that routine immunization is low in some countries, especially in Nigeria where coverage is strong in the South and much weaker in the North. Successful IPV door-to-door campaigns have been conducted in Kenya. It remains unclear how high coverage rates will be with the shift away from trivalent OPV. However, the bivalent OPV will continue to be used. The bivalent will not be suspended until all three serotypes are eradicated. The problem with Type 2 in recent years has been the Type 2 vaccine-derived polioviruses from the trivalent vaccine. Once that is removed, it is not anticipated that this will be as serious a problem. Routine immunization rates must be raised as much as possible worldwide.

Dr. Romero emphasized that this has been a Herculean effort that has been shepherded and led by Dr. Kew, who deserves a lot of credit for assembling these data.

Given that it is stored in laboratories throughout the US, Dr. Smith wondered how the infectious material is destroyed, where this is done, and whether it has to be shipped.

Dr. Kew responded that the virologists and microbiologists are well-trained in how to destroy poliovirus. They simply put it in the autoclave and it is destroyed. All of the laboratories have autoclaves, which allows them to destroy the virus readily. There are a number of other ways as well. The greater challenge has been to destroy the trivalent OPV stocks so that they are never used again in the field.

Dr. Cohn requested that someone discuss the plan to address the serology alternative approach.

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Mona Marin indicated that an effort is being made to assess the scope of this problem. There has been informal contact with companies that have been providing this service. There are certain state laboratories that also have been providing it. The second part is understanding the degree to which that particular element in Table 14 in the General Recommendations has been incorporated into either local regulations or even in the case of some federal facilities. Currently, they are at the data gathering stage trying to understand the scope of this problem in terms of providing that service and the impact to state, local, and federal institutions due to using this particular element of the General Recommendations. At that point, it is anticipated that the change would be proposed to remove it.

Dr. Koger indicated that post-ACIP vote on CDC clearance in September 2015, the language was taken out to offer serology as an alternative approach. Revaccination is now the primary approach per the CDC-level cleared draft of the General Recommendations for people vaccinated outside of the US who enter the US with questionable records. This is going through clearance currently, so at least from an implementation perspective, that language should be published soon.

Dr. Sun (FDA) asked whether the long-range plan was to continue with polio vaccination until eradication, or if there is an anticipation that vaccination of laboratory workers would be continued just in case they are exposed.

Dr. Kew replied that the long-term plan would be to use IPV for an indeterminate period of time, and assess the risks moving forward. There is no date set for the cessation of IPV use. It may simply become part of a multi-antigen vaccine that is used for many years. Some countries have stated that they will be using IPV indefinitely, depending upon its availability and a number of other factors. Continued use will depend upon the epidemiology moving forward.

Human Papillomavirus (HPV) Vaccines

Introduction

Allison Kempe, MD, MPH
Chair, ACIP HPV Vaccines WG

Dr. Kempe reminded everyone that the WG has been reviewing evidence on HPV vaccine 2-dose schedules. During the February 2016 ACIP meeting, the HPV session focused on data from the 2-dose immunobridging trial. The June 2016 session provided further evidence needed for consideration of a 2-dose HPV vaccination schedule that the WG hoped would result in a vote during the October ACIP meeting.

During the February 2016 meeting, background information was provided on 2-dose schedules; data were presented from the 9-valent HPV vaccine 2- versus 3-dose immunogenicity trial, which showed non-inferior immunogenicity with 2 doses using either a 0, 6 month or 0, 12 month schedule in 9 through 14 year olds compared with 3 doses using a 0,2,6 month schedule in 15 through 26 year olds. Subsequently, a sBLA was submitted to the FDA in early 2016. Bivalent and quadrivalent HPV vaccine 2- versus 3-dose immunogenicity data and HPV WG plans also were presented at the ACIP meeting in February 2016.

Since February 2016, the WG has reviewed data on duration of protection after HPV vaccination and on post-licensure effectiveness studies, drafted policy questions, conducted a systematic literature review and completed initial GRADE evaluation of evidence for 2-dose schedules, and discussed considerations for recommendations.

During this session, presentations were given on the following topics:

- ❑ Duration of protection after HPV vaccination
- ❑ Modeling and cost-effectiveness of 2-dose schedules
- ❑ Review of vaccine effectiveness studies
- ❑ GRADE for 2-dose schedules
- ❑ Initial considerations for recommendations

HPV Vaccine Availability in the US / HPV Vaccine Duration of Protection

Lauri Markowitz, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Markowitz began by mentioning the status of HPV vaccine availability in the US since this would impact some of ACIP's discussions and approaches. There are 3 HPV vaccines licensed in the US: Quadrivalent (4vHPV), bivalent (2vHPV), and 9-valent (9vHPV). Through 2014, almost all HPV vaccine used in the US was 4vHPV. 9vHPV was licensed in 2014 and was recommended in 2015. Currently, almost all vaccine being ordered in the US is 9vhpv. As expected with the transition from 4vHPV to 9vHPV, Merck has decided to withdraw 4vHPV from the US market by the end of 2016. 4vHPV has not been on CDC vaccine contracts since April 2016. Regarding 2vHPV, GSK has made a strategic business decision to stop supplying 2vHPV in the US due to very low market demand. Vaccine supplies in the US are expected to be used up by November 2016. 2vHPV has not been on CDC vaccine contracts since April 2016. GSK will maintain the 2vHPV license in the US. 4vHPV and 2vHPV will continue to be available outside of the US. While by the end of the year all vaccine being used in the US will be 9vHPV, during this session the WG presented data on 4vHPV and 2vHPV for two reasons: 1) data from these studies provide information that can inform the discussion about 2-dose schedules; and 2) millions of persons have been vaccinated with 4vHPV in the US.

Dr. Markowitz reviewed data on duration of protection. HPV vaccination is targeted to young adolescents to achieve protection of the largest percentage of vaccinees before exposure to the virus, but protection is needed through many years of sexual activity. Therefore, long duration of protection from HPV vaccination is important and duration could impact the effectiveness of vaccination programs. It is important to review available data on duration of protection for a 3-dose vaccination schedule as ACIP considers reducing the number of recommended doses. Another reason the WG presented these data at this time was because the modeling of 2 versus 3 doses examines different assumptions of duration of protection; understanding available t data on duration is needed to put the modeling into context.

In this talk, Dr. Markowitz provided an update on what is known about duration of protection from 3-dose HPV vaccines trials as well as immunogenicity data, including persistence of antibody and challenge studies to evaluate immune memory by anamnestic response to an additional vaccine dose. She also reviewed some data on persistence of antibody from 2-dose trials that were presented in February 2016.

Briefly as background, all available HPV vaccines are virus-like particle vaccines made from the L1 major capsid protein of the virus. Vaccines differ in their production system and adjuvants. For the bivalent vaccine, the adjuvant is AS04, which includes MPL (3-O-desacyl-4'-monophosphoryl lipid A) which stimulates Toll-like receptor 4 and enhances the vaccine induced immune response. The adjuvant for quadrivalent and 9-valent vaccines is amorphous aluminum hydroxyphosphate sulfate.

Data available on duration of protection that Dr. Markowitz reviewed during this session were from follow-up of randomized clinical trials. Most efficacy and immunogenicity trials had about 3 to 4 years of follow-up. At the end of most of these trials, the control group was vaccinated. Extended follow-up for persistence of antibody and infection / disease outcomes was conducted for some trials after the original or base trial period was completed.

The following table lists trials that have data on long-term duration of protection after a 3-dose schedule. Included on this table are trials of monovalent HPV 16 vaccine, 2vHPV, and 4HPV:

Base Trial				
Trial	**Participants age (yrs)**	**Trial duration (yrs)**	**Reference**	**Long term follow-up available (planned)**
HPV16 phase II efficacy	Females 16–23	4	Koutsky, NEJM 2002 Mao, OBGYN 2007	8.5
2vHPV Phase II efficacy	Females 15–25	2.3	Harper, Lancet 2004	8.9
4vHPV immunogenicity	Females/males 9–15	3	Reisinger, PIDJ 2007	10
4vHPV phase III efficacy	Females 15–26	4	Future II, NEJM 2007	10 (14)
4vHPV phase III efficacy	Males 16–26	3	Giuliano, NEJM 2011 Palefsky, NEJM 2011	8.5 (10)
4vHPV phase III efficacy	Females 24–45	4	Castellsague, Br J CA 2011	7.2 (10)

For the base or original trial shown on the left is the type of trial, population, age group at time of vaccination, and the duration of the study in years. The last column, on far right, shows the long-term follow-up period with the years of follow-up available and for those not completed, with the longest planned follow-up time in parentheses.

The monovalent HPV 16 vaccine trial was a proof-of-concept Phase II trial in women aged 16 through 23 years conducted by Merck. At final follow-up, the mean time since first dose was 8.5 years. Enrollment for the original or base RCT was conducted in 1998-1999 and included over 2000 women. Vaccine efficacy against HPV 16 persistent infection was 94%, and was 100% for cervical intraepithelial neoplasia (CIN). The final follow-up included 290 participants from Seattle. During the follow-up period, vaccine efficacy for HPV16 infection was 100%. There were no cases of HPV 16-related infection in the vaccine group and 6 in the control group. There were no cases of HPV 16-related CIN in the vaccine group and 3 in the control group.

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The 2vHPV Phase II trial among women aged 16 through 23 years had long-term follow-up with a mean of 8.9 years. The base trial was initiated in 2001 and included over 1000 participants. Vaccine efficacy for HPV 16/18 persistent infection was 100%. Several follow-up evaluations were conducted. The final follow-up included participants from Brazil. This study found vaccine efficacy for HPV 16/18 infection was 100% during the follow-up period. There were no HPV16/18 infections in the vaccine group and 9 in the control group. There were no cases of HPV 16/18-related CIN in the vaccine group and 1 case in the control group. Several different follow-up periods were investigated for this study. VE was 95.6% [Naud, Human Vaccin Immunol 2014].

The four 4vHPV trials had no unvaccinated control group during follow-up; therefore, there will be no efficacy determination in the follow-up studies. The results are disease detection and incidence. The 4vHPV immunogenicity trial in adolescents 9 through 14 years of age has completed the planned 10 year follow-up. The base RCT included sexually naïve boy and girls. Follow-up for effectiveness began after age 16 and there was twice yearly evaluation. The population and the median follow-up time for the early and the catch-up vaccination groups 9.9 years and 7.4 years, respectively. The final 10 year follow-up data from this study were presented in June at an international meeting. There were no cases of HPV 6,11,16,18 disease in the per protocol population during the follow-up period. Ten persistent infections of $\geq$6 months duration, including 2 of $\geq$12 months duration, were detected. All participants with persistent infection had antibody to the respective type, and there was no correlation between the persistent infection and waning titers for that HPV type. Incidence of persistent vaccine type infection per 100 person years ranged from 0.3 to 0.6. For comparison, the incidence of persistent 6/11/16/18 infection in the placebo group of trials in 16 through 26 year olds was more than 10-fold higher, with males 6/100 person-years and females 4/100 person-years.

For the large 4vHPV efficacy trial in women 16 through 23 years of age, interim 10-year follow-up data are available. This study will be completed after 14 years of follow-up. The base RCT included 12,000 women from 13 international sites. Follow-up is being conducted through the Nordic Cancer Registries, which includes women enrolled from Demark, Iceland, Norway, and Sweden. Registry searches are done every 2 years. Disease detection was very low. There was one case of CIN1 at 6 to 8 years after vaccination. HPV types 16, 45, and 52 were detected in the lesion concurrently.

The 4vHPV efficacy trial in males age 16 through 26 years now has 8 years of follow-up. The base RCT included over 4000 men from 18 countries. Annual visits are being conducted among men enrolled in long-term follow-up, including anal cytology for men in the MSM sub-study. There have been no cases of HPV 6,11,16,18 genital warts or external genital lesions in the per protocol population in the early vaccine group. There was one case of anal intraepithelial neoplasia (AIN)1, with HPV 6 and 58 detected in the lesion concurrently. Again, there is no unvaccinated control group, but the risk of AIN was 0.3/100 person years at risk. As an historical comparison, the risk of AIN was 5.8/100 person-years in the placebo group of the base study.

In a follow-up of the 4vHPV efficacy trial in women 24 through 45 years of age, interim data through 7.2 years of follow-up are available. This was an RCT that included women from 7 countries. Follow-up is being conducted among women enrolled from Columbia with evaluation every 2 years. There were no cases of HPV 6,11,16,18 external genital lesions or CIN2+ in the per protocol population during the follow-up to date.

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In addition to the studies just reviewed, there are other trials with long-term follow-up planned or ongoing but that do not yet have data. These include two 2vHPV Phase III efficacy trials (PATRICIA and the Costa Rica Vaccine trial), with planned follow-up of 14 and 10 years, respectively, the 9vHPV Phase III efficacy study with planned follow-up of 14 years, and the 9vHPV immunogenicity study in adolescents with planned follow-up of 10 years.

Dr. Markowitz briefly reviewed what is known about the immunogenicity of HPV vaccines. There is high seroconversion after vaccination: >97% in the clinical trials at one month after the third dose. Vaccination induces higher antibody titers than natural infection. Titers peak at 1 month after the last dose, decline, and then plateau by 18 to 24 months. The main basis of protection is neutralizing antibody. However, the minimum protective antibody threshold is not known. The predominant response to vaccination is neutralizing immunoglobulin G (IgG) antibody. It also is important to know that the clinical trials of the 2vHPV and 4vHPV vaccines used different serologic assays and results are difficult to compare across studies or HPV types. The 2vHPV trials used an enzyme-linked immunosorbent assay (ELISA), which measured both neutralizing and non-neutralizing antibody but detects antibody to one immunoglobulin class. The trials for the 4vHPV and 9vHPV vaccine used a competitive Luminex® immunoassay (cLIA), which measures antibody restricted to one neutralizing epitope. In clinical trials, some 4vHPV vaccinees lost detectable HPV 18 antibody by the cLIA, but there was no loss of protection. In a direct head-to-head comparison of the two vaccines using the same assay, antibody titers were higher after 2vHPV than 4vHPV vaccination.

Many of the trials have or are following participants for persistence of antibody in addition to infection or disease outcomes. Shown here are the monovalent and 4vHPVtrials with long-term available or planned follow-up for persistence of antibody:

Base Trial		**Follow-up**		
Trial	**Participants (yrs)**	**Yrs available (planned)**	**Seropositive for 6,11,16,18**	**Reference**
HPV 16 phase II efficacy	Females 16–23	8.5	86% seropositive for HPV 16 in vaccine group; 9% in placebo	Rowhani-Rahbar, Vaccine 2009
4vHPV immunogenicity	Females/Males 9–15	10	89%, 89%, 96%, 61%	Das and Saah EUROGIN 2016
4vHPV phase III efficacy	Females 16–23	9 (14)	94%, 96%, 99%, 60%	Nygard, Clin Vaccin Immunol 2015
4vHPV phase III efficacy	Males 16–26	6 (10)	84%, 87%, 97%, 48%	Das and Saah EUROGIN 2016
4vHPV phase III efficacy	Females 24-45	8 (10)	89%, 89%, 96%, 61%	Das EUROGIN 2015

On the left is the base trial with the participant age group, and on the right is the follow-up available with the planned number of years in parentheses. These trials have planned follow-up up to 10 or 14 years. Also included is a summary of the results at the latest follow-up time point. The monovalent vaccine trial followed women for 8.5 years. At that time, 86% were positive to HPV 16 in the vaccine group compared to 9% in the placebo group. For the 4vHPV immunogenicity trial in adolescents, the 10 year follow-up is complete as mentioned before. At

10 years, seropositivity was 89%, 89%, and 96% for HPV 6, 11, and 16, respectively, and 61% for HPV 18. Similar patterns were observed in the follow-up of other 4vHPV trials with high seropositivity to 3 vaccine types, and lower for HPV 18. Although some persons lost detectable HPV 18 antibody by cLIA in the 4vHPV clinical trials, there was no breakthrough disease. Since efficacy remained high, this suggests that protective levels are lower than the minimum detectable level by the assay or that antibodies against additional epitopes can be protective. When sera in these trials were retested using a total IgG assay, seropositivity to all types increased and seropositivity to HPV 18 reached 78% to 90%.

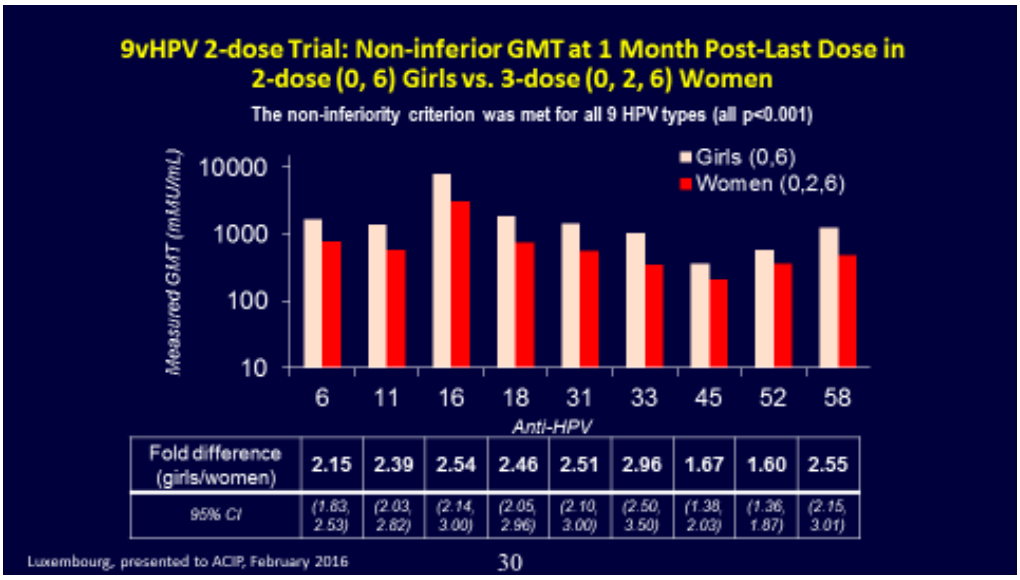
The following table shows 2vHPV trials with long-term follow-up for persistence of antibody:

Base Trial		**Follow-up**		
Trial	**Participants (yrs)**	**Yrs available (Planned)**	**Seropositive for 16,18**	**Reference**
2vHPV Immunogenicity[1]	Females 10–14	10	100%, 100%	Schwarz, WSPID 2015
2vHPV Phase II efficacy[2]	Females 15–25	9	100%, 100%	Naud, Hum Vaccin Imm 2014
2HPV Immunogenicity[3]	Females 15–55	6 (10)	100%, 97%	Schwarz, BJOG 2014

The assay used for these studies was an ELISA. The longest follow-up available is 10 years from the adolescent immunogenicity study shown on first line. All participants in the follow-up remained seropositive for HPV 16 and 18. HPV 16 and 18 GMTs were 53- and 26-fold higher than those associated with natural infection. Similarly, in the other studies with 9 and 6 years of follow-up, all vaccinees remained seropositive to HPV 16 and >97% to HPV 18.

Three studies have assessed immune memory by evaluating immune response after administration of an additional vaccine dose after completion of the 3-dose series. In the monovalent HPV 16 vaccine study, this was at 8.5 years after enrollment into the base study in the 4vHPV trial, 5 years after, and in a 2vHPV vaccine trial 7, years after. In all studies, an anamnestic response was observed to the types in the original vaccination [[1]Rowhani-Rahbbar, J Clin Virol 2009; [2]Olsson, Vaccine 2007; and [3]Moscicki, Vaccine 2002].

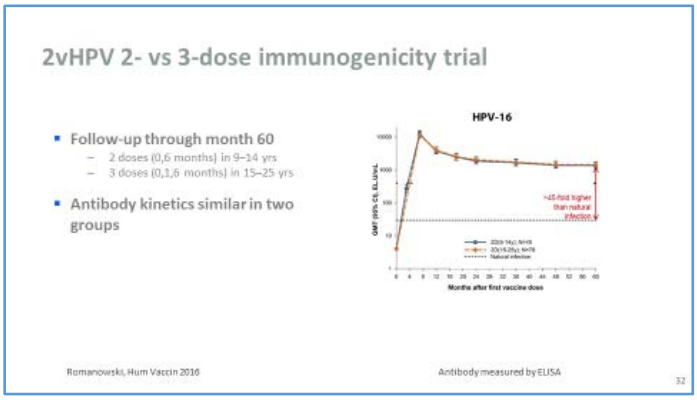
Data are or will be available from trials of 2-dose schedules. The following table has results from 9vHPV 2-dose trial presented to ACIP in February 2016:



As shown in the lighter bars, the GMTs in girls who received 2 doses at 0,6 months were non-inferior and in fact higher than the titers in women (shown in red) who received the standard 3 dose schedule for all 9 types.

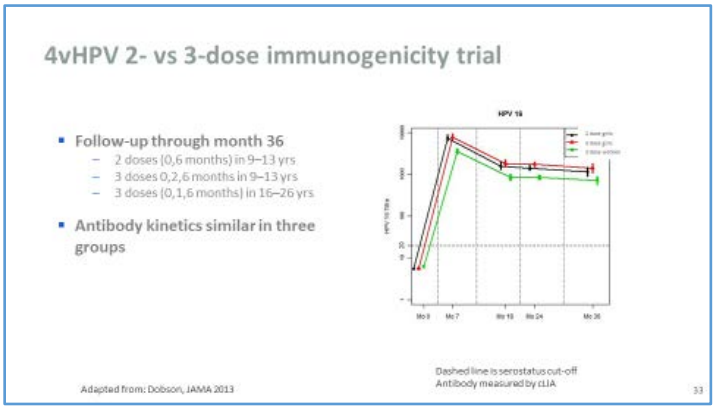
The 9vHPV 2- versus 3-dose immunogenicity data, which was presented to ACIP in February 2016 included data 1 month after the last dose. This trial will continue for 2 more years for assessment of antibody persistence. One additional dose will be given at month 36 to access immune memory. A separate long-term effectiveness study is being planned.

While there are data only through 1 month after the last dose from the 9vHPV trial , there are longer follow-up data from studies of 2vHPV and 4vHPV trials that show that the kinetics of the antibody response of a 2-dose schedule when given at an interval of at least 6 months is similar to that of a 3-dose schedule. This graphic was shown to ACIP in February 2016 and displays GMTs after 2vHPV vaccination in a 2-dose schedule (0, 6 months) at 9 through 14 years of age and a 3-dose schedule at 15 through 25 years of age:



Follow-up in this study is through 60 months. All subjects remained seropositive for HPV 16 and 18. The lines on the graph in orange and blue are superimposed as the GMTs and kinetics of antibody was similar in the 2- and 3-dose groups.

Similarly, for 4vHPV, this graphic was shown to ACIP in February 2016 and displays antibody after 4vHPV vaccination after 2-doses at 9 through 13 years of age and a 3-doses at the same age and at 16 through 26 years of age:



Follow-up in this study was though 36 months. For HPV 16, the general kinetics of the antibody response and persistence are similar for 2 doses in girls (in black), 3 doses in girls (in red), and 3 doses women (in green).

In summary, there is no evidence of waning protection after a 3-dose schedule. Data are available through approximately 10 years for 2vHPV and 4vHPV. Longer follow-up through 14 years is ongoing in some studies. Antibody responses are maintained over time after a 3-dose schedule. Data are available through approximately 10 years for 2vHPV and 4vHPV. Longer follow-up through 14 years is ongoing in some studies. Waning of detectable antibody to HPV 18 by cLIA in 4vHPV vaccinees is not associated with loss of protection. Long-term protection data are not available yet from 2-dose trials. Antibody kinetics are similar with 2vHPV and 4vHPV 2-dose schedules, with an interval of > 6 months between doses, in adolescents compared with standard 3-dose schedule in women.

Modeling and Cost-Effectiveness of 2-Dose Vaccination Schedules

Marc Brisson, PhD
Canadian Research Chair Modeling Infectious Diseases
Professor, Université Laval

Dr. Brisson reported that a 2-dose 9-valent vaccine Phase III immunogenicity trial has been completed. In this trial, 2 doses of 9-valent in girls and boys 9 through 14 years old was shown to be as immunogenic as 3 doses in women 16 through 26 years old. The cost-effectiveness study question the investigators were given was:

> *From the societal perspective, what is the health and economic impact of switching from a 3- to a 2-dose schedule, in the context of an established 9-valent HPV vaccination program in the US? (i.e., what is the additional impact of the 3rd dose of 9-valent vaccine vs. 2 doses?)*

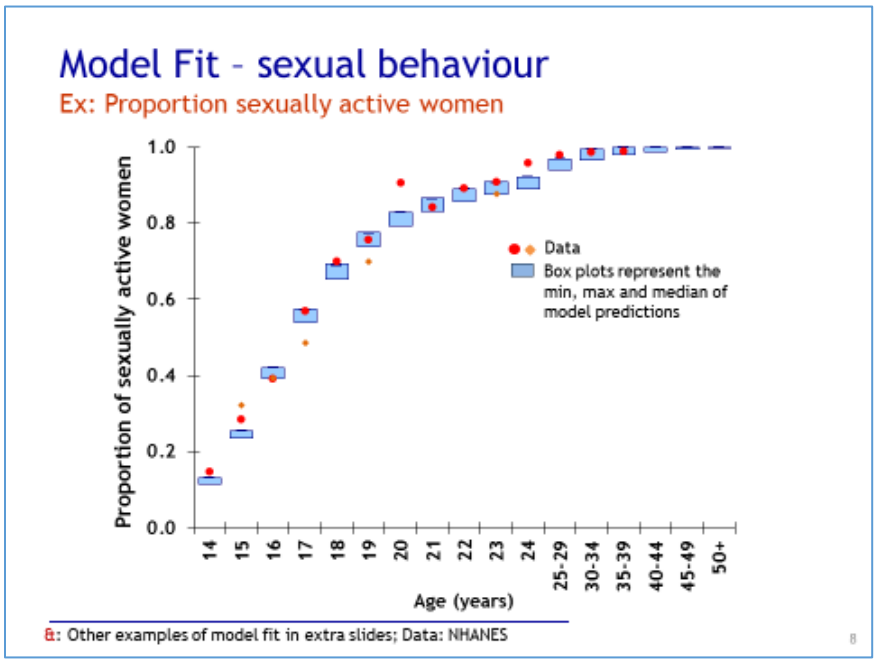
The objective of the study was to evaluate the population-level effectiveness and cost-effectiveness of 3- versus 2-dose 9-valent vaccination in the US. To do this, the investigators used a model called HPV-ADVISE. HPV-ADVISE was previously developed by Dr. Bisson's

group to answer HPV vaccination policy decisions in Canada and the US, and also has been used in the UK and Australia. The model is an individual-based transmission-dynamic model. What must be understood is that this model takes into account the direct effects of vaccination on vaccinees, but also takes into consideration herd immunity effects. The model includes 6 important components:

- ❑ Demographics, with individuals of different age groups
- ❑ Sexual behaviour and HPV transmission between individuals
- ❑ Natural history of HPV-related diseases
- ❑ Vaccination
- ❑ Screening and treatment of cervical lesions and cervical cancer
- ❑ Economic

The population is open, stable, and includes individuals 10 to 100 years of age. Eighteen genotypes are modeled individually, including the 9 types in 9vHPV (6/11/16/18/31/33/45/52/58). Also included are different HPV-related diseases: Anogenital warts, cervical cancer (SCC and adenocarcinoma), and cancers of the anus, oropharynx, penis, vagina, and vulva [Brisson et al. JNCI 2016 108(1) doi:10.1093/jnci/djv282].

This is a quite complex model, but it does not mean anything unless the model is fit to data and parameterized appropriately. In order to do a model of predictions, the first 50 parameter sets were identified that fit to highly stratified data from the US. The following graphic is an example of the model fit to sexual behavior data from the US:



In the above example, the dots represent the data and the boxes represent the variability and predictions of the 50 parameter sets. Model fits also were done for HPV prevalence in women stratified by type, age, and number of sexual partners; screening outcomes such as the incidence of high grade cervical lesions; and disease outcomes such as cervical cancer.

Once the parameters sets were identified and the model was programmed, the analysis was performed. The economic analysis was done from the societal perspective. The costs included all direct medical costs in 2013 US dollars. The main outcome was the usual outcome in health economics of cost per QALY gained. Future benefits and costs were discounted at 3%, the time horizon was 100 years, and the vaccine cost per dose assumption was $158 with administration costs.

In these predictions, the investigators modeled not only the decisions of 3 versus 2 doses prospectively, but also the policy decisions made in terms of HPV vaccination in the US. In these models, vaccination was begun in 2007 with a girls-only 4vHPV program. In 2011, there was a switch to a 4vHPV program vaccinating boys and girls. In 2015, there was a switch to a 9vHPV program vaccinating boys and girls. This is followed by a policy question that regards whether to continue with a 9vHPV 3-dose program, or to vaccinate with a 9vHPV 2-dose program. The model prediction compares these two scenarios. To do this, vaccination coverage is also needed. For vaccination coverage, age-specific uptake rates were used. For 2007-2014, observed uptake rates were used from the US National Immunization Survey (NIS). For 2015 onward, uptake rates were assumed to be constant at 2014 levels.

In terms of vaccine characteristics, it is known that if efficacy and duration are similar, 2 doses will be cost-saving compared with 3 doses. This means that both the 2-dose and 3-dose schedules would be equivalent in terms the health outcomes they would prevent, but the 2-dose schedule would be cheaper. Therefore, the analysis examined the potential impact if 2 doses provided lower or equal efficacy or shorter or equal duration of protection than 3 doses. So, in the scenarios, the 3-dose scenario was fixed. That is, 3 doses were assumed to provide lifelong protection, vaccine efficacy of 95% was used, and observed vaccine coverage was used. Numerous 2-dose scenarios were used, including lifelong protection versus durations of 30, 25, 20, and 15 years; a scenario of 95% versus 85% efficacy; and observed vaccination coverage versus a 5% to 15% percentage point increase. That is, a scenario was examined in which switching to a 2-dose vaccination schedule would lead to an increase in vaccination coverage.

Dr. Brisson presented two outcomes from these models: population-level effectiveness and cost-effectiveness. In terms of population-level effectiveness the key question was, “What vaccine characteristics are most important when considering reducing doses?” This refers to the characteristics that are most desired when switching from 3 doses to 2 doses. Sensitivity analyses were performed. The first assessed the impact of vaccine efficacy assumptions on the model predictions of effectiveness. In this scenario, it was assumed that vaccine duration is lifelong. The two outcomes assessed were anogenital warts and cervical cancer. For both vaccine efficacy scenarios, 85% and 95%, important reductions are predicted in anogenital warts and cervical cancer over time. The differences in population-level effectiveness between scenarios are quite small due to the fact that these differences in vaccine efficacy are counterbalanced by herd immunity effects. With respect to a 3-dose versus a 2-dose strategy, this suggests that if a 3-dose schedule provides 95% efficacy and in a worst case scenario a 2-dose schedule provided 85% vaccine efficacy, there still would be very little difference in population-level effectiveness of 85% versus 83% respectively.

In terms of the impact of duration of vaccine protection on the model predictions, vaccine duration of protection has a greater impact than vaccine efficacy. If vaccine efficacy is presumed to be 95% in the two outcomes of anogenital warts and cervical cancer, even with 15 years of duration of protection, there are substantial reductions in anogenital warts (53%) and cervical cancer (71%). It also is important to understand that once a duration of protection of 20

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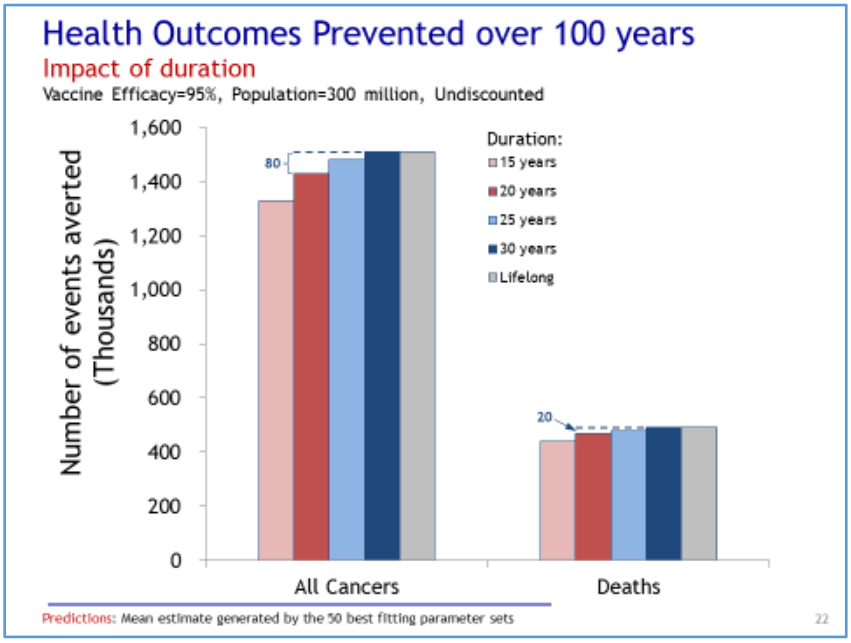
to 25 years is reached, any benefits of increases in duration of protection beyond 20 to 25 years are very small. This can be shown by the following figure which shows predicted health outcomes prevented over 100 years with different assumptions of duration of protection with vaccine efficacy predicted of 95%, a population of 300 million that is similar to the US, and undiscounted results:



What the above figure shows is that if the duration of protection is assumed to be 15 years, there would be substantial reductions in all cancers related to HPV, with over 1.2 million cancers averted through vaccination over 100 years of duration. If the duration is 20 to 25 years, there would be increases in the predicted number of events that are averted, but once that range of vaccine protection is reached, the additional benefits are very small. In terms of 3 doses versus 2 doses and the worst case scenario in which the 3-dose duration is lifelong and the 2-dose duration is 20 years, there would be very little difference in the number of cases that would be averted between the two scenarios. The reason this is the case is that most HPV infections are acquired between the ages of 17 through 30. If a vaccine is able to protect individuals during these key ages of peak sexual activity, it is doing a good job.

Therefore, duration of vaccine protection is quite important to population-level effectiveness. In terms of cost-effectiveness, this means that the key question is, “What is the cost-effectiveness of 2-dose and 3-dose vaccination for different assumptions of duration of protection?” In this analysis, 3-dose duration of protection was fixed at lifelong. The population is similar in size to the US. The first results regard the cost-effectiveness of 2 doses versus no vaccination. In all scenarios examined for 2-dose duration of protection, 2-dose schedules are cost-savings versus no vaccination. This means that it produces QALYs gained, or health benefits, and saves costs. The second result is from a comparison of the cost-effectiveness of receiving 3 versus 2 doses, in which 2-dose and 3-dose duration were presumed to be lifelong. In this case, the cost-effectiveness of the third dose is dominated because while saving money by going to a 2-dose schedule, there is no change in benefits. The other question is, “What is the impact of the cost effectiveness of a third dose versus two doses depending on the duration of the protection of

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two doses?" The results suggest that if a duration of protection of 2 doses is at least 20 years, the cost-effectiveness ratios of giving the third dose are quite high.

Regarding the sensitivity analysis to influential variables, scenarios were assessed in which giving a 2-dose schedule would facilitate an increase in coverage of 5%, a 2-dose schedule would lead to a 15% increase in coverage, and a scenario in which 2-dose efficacy is lower than a 3-dose. In the base case, it was assumed that screening is cytology-based, but an assessment also was done in which a screening program is co-testing. Then the sensitivity analyses are varied to economic parameters. The first results pertaining to the cost-effectiveness of 2-dose vaccination compared to no vaccination; in most of the scenarios, even if it is assumed that 2-dose protection lasts for 20 years, a 2-dose strategy is cost-saving versus no vaccination. There are certain exceptions, but even in these exceptions, the cost-effectiveness ratio is very low. The second result pertains to the cost-effectiveness of 3 versus 2 doses, in which both schedules provide lifelong protection. In all of the scenarios, the 3-dose schedules are dominated by 2-dose schedules except one in which it was assumed that 2-dose vaccine efficacy was lower than 3-dose vaccine efficacy. Even in this scenario, the cost-effectiveness ratio for 3-dose vaccination is quite high. Finally, a worst case scenario was assessed in which 2-dose duration of protection was 20 years and 3-dose protection was lifelong. For most scenarios, the results vary at around $100,000 / QALY gained. In terms of switching to a 2-dose strategy with higher coverage, in this scenario the model predicts that if vaccination coverage can be increased by moving to a 2-dose strategy, this would provide equal or additional gains than a 3-dose strategy. Therefore, the 3-dose strategy would be dominated.

In terms of limitations, two are related to uncertainty. The first is that a duration of 2-dose and 3-dose 9-valent vaccine efficacy and future vaccination coverage remain unknown. This is why duration of protection and vaccination coverage were varied in these analyses. Duration of protection and coverage assumptions have an important impact on conclusions. The second uncertainty is that screening may change in the coming years, which may modify the incidence of lesions and cervical cancer. While both cytology-based screening and HPV co-testing were modeled, the screening method did not impact the conclusions.

This is the first effectiveness and cost-effectiveness analysis of 2- versus 3-dose vaccination with 9vHPV in the US or elsewhere. Thus, it is very difficult to compare the results with other studies. Nevertheless, the conclusions are consistent with a 4vHPV effectiveness and cost-effectiveness analyses in Canada and the UK[1,2] and recently an Australian study. In these studies, the conclusion is that 2 doses must protect for more than 20 years for the third dose to be cost-*in*effective [[1]Laprise *Vaccine*, 2014; [2]Jit *BMJ*, 2015].

In summary, the incremental health benefits and cost-effectiveness of a third dose of HPV vaccine depends upon relative duration of efficacy provided by 2 versus 3 doses. A 2-dose vaccination schedule is predicted to reduce HPV-burden of disease substantially and is cost saving if 2 doses provide protection for greater than 20 years. A 3-dose vaccination is predicted to have a high cost per QALY gained of greater than $118,000 compared to 2-dose vaccination, except when 2-dose protection is less than 20 years. A 2-dose vaccination will provide similar population-level health benefits to 3-dose vaccination, unless 2 doses provide shorter duration of vaccine protection and 2-dose schedules do not enable higher vaccination coverage.

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Discussion Points

Dr. Messonnier asked whether cost-effectiveness was assessed if the cost per dose in a 2-dose regimen is higher than the cost per dose in a 3-dose schedule.

Dr. Brisson responded that this was not assessed, and he felt uncomfortable defining a cost where it would be better to stick with a 2- versus 3-dose strategy. However, this can easily be done. There is a price at which a 2-dose strategy would not be cost-effective.

To build upon that, Dr. Bennett asked how much of the costs are actually the cost of the vaccine and how much are other costs (administration) such that even if the cost of the vaccine increased, it might still be cost-effective for 2 doses.

Dr. Brisson replied that if both schedules are equally effective, the cost per dose would have to increase substantially not to be cost-effective or dominate the 3-dose scenario. It is up to the companies, but they may vary their vaccine costs. That is a key question.

Regarding the antibody kinetics of 9vHPV versus 4vHPV, Dr. Stephens asked whether it was anticipated that there would be equivalent 9vHPV data at least for the types that are in both vaccines.

Dr. Markowitz replied that this is the assumption since the monovalent, 2vHPV, and 4vHPV trials have all shown the same pattern of an antibody peak one month after the last dose followed by a plateau. The data available are only for one month past the last-dose, but more data should be available soon that would include a later time point to assess whether that is true. She called upon a representative from Merck to address this.

Dr. Luxembourg (Merck) responded that additional data would be available for Months 25 and 36 by the end of 2017. Regarding whether the 9-valent has similar immunogenicity, so far for all studies measured, no substantial differences have been found in immunogenicity between the vaccines. Therefore, it is a reasonable to assume that it will be the same.

Dr. Kempe acknowledged that duration of protection is the most important aspect of modeling, but the other thing that they tried to vary was the percentage of potential increase in immunization. She wondered whether data are available from the countries that have made the switch from 3 to 2 doses and if changes in uptake greater than 15% have been observed.

Dr. Markowitz responded that many of the countries that have switched have school-based vaccines so the impact of changing from a 3-dose to a 2-dose schedule on coverage might not be relevant to the US situation. An effort is being made to acquire data to find out what is occurring. Some countries in Europe have clinic/primary care-based vaccination programs and there may be some data available from those programs.

Regarding vaccination coverage and trends over the 100 year time period, Dr. Thompson (NVAC) wondered whether it would be cost-effective to give 9vHPV vaccine to those who already received 2vHPV or 4vHPV.

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Dr. Brisson replied that in terms of the assumptions regarding coverage based on observed rates, from 2000 through 2014, they used the percent of coverage with 3 doses only. That was predicted into the future, so for 2015 onward those would be the assumptions if the uptake rates remain the same. When the 2-dose schedule was modeled without any increase in coverage, the same assumptions about coverage were used. When a predicted increase in vaccination coverage was modeled with a 2-dose program, it was cost-saving. Regarding revaccination of those previously vaccinated with 2vHPVt and 4vHPV, Dr. Chesson has published a paper on that in which this question was assessed with 3 doses with the HPV-ADVISE model and with a CDC model. The cost-effectiveness ratios were quite high. In terms of the results with 2 doses, a sensitivity analysis was performed.

Dr. Chesson added that the result for 2 doses was approximately $100,000 per QALY to revaccinate.

Dr. Reingold suggested that if by the October 2016 ACIP meeting they were able to use this information to shift from a 3- to a 2-dose strategy, perhaps it would be possible to model pneumococcal conjugate vaccine doses shifting from 4 to 3.

HPV Vaccine Effectiveness Studies

Sara Oliver, MD, MSPH
EIS Officer, Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Oliver reminded everyone that to inform policy decisions, current evidence is being reviewed for 2 doses of HPV vaccine, including evidence regarding immunogenicity, efficacy, and post-licensure effectiveness. A previous presentation to ACIP in February 2016 reviewed data from HPV vaccine 2-dose immunogenicity studies and presented data from the major efficacy studies. During this session, Dr. Oliver presented a systematic review of vaccine efficacy and effectiveness for 2 doses. She began by searching for studies on HPV vaccine effectiveness, identifying 930 papers on vaccine impact or effectiveness. Studies were selected if they evaluated effectiveness by number of doses. Thirteen papers were reviewed that discussed vaccine effectiveness with 2 doses. The WG reviewed these studies in detail previously. During this session, Dr. Oliver presented studies by vaccine and outcomes evaluated. She described all 13 studies, and showed detailed data for studies evaluating outcomes by timing of interval between Dose 1 and Dose 2.

To better understand the background of the studies presented, it is worth nothing that there are many methodological challenges to using post-licensure effectiveness studies within the context of a 3-dose program to evaluate 2-dose effectiveness. Most vaccinees received 2 doses at a 0,1 or 0,2 month interval. In addition, many studies were conducted during a catch-up vaccination period, meaning that many females were vaccinated at ages older than current recommendations. Also, the partially vaccinated population is different from those fully vaccinated, potentially having implications for exposure to HPV prior to vaccination and different sexual risk status. However, in spite of these challenges, Dr. Oliver presented an overview of 2-dose effectiveness studies for a complete review of the evidence and in order to highlight their limitations with interpretation. No studies on 2-dose effectiveness of 9vHPV have been published to date, since 9-valent was licensed only recently.

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For 4vHPV, 8 studies have been published on effectiveness by number of doses: 1 study evaluating effectiveness with regards to HPV infection (Sankaranarayanan Lancet Oncol 2016), 3 studies evaluating genital warts (Herweijer JAMA 2014, Dominiak-Felden PLOS ONE 2015, and Blomberg Clin Infect Dis 2015), and 4 studies evaluating cervical pre-cancers (Hofstetter JAMA Peds 2016, Crowe BMJ 2014, Gertig BMC Medicine 2013, and Brotherton Papillomavirus Res 2015).

The Sankaranarayanan study was a 2- versus 3-dose trial conducted in India. Immunogenicity data was discussed at the previous ACIP meeting in February. Infection outcomes also were reported, evaluating incident and persistent cervical HPV infections. The study was designed as a cluster-randomized trial, but was stopped prior to completion, so it was analyzed as an observational cohort study. Subjects were randomized to receive 3 doses or 2 doses at a 0,6 month interval. In addition, since the trial was stopped early, some participants received 2 doses at a 0,2 month interval or 1 dose. There were no persistent infections in any group. Overall, 2 doses at a 0,6 month interval was similar to 3 doses. The primary limitation with interpretation remains that the study was designed as a randomized trial that was analyzed as a cohort study. Because randomization was disrupted, there could be differences between groups as well.

Three studies evaluated 4vHPVeffectiveness for genital warts by number of doses (Herweijer, Dominiak-Felden, and Blomberg). Each study had a slightly different study population, but all were designed as population-based retrospective cohorts. The conclusion of all 3 studies was that maximum vaccine effectiveness was noted with 3 doses. However, all studies evaluated effectiveness from those partially vaccinated in the setting of a 3-dose recommendation. The partially vaccinated cohort was different than the fully vaccinated cohort in that they were generally older at the time of vaccination and most received 2 doses at a (0,2 month) interval. The Blomberg study evaluated 2-dose effectiveness for genital warts by interval. As the time between Dose 1 and Dose 2 increases from 2 to 6 months, the incidence rate ratio for 2 versus 3 doses approaches 1, meaning the effect of 2 doses when given at a longer interval, approaches 3 doses. This is the only effectiveness study to clearly demonstrate this effect by interval. However, while the findings are of interest, the authors point out that a limited number of vaccinees received 2 doses at the longer interval, compared with those who received the shorter interval.

Four studies assessed 4vHPV effectiveness for cervical pre-cancer by number of doses (Hofstetter, Crowe, Gertig, and Brotherton). One was a case-control study and the other 3 were retrospective cohort studies. All 4 studies concluded that maximum vaccine effectiveness was found with 3 doses. However, as before, all evaluated a partially vaccinated population in the setting of 3 recommended doses. Again, the partially vaccinated cohort was different than the fully vaccinated cohort in that they were generally older at time of vaccination and had potential indicators of earlier sexual exposure, including younger cervical screening, vaccinated at a family planning clinic, or sexually transmitted infection (STI) screening. Most received 2 doses at a (0,2 month) interval.

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The Brotherton study from Australia assessed risk reduction for cervical pre-cancer by number of doses and interval. This table shows hazard ratios by number of doses and timing of the 2-dose interval:

Vaccination	Time between doses	Hazard Ratio
3 doses	-	0.71 (0.64–0.80)
2 doses	<6 months	1.25 (1.03–1.51)
2 doses	≥6 months	1.05 (0.72–1.55)

For 2 doses, an interval greater than or equal to 6 months had a slightly lower hazard ratio compared to an interval less than 6 months, but neither ratio was significantly lower than the unvaccinated population. However, in this particular study, the partially vaccinated females were older at vaccination, younger at first cervical screening, and had a lower socioeconomic status (SES). The numbers were small in the 2-dose cohort, with less than 20% of vaccinees receiving 2 doses, and less than 5% receiving 2 doses at least 6 months apart.

Moving now to 2vHPV, there have been 5 studies evaluating vaccine effectiveness or efficacy, 4 evaluating HPV infection (Kavanagh BJC 2014, Cuschieri BJC 2016, Kreimer JNCI 201, and Kreimer Lancet Oncol 2015), and 1 evaluating cervical pre-cancers (Pollock BJC 2014).

Two studies evaluated 2vHPVeffectiveness for HPV infection by number of doses, both conducting a cross-sectional study using residual cervical screening samples and registry data (Kavanagh and Cuschieri). In the first study, no statistically significant risk reduction was found with 2 doses compared to the unvaccinated population. However, the study noted that they were not powered to detect a difference for two doses. The second study was conducted, over-selecting for those who were partially vaccinated. An impact was then found for 2 doses, but still less than the impact observed for those fully vaccinated. However, Scotland had a 3-dose recommendation at the time both studies were conducted, and the partially vaccinated females were older at the time of vaccination than those fully vaccinated, and primarily received a 0,1 month interval.

Two published studies evaluated 2vHPV efficacy by number of doses, both as a post-hoc analyses of clinical trials (Kreimer 2011 and Kreimer 2015). The first study was a post-hoc analysis of the Costa Rica Vaccine Trial, evaluating those who did not receive all 3 doses. The second analysiscombined the data from both the Costa Rica Vaccine Trial and the PATRICIA trial, again evaluating those partially vaccinated. In both studies, a high efficacy was found with 1, 2, and 3 doses. However, all subjects were initially randomized to receive 3 doses of HPV vaccine, and a small proportion were unable to complete the series, most commonly due to pregnancy.

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A sub-analysis from the 2015 Kreimer paper, only including data from the Costa Rica Vaccine Trial, evaluated efficacy by timing of a second dose. This table shows vaccine efficacy by number of doses and timing of the 2-dose interval:

Vaccination	Interval	Vaccine efficacy (95% CI)
3 doses*	—	77.0% (74.7–79.1%)
2 doses	1 month	75.3% (54.2–87.5%)
2 doses	6 months	82.6% (42.3–96.1%)

For comparison, the efficacy for 3 doses is shown. Of note, the 3-dose cohort includes participants from both the Costa Rica Vaccine Trial and the PATRICIA trial. High efficacy was seen for both a 1-month and 6-month interval, with an estimate slightly higher for a longer interval. However, a small percentage of study participants received the second dose after 6 months, providing wide confidence intervals for the estimate.

A final study evaluated 2vHPVeffectiveness for cervical pre-cancers by number of doses (Pollock). Only females who had received a colposcopy were included in this analysis. No risk reduction was found with 2 doses compared to those unvaccinated. However, the partially vaccinated females were older and more likely to have received their vaccination after graduation from school. Most were vaccinated a 0,1 month interval and, in the setting of a 3-dose recommendation, only a small proportion of the population received 2 doses.

In summary, 13 studies evaluated 2-dose effectiveness. Of these, 3 were post-hoc analyses of clinical trials and 10 were post-licensure effectiveness studies evaluating partially vaccinated individuals in settings of a recommended 3-dose schedule. Additionally, 4 studies included evaluations of at least a 0,6 month interval.

In conclusion, 3 studies found similar outcomes for 2 doses compared to 3 doses, and all 3 of those studies were post-hoc analyses of clinical trials. Ten studies found 2 doses were not as effective as 3 doses. However, it is important to note that all 10 were post-licensure effectiveness studies performed within settings of a recommended 3-dose schedule, where most received a 0,1 or 0,2 month interval. Persons who only received 2 doses were different from those completing the series. Several studies found the partially vaccinated females to be older, of lower SES, or to have earlier cervical screening—a potential indicator for earlier onset of sexual activity. All of those factors have implications for exposure to HPV prior to vaccination. There were 4 studies evaluated a 0,6 month interval compared to a shorter interval. Of those four studies, 1 showed a longer interval was more effective. The other 3 studies suggest that a longer interval could impact vaccine effectiveness, but statistical significance was not always tested or achieved. As mentioned previously, there are many methodological challenges to using post-licensure effectiveness studies within the context of a 3-dose program to evaluate 2-dose effectiveness. Data from these post-licensure effectiveness studies may not be directly applicable to the currently policy question of a 2-dose recommendation due to differences in age at vaccination, the interval between the 2 doses, and the population in the studies receiving 2 doses compared to those who received 3 doses. These important factors have impacted the studies included in GRADE, which are addressed in the next presentation.

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GRADE for 2-Dose Schedules

Elissa Meites, MD, MPH
Medical Epidemiologist
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Dr. Meites discussed the GRADE process for 2-dose schedules of HPV vaccine. During this and the February 2016 ACIP meeting, there were discussions of various components of the GRADE process. Before making an ACIP recommendation and assigning a GRADE category, the steps of this evidence-based method are to:

- ❑ Develop policy questions
- ❑ Consider critical outcomes
- ❑ Review and summarize evidence of benefits and harms
- ❑ Evaluate the quality of evidence
- ❑ Assess population benefit
- ❑ Evaluate values and preferences
- ❑ Review health economic data
- ❑ Offer considerations for formulating recommendations

The WG's main policy question was, "Should 2 doses of any HPV vaccine be recommended for 9-14 year-olds?" Given anticipated changes in availability, each HPV vaccine was considered separately. The population of interest was girls and boys aged 9 through 14 years. The intervention was 2 doses of HPV vaccine, separated by 6 to 12 months. The comparison was 3 doses of HPV vaccine on a standard schedule, among women in the age group in which vaccine efficacy has been demonstrated against infections and histopathological lesions associated with HPV vaccine types. This was done in immunobridging studies. Note that exploratory analyses comparing groups in the same age range of 9 through 14 years were considered supplemental data in this presentation. The main outcome of interest was immunogenicity or antibody response to vaccine-type HPV.

Most of the studies in this presentation were immunobridging studies, because the minimum threshold level of HPV antibodies required for clinical protection has not been established and might vary depending on the assay. Data from clinical trials suggest that this minimum level of antibody needed for protection could be below that which is detected by current assays. Immunobridging studies are used to compare immunogenicity in a group of interest (for example, those aged 9 through 14) with a comparison group in which efficacy has been demonstrated in clinical trials (for example, those aged 16 through 26). Non-inferiority criteria are met when the lower bound of the 95% confidence interval for the ratio comparing the two groups is not less than a pre-set value such as 0.5. Immunobridging studies are the basis upon which HPV vaccines were originally licensed in the US for use in 9 through 15-year-olds.

In terms of outcomes relevant to HPV vaccination as determined by the WG, immunogenicity is an early measurable effect of HPV vaccination, and a surrogate marker for prevention of other important outcomes such as HPV infections, genital warts, or condylomas; and critical outcomes including HPV-associated pre-cancers and cervical, oropharyngeal, anal, and other cancers. Immunogenicity outcomes are included in the evidence profile for GRADE. These include the following:

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- Rates of seroconversion, which means having any detectable vaccine-type antibody after vaccination
- GMTs, which quantify antibody levels
- Antibody avidity, which measures how strongly antibody binds to its antigenic target

Data on other important outcomes, including the efficacy studies reviewed in the previous presentation by Dr. Oliver, were considered by the WG, but were not included in GRADE because they did not include data on the relevant dosing interval or age range specified in the policy question. To date, no data are available on the later outcomes listed as critical.

For evidence retrieval, the WG conducted a systematic review of studies from PubMed and Clinicaltrials.gov published between 2006, when HPV vaccine was first licensed in the US, and June 17, 2016. Efforts were made to obtain unpublished or other relevant data. Initial search terms included both:

- "HPV" and "vaccine," or "HPV vaccine," or "papillomavirus" and "vaccine," or "papillomavirus vaccine," AND
- "2-dose" or "2 doses" or "two-dose" or "two doses"

Relevant studies included human subjects, primary data, and data relevant to the outcomes shown above for 9-valent, quadrivalent, or bivalent HPV vaccines.

The search identified 117 publications listed in PubMed. Nine relevant publications were reviewed in detail, and six immunogenicity studies that were non-redundant were included in the evidence tables. The other 108 were excluded as 31 were not primary data (reviews, editorials); 57 had other outcomes (coverage, knowledge/preferences, cost-effectiveness); and 19 assessed relevant outcomes, but did not report results by timing of doses administered or number of doses in the age group of interest. In addition, 14 studies were identified that were registered on clinicaltrials.gov, including 1 additional relevant study with unpublished data. This was the 9-valent vaccine 2-dose trial that was presented by the manufacturer during the February 2016 ACIP meeting. All of the relevant immunogenicity studies and additional data included in GRADE were previously presented to ACIP during the February meeting.

Initial evidence types in GRADE are either a type 1 for RCTs or Type 3 for observational studies. For immunobridging studies, the main analyses are considered observational since it is not possible to randomize participants to an age group even if these studies are considered strong evidence. Therefore, an evidence type of 3 is the highest possible for this type of study.

For the GRADE evaluation of 9-valent HPV vaccine, the policy question was, "Should 2 doses of 9-valent vaccine be recommended routinely for 9 through 14 year-olds?" Regarding the characteristics of included studies, one immunobridging study funded by the manufacturer that was submitted to FDA and was presented to ACIP in February 2016. This study compared 2 or 3 doses of 9-valent vaccine in girls and boys 9 through 14 years of age with 3-doses given to women 16 through 26 years of age. The two doses were given at an interval 0 and 6 months apart, or 0 and 12 months apart, plus or minus 4 weeks. The main immunogenicity outcomes from the study were seroconversion and GMTs.

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For seroconversion, in each group of vaccinees at least 97.9% had seroconverted to all 9-valent vaccine types at 4 weeks post-last dose. When comparing 2-dose girls-and-boys to 3-dose women, noninferiority criteria were met for all 9-valent vaccine types regardless of whether the 2 doses were administered at a 0,6 or a 0,12 interval, and whether girls and boys were assessed separately. GMTs for 9-valent vaccine types were significantly higher in the 2-dose girls and boys compared with the older controls. For the finding of non-inferior immunogenicity with 2 doses of 9-valent HPV vaccine in girls and boys compared with 3 doses in a group in which clinical efficacy has been demonstrated, this immunobridging study is considered observational and receives an initial evidence level of 3. Evidence type was not downgraded for risk of bias, inconsistency, indirectness, imprecision, or any other considerations, giving a final evidence type of 3.

For the sake of transparency, Dr. Meites mentioned additional analyses from this study that compared 2-doses in girls-and-boys with 3 doses in the same age group. These analyses are considered exploratory or supplemental because the comparison was not with the group in which efficacy was demonstrated in the clinical trials and, therefore, falls outside of the parameters of the study question. For seroconversion, in the first row, at least 99.2% in all the 2-dose groups seroconverted to all 9-valent vaccine types at 4 weeks post-last dose. GMTs were statistically lower in the 2-dose group for some HPV types at 4/9 for the 0,6 month group and 1/9 in the 0,12 month group, although formal non-inferiority comparisons were not performed.

For quadrivalent HPV vaccine, the policy question was, “Should 2 doses of quadrivalent vaccine be considered adequate vaccination for 9 through 14 year-olds?” In terms of the characteristics of the included studies, two published studies were identified. Both were publically-funded immunobridging studies, one from Canada (Dobson) and one from Mexico (Hernandez-Avila). These studies compared girls in the 9 through 13 year-old age range with women in the age group in which efficacy was demonstrated in the clinical trials. In both studies, the 2-doses were given at an interval of 0, 6. The main immunogenicity outcomes from these studies were seroconversion and GMTs. In both studies, among all vaccinees at least 97.1% were seropositive to all quadrivalent vaccine types at 7 months in all groups. For GMTs, both studies found that when comparing 2-dose girls to 3-dose women, noninferiority criteria were met for all four quadrivalent vaccine types through 36 months, and GMTs for 9-valent vaccine types usually were significantly higher in the 2-dose groups. For the finding of non-inferior immunogenicity with 2 doses of quadrivalent HPV vaccine in girls compared with 3 doses in a group in which clinical efficacy has been demonstrated, these two immunobridging studies are considered observational, and received an initial evidence level of 3. Evidence type was not downgraded, giving a final evidence type of 3.

Supplemental analyses of same-age comparisons from these studies were presented for completeness, although they were not included in the GRADE analysis. For seroconversion, at least 97.2% in all the 2-dose groups were seropositive to all quadrivalent vaccine types at month 7. For GMTs, the two studies had similar findings in that GMTs to quadrivalent vaccine types were high in all vaccinees, but relatively lower in the 2-dose girls compared with the 3-dose girls, even though noninferiority criteria usually were met. One study showed that noninferiority was lost for HPV 18 by month 18, and also HPV 6 by month 36. However, the other study showed that noninferiority was not lost by the end of the study at month 21 for any of the quadrivalent vaccine types.

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For bivalent HPV vaccine the policy question was, “Should 2 doses of bivalent vaccine be considered adequate vaccination for 9 through 14 year-olds?” Regarding the characteristics of the included studies, there were 4 published studies. There were 3 immunobridging studies from various countries (Romanowski, Puthanakit, Lazcano-Ponce), and 1 observational laboratory study (Boxus). These studies compared girls in the 9 through 14 age range with women in the age group in which efficacy was demonstrated in the clinical trials. Interventions included either 2 doses at an interval of 0,6 months or 0,12 months versus 3 doses on a standard schedule. Main outcomes for the three immunobridging studies were seroconversion and GMTs, and the laboratory study assessed antibody avidity.

In all three immunogenicity studies, 100% of vaccinees seroconverted to both bivalent vaccine types and were seropositive through Month 60. For GMTs, all three studies found that when comparing 2-dose girls to 3-dose women, noninferiority criteria were met for both bivalent vaccine types through 60 months, and GMTs for 9-valent vaccine types were higher in the 2-dose groups. For antibody avidity (bivalent vaccine), there were no differences in avidity index, suggesting similar quality of antibody response in 2-dose versus 3-dose recipients. For the finding of non-inferior immunogenicity with 2 doses of bivalent HPV vaccine in girls compared with 3 doses in a group in which clinical efficacy has been demonstrated, these four studies are considered observational and received an initial evidence level of 3. Evidence type was not downgraded, giving a final evidence type of 3.

Again for completeness, same-age comparisons from the graded studies in this section were presented. Two studies had both a 2-dose and a 3-dose arm for girls in the same age group. For seroconversion in two studies, 100% of vaccinated girls seroconverted to both bivalent vaccine types and were seropositive through month 60 (Romanowski, Lazcano-Ponce). For GMTs, one paper provided GMT results for both 2-dose girls and 3-dose girls (Lazcano-Ponce). At month 21, GMT ratios were lower in the 2-dose group, but noninferiority criteria were met for both bivalent types.

In addition to benefits, the workgroup also discussed potential harms. For AEs, the safety profile has been well-established for HPV vaccines, and SAEs are extremely rare. Dr. Meites reiterated that in the 9-valent vaccine trial presented to ACIP and included in GRADE earlier, there were no serious vaccine-related adverse events. In 2-dose cohorts, the incidence was zero among 883 participants, and in 3-dose controls it was zero among 616 participants. Any potential AEs following a dose of vaccine, for example injection site reactions, can be expected to be reduced when fewer doses are given. No data suggest that AEs would increase with fewer doses.

In summary, for 2 doses of HPV vaccine in girls or boys age 9 through 14 years, compared with 3 doses of HPV vaccine in a group in which clinical efficacy has been demonstrated, data were available on immunogenicity outcomes for 9-valent, quadrivalent, and bivalent HPV vaccines. All found evidence of non-inferior immunogenicity with 2 doses, and the overall evidence type is 3. Considerations for formulating recommendations for 2-doses of HPV vaccine include balances between benefits and harms, evidence type for benefits, values, and cost-effectiveness. In terms of benefits and harms, benefits are non-inferior and harms are reduced compared to 3 doses. If benefits are expected to be similar and the potential AEs are lower, then the balance of benefits over harms is greater. The evidence type for benefits was evidence type 3. Regarding values, the WG placed a high value on programmatic considerations, as well as prevention of outcomes due to HPV vaccine types. As discussed by Dr. Brisson, 2-doses are likely cost-effective compared to 3 doses.

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Discussion Points

As a matter of principle, Dr. Sun (FDA) asked whether when considering potential harm, the potential for infection during the period after the first dose before the second dose was considered. All of the immunogenicity studies compared post-six month dose. Theoretically, if one acquired infection during that interval, that could represent potential harm. In this particular case, the immunogenicity of the vaccine is probably so high that this is not an issue. Nonetheless, that would be important to consider as a potential harm in any reduced dose strategies. One can look at the boost response when the second vaccine is given at 1 month versus at 6 months and could compare it with the quality of the anamnestic response.

Dr. Meites responded that in terms of how the WG assessed harms, several studies have evaluated any reported AEs after each dose—so by timing and dosing of the different vaccines. Comparing after dose 1, dose 2, dose 3, there was not an appreciable difference. Dr. Markowitz added that the recommended age for vaccination in the US is at 11 or 12 years. Ideally, people would be vaccinated before risk of exposure. The 2-dose recommendation would be exclusively in the younger age group based on the data being submitted to the FDA. This is a strong argument for vaccinating at the younger age.

Recommendation Options

Lauri Markowitz, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Markowitz presented the draft proposed recommendations for a 2-dose schedule. She emphasized that these were general recommendations rather than specific wording, and that they do not include specifics on minimum intervals, special conditions, or precautions. This is simply a general outline of what the WG has been considering. The WG's proposed recommendation for routine vaccination is that:

- ❑ ACIP recommends routine HPV vaccination at age 11 or 12 years*
- ❑ A 2-dose schedule is recommended[+]. The second dose should be administered 6 to 12 months after the first dose.

*Vaccination series can be started at age 9 years
[+]A 3-dose series can be given (0, 1-2, 6 months)

The text in blue indicates issues for further discussion. For example, the interval between doses could be a range as stated here, specific intervals, or just a lower minimum interval. Furthermore, the specific range might change depending what is in label. The other text for discussion is the statement about an optional 3-dose series, so that although the recommendation is for a 2-dose schedule, a 3-dose series could be given at the discretion of the provider.

Consistent with ACIP's current recommendations, the draft includes a recommendation for vaccination through 26 years of age for females and 21 years of age for males if not previously vaccinated. For this recommendation, there would be different recommendations for those who initiate vaccination before or after their 15th birthday as follows:

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- Vaccination is also recommended for females through 26 years and for males through 21 years not previously vaccinated

- For persons initiating vaccination before their 15th birthday, ACIP recommends 2 doses of HPV vaccine.* The second dose should be administered 6 to 12 months after the first dose.

- For persons initiating the vaccination series after their 15th birthday, ACIP recommends 3 doses of HPV vaccine. The second dose should be administered 1 to 2 months after the first dose and the third dose 6 months after the first dose (0, 1-2, and 6 month schedule).

  *A 3-dose series can be given (0, 1-2, 6 months)

Again, the text in blue indicates wording for further discussion related to how to state the interval between doses and whether a 3-dose series should be an option for those initiating vaccination before the 15th birthday.

The following wording pertains to what would be considered adequate vaccination for those who started vaccination in the past.

If vaccination was initiated before the 15th birthday:

- Persons who started the HPV vaccination series with 9vHPV, 4vHPV or 2vHPV and
  - received 2 doses ≥ 6 months apart: are considered adequately vaccinated
  - received 2 doses < 6 months apart: should receive a third dose ≥ 6 months after dose 1
  - received 1 dose: should receive a second dose ≥ 6 months after dose 1

If vaccination was initiated on or after the 15th birthday:

- Persons who started the HPV vaccination series with 9vHPV, 4vHPV or 2vHPV and
  - received 3 doses with the third dose ≥ 6 months after dose 1: are considered adequately vaccinated
  - received 2 doses: should receive a third dose ≥ 6 months after dose 1
  - received 1 dose: should complete a 3-dose series (0, 1-2, 6 months)

The draft recommendation for special populations is:

- For immunocompromised patients of any age, including those with HIV infection, ACIP recommends 3 doses of HPV vaccine (0, 1-2, 6 months)

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- Dr. Markowitz posed the following issues for discussion:

- General support for a 2-dose recommendation
- Whether ACIP recommends "HPV vaccine" or "9vHPV" since that will be the only vaccine available going forward in the US
- Recommendations for those starting series before 15th birthday
  - Whether ACIP feels that it will be helpful to specify intervals between doses (0, 6 months or 0, 12 months), to have a range of the interval (6 to 12 months), or a minimal interval (at least 6 months)
  - If a 2-dose schedule is recommended, should there be an option for a 3-dose schedule?

Discussion Points

Dr. Reingold said he assumed that if there were an option for a 3-dose schedule formally, that would have implications in terms of who would pay for it or whether it would be covered by a program or insurance company. He asked for further insight into what the rationale would be for continuing to include a 3-dose schedule option.

Dr. Markowitz replied that while discussion regarding this issue is ongoing, it is partially a legacy issue, since a 3-dose scheduled has been recommended. Also, some practices may be vaccinating a wide age range and may give a 3-dose schedule to some individuals inadvertently, and would want that to be covered. Some individuals may want a 3-dose schedule. While it was not a unanimous consideration among the WG members, some members felt strongly about including this option.

Dr. Riley said she was confused with the 3-dose option as well. She asked for clarity regarding whether this meant an option for a 3-dose schedule in those less than 15 years of age. She wondered whether this made sense for some medical reason. Using HIV as an example, she asked whether that would be a patient for whom there would be concern about the immune response.

Dr. Markowitz confirmed that this was what was for those less than 15 years of age at the time of vaccine initiation. Some WG members wanted a 3-dose option for this group. However, the recommendation for 3-doses would remain for immunocompromised persons, including those with HIV infection for all age groups.

As a Program Manager, Dr. Moore weighed in on the interval suggestions. She would not include the "at least 6 months" with the open end, because it makes it very hard for any registry to calculate whether a patient is overdue for something. With just "at least 6 months" they would never be overdue theoretically. Understanding the antibody data, she liked the range of 6 to 12 months rather than being prescriptive with 0 to 6 or 0 to 12 because from a practice standpoint, a 6-month interval will work easily into the schedule for others having their first vaccine at their 11-year old visit and their next vaccine at their 12-year old visit. Depending upon the setting, both are reasonable and the 6 to 12 month range offers that flexibility.

Dr. Kempe agreed that the 6 to 12 month range offers clinicians the option with individual patients. Some patients are 11 years old who are clearly far away from sexual activity for whom it might make much more sense to wait a year. That might be much easier for programmatic

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reasons, so she really liked that. With regard to Immunization Information Systems (ISS), she requested further information on whether having a range is problematic for that.

Dr. Moore replied that there are other vaccines that have ranges for when doses are due, so that is programmable.

Dr. Finley (AIM) added that the range of 6 to 12 months would be very helpful, and it is in all of the forecasters so it would work well for them.

Dr. Walter noted that many children in his practice present on yearly intervals and are currently receiving their vaccine that way.

Dr. Schaffner (NFID) asked whether they may infer that because of what had been said about people who have completed their immunization series, ACIP would not be considering at this time the question of whether the series was completed with a 2vHPV or 4vHPVand if patients who had completed either of those series should receive 9vHPV. He also made a plea for simplification of the adult immunization schedule, perhaps considering the upper age limit of women and men and making them the same.

Dr. Markowitz responded that the WG has been dealing exclusively with reviewing the evidence for 2 doses since February and has not revisited some of the issues that have arisen previously. They are aware of the upper age range differing for males and females, and can further consider this issue. They have not addressed again the issue of the additional vaccination with 9vHPV.

Dr. Kempe requested people's perspective on "HPV vaccine" or "9vHPV". ACIP has been careful not to specify specific vaccines in the past. In this case, two of the vaccines are essentially being phased out. She personally could foresee a problem with having the specificity. If people come in from other countries, there may be confusion about whether they received the correct vaccine. Some members of the WG felt that it should be specified. She said she would like to hear from anyone who felt that it should be specified and why.

Dr. Lett (CSTE) agreed with not specifying. The concern is that it will raise questions about revaccination, which it seemed the WG did not wish to address at this point.

Dr. Belongia agreed, given that as of the end of the year, only 9vHPV would be available in the US.

Dr. Moore agreed with Drs. Lett and Belongia. Many individuals come in from other countries, and they do not want to cause confusion in the schedule. No evidence has been presented to raise concern about the other vaccines.

Dr. Reingold asked whether this was relevant because of requirements to have had the vaccine to attend school. He was not clear why others entering the country were relevant in terms of whether they received a different HPV vaccine with regard to what ACIP specifies.

Dr. Moore clarified that they were saying it is not relevant. The preference is to say "HPV vaccine" rather than specifying 9vHPV.

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Dr. Bennett thought the concern was that if a practitioner was assessing someone's vaccination status, if the recommendation is 9vHPV, if the person might be perceived as being un-immunized if they received 2vHPV or 4vHPV. That was not what was intended.

Regarding the 6- to 12-month span in terms of the second dose, Dr. Middleman (SAHM) reminded everyone that the Youth Risk Behavior Survey (YRBS) indicates that approximately 25% of adolescents have had sex by 9th Grade. She thought they should keep that in mind when considering a 6 to 12 month window in terms of whether people may have intercourse before the series is completed.

Dr. Wexler (Immunization Action Coalition) said that if ACIP decided to use "9vHPV," she recommended use of HPV9, HPV4, HPV2 as 9vHPV has posed difficulties in terms of the use of abbreviations in tools and informational pieces. They have emailed CDC about this issue. HPV9, HPV4, HPV2 would be consistent with PPSV23 and PCV13. Putting the number afterward is less awkward in terms of writing / space.

Dr. Markowitz noted that the feedback received suggested that only "HPV" should be used in the recommendation.

HPV Public Comments Submitted Via Email

From: sullivan75@comcast.net
Sent: Sunday, June 12, 2016 8:09 PM
To: Advisory Committee on Immunization Practices (CDC)
Subject: June 22 meeting

My Name is Deborah Sullivan. I live in Little Silver New Jersey. I have been an oncology nurse in New York City for 25 years. My family sits on the board of many NY hospitals and have floors named after them. I would like my voice to be heard at the June 22nd meeting. I have four children, all of whom have been fully vaccinated. Although one of my daughters was diagnosed with type 1 diabetes at the age of 5, and it was speculated at the time it could have been triggered by the R part of the MMR. Anyway, I still continued to vaccinate my children with the understanding there is always a risk of reaction. However, in the summer of 2015, my daughter received the HPV vaccine Gardasil and in less than 24 hours she was on the floor having what looked to be a panic attack. This occurred for three days and then tonic clonic seizure like activity began. I won't get into the whole story, but my daughter now has POTS, a cardiac arrhythmia ventricular tachycardia as well as joint pain, brain fog, repeated throat infections, and severe new allergies. My other daughter as well was affected and had all of the same symptoms with added vomiting and diarrhea. This is my type 1 diabetic daughter who received two shots all symptoms became worse after second shot, including debilitating headaches.

This is what I want to be heard!! I understand the benefit of vaccines. I also understand there is potential risk. What I don't understand is WHY when someone is affected that no doctors will help and the government does all it can not to payout to the victims.

The anti-vaccine people get a bad wrap because they have had to go out and fend for themselves with no help from doctors, so now they go out and promote "don't give vaccines". They know their child was affected, but because the link can't be proven, it is just dismissed. IF the government would take measures to set up protocols to treat victims and then try to change

formulas of vaccine, or at least look into and honestly evaluate, perhaps there would not be such a distrust. What happened to our system? What happened to doctors' oath of "Do No Harm"?

I can say this, my daughters were straight A honor students, AP and IB classes, recruited athletes, and then became chronically ill after the first Gardasil injection. Because I did not know symptoms were because of vaccine my oldest daughter got the second shot at same time my second daughter got first shot. My daughter became increasingly ill. I have been in over 20 ambulance rides in the last 10 months. I deal with their lines on a daily basis. My kids have been dismissed by many as having a psychological cause for the symptoms. However, because of my connections at hospitals in NY, we got to the bottom of their issues: Autonomic dysfunction, histamine intolerance, and high levels of circulating levels of epinephrine, norepinephrine, renin, and vasopressin. My once brilliant loving daughter cannot even have empathy for others as her affect completely changed within five days of vaccine.

Please hear the cry of these parents. I personally talk on a daily basis with 800 other moms whose children have been affected in the exact same way. I am out over 20,000 in doctor bills. It is unfair that I had to seek and seek and seek just for someone to listen. And I am the lucky one. Please look into the study done by Dr. Sin Hang Lee. I know you are aware of his letter to the WHO, but his science is good and it is what happened to our children.

God is watching and weather you believe or not, on Judgement day all who knew something was ignored and did it anyway will pay. My children have lost so much and not sure they will ever get it back. There are ways to help these kids. Take responsibility get this vaccine off the market and demand doctors find ways to help. I am begging.

Sincerely a grieving Mother
Deborah Sullivan

Day 2: Public Comment

No public comments were offered during this session.

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Certification

Upon reviewing the foregoing version of the June 22-23, 2016 ACIP meeting minutes, Dr. Nancy Bennett, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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February 18, 2016
Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2015 – June 30, 2016

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