Report: Complacency, misperception stymie quest for better flu vaccines

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Oct 15, 2012 (CIDRAP News) – The world needs much better influenza vaccines, but the quest for them faces a formidable barrier: overconfidence about the effectiveness of existing influenza vaccines.

So runs the essential message of a new report from University of Minnesota researchers who conducted an exhaustive study of the flu vaccine landscape and interviewed scores of experts in all aspects of flu vaccine research, development, production, policy, and use.

The 125-page report, "The Compelling Need for Game-Changing Influenza Vaccines," says that existing flu vaccines are moderately effective in healthy, nonelderly adults and young children, but there is little evidence of consistent effectiveness in older children, seniors, and those at risk for flu complications. Protection is "substantially lower" than what is offered by other routinely recommended vaccines.

Despite this, the vaccines are generally perceived as highly effective, and this misperception has become a barrier to creating new, more effective vaccines, according to the report from the university's Center for Infectious Disease Research and Policy, publisher of CIDRAP News (see sidebar article, "A game-changing approach to investigating flu vaccines").

Further, some of the policy steps that culminated in the current "universal" recommendation of flu vaccination for everyone over 6 months old were based on professional judgment, not sound data on vaccine effectiveness, the authors assert.

What's needed are "game-changing" vaccines that can yield greater, more consistent protection, according to the report. It says that will require designing vaccines that target viral components other than the head of the hemagglutinin (HA) protein on the virus's surface, a structure that mutates often, requiring annual reformulation of the vaccine and annual vaccination.

A vaccine that targets more stable pieces of the virus could provide more lasting protection against more flu strains, the report says. Also, a "novel antigen" vaccine could activate more elements of the immune system than are simulated by existing vaccines.

Some novel-antigen vaccines are in development and testing, but they face a steep uphill road, because the current regulatory system is designed to deal with small changes in existing vaccines, the authors concluded. Truly innovative vaccines would face tough regulatory hurdles.

None of this means that people should skip getting a flu shot, the authors say. "I've received my flu shot this year," said CIDRAP Director Michael T. Osterholm, PhD, MPH, lead author of the report, at a press conference today.

"We urge people to get their flu shot," he added in a university press release. "The present vaccines are the best interventions available for seasonal influenza. However, these vaccines do not offer consistent, high-level protection—especially in individuals at risk of medical complications or those aged older than 65 years. Unfortunately, these are the populations where we need the vaccines to work the best."

Experts contacted about the report were generally positive about its depth and findings, though there was some concern over how the media might portray the information.

Building on 2011 analysis

The report builds on a case the CIDRAP team made in a meta-analysis of flu vaccine efficacy and effectiveness studies that they published in the *Lancet Infectious Diseases* a year ago. Applying very strict criteria to filter out potential bias and confounding, they sifted more than 5,000 studies and found only 31 that they felt provided reliable evidence.

The findings of that analysis are re-emphasized in the new report: trivalent inactivated flu vaccines (TIV) yield about 59% protection in adults aged 18 through 64, but consistent evidence of protection is lacking for children aged 2 to 17 and people 65 and older.

Also, the team concluded that the live-attenuated flu vaccine (LAIV, the nasal-spray version) is about 83% protective in children aged 6 months to 7 years, but there is inconsistent evidence of protection in people 60 and older and no evidence of protection in those 8 to 59 years old.

By comparison, the vaccines in the standard childhood immunization series provide protection in the 80% to 90% range or higher, Osterholm said at today's press conference.

The report lays out the major health threats from influenza, including seasonal flu's deadly impact on older people and the global disruption that could occur from a severe pandemic. Though it's not clear if flu

vaccination can blunt the impact of the disease, helping to prevent its spread to unvaccinated people, the impact is still significant enough to warrant better, state-of-the-art vaccines, the authors state.

The report asserts that flu vaccines are a crucial national security tool, noting that the US government made the battle against flu a national priority after the 1918 pandemic decimated US military personnel during World War I. "This experience vividly demonstrated the national security implications of a severe pandemic," they wrote.

Regarding flu vaccine efficacy, the authors assert that polymerase chain reaction is the most specific and sensitive way to measure efficacy and explain that serology testing (using hemagglutination inhibition [HAI] to assess antibody levels) has a built-in case-detection bias, leading to overestimates of vaccine efficacy.

They describe the rigorous methodology they used in the *Lancet ID* study, and they add eight additional studies that were published after the study cutoff, all of which support the conclusions in the *Lancet ID* paper.

They also explore what the research says about the ability of the flu vaccine to reduce mortality, especially in high-risk groups. They estimate that over the last 31 years, 33,000 deaths in older people have been averted. "While this reduction is an important public health accomplishment, it falls short of the mortality reduction necessary to conclude that influenza vaccination is having a significant impact on influenza mortality in either the United States or globally."

The CCIVI researchers also explored the limited efficacy data for flu vaccines produced using alternative manufacturing platforms, including those based on mammalian cell, Vero cell, and baculovirus-expression inside insect cells. The results so far are similar to those for current US-licensed flu vaccines, which suggest they won't likely offer additional benefits.

Though cell-based flu vaccine manufacturing has been promoted as a way to speed vaccine production, the platform didn't deliver 2009 H1N1 pandemic vaccine any quicker to the European market, the report says.

The 2009 H1N1 pandemic provided the first rigorous look at the efficacy of adjuvanted vaccines, which had a median effectiveness of 72%, primarily in healthy young adults. However, studies done on them before the pandemic show that the adjuvant role in enhancing flu vaccine effectiveness remains unclear.

Assessing safety and public acceptance

On the safety side, licensed vaccines have a good track record, though Guillain-Barre syndrome, febrile seizures, and narcolepsy issues bear watching, according to the report. It says it will be challenging for new flu vaccines to meet or exceed the current safety profile.

The team also digs into how well the public has accepted flu vaccines. In 1987, a federal flu vaccine project was launched that eventually secured Medicare coverage for the vaccines, and by 1997, 60% of seniors were being immunized each year against flu, and the rate has pretty much stayed the same since.

Despite the 2010 universal flu vaccine recommendation and health promotion campaigns over the past 10 years, most Americans reported not getting a vaccine for last year's flu season, a lukewarm response that markedly contrasts with the rate of immunization against childhood diseases, which ranges around 90%. The reasons adults cite for not getting vaccinated against flu vary little from the responses 50 years ago.

"As new influenza vaccines are developed, the public's acceptance of these vaccines will continue to be an issue," the authors wrote.

The 2009 H1N1 pandemic showed that even if demand had been higher, global production would have been far below the previously estimated 3 billion doses in the 12 months following the pandemic declaration. The fact that the vaccine wasn't available until after the peak of the second wave significantly reduced its potential public health impact.

Problems with vaccine availability—seen in the last three pandemics—combined with the efficacy issue show that it's difficult to quantify the global health benefit of pandemic vaccines. "Regardless, the information presented here clearly demonstrates that influenza vaccines and their respective manufacturing platforms need to fundamentally change to meet future demands."

How vaccination advisories grew

The researchers also studied the history of US flu vaccination recommendations and the rationale and science—and sometimes the lack of science—behind them. They conducted a painstakingly detailed investigation of flu recommendations since 1964.

Military members were the first group singled out to receive the inactivated vaccine in the 1940s. Following the 1957-58 pandemic, the US surgeon general recommended annual vaccination for certain groups at higher risk for flu complications, including pregnant women, seniors, and those with chronic medical conditions.

In 1964, the newly formed Advisory Committee on Immunization Practices (ACIP) echoed the recommendations, though there were no data showing that the vaccine was effective in those groups. Over the next decades, the ACIP took several steps to further broaden the recommendation, culminating in a 2010 universal recommendation that everyone except infants younger than 6 months old receive the vaccine.

The authors' review of ACIP meeting records found that the decisions were based on professional opinions and goals of increasing overall vaccination levels, but not additional efficacy or effectiveness data showing benefits in the newly targeted groups.

In the early 1980s, the ACIP addressed effectiveness concerns by recommending a doubling of the antigen dose from 7 to 15 micrograms, based on limited data using HAI responses (starting with the 1981-82 flu season). The committee also started addressing the concept of herd immunity, and in 1984 added healthcare workers to the group recommended to be immunized.

In 1999 and the years that followed, the major emphasis was on increasing population coverage rates, boosting indirect benefits, and improving other outcomes related to morbidity (such as reducing antibiotic use

for secondary infections or reducing absenteeism).

More opinions than data

Some of the push to vaccinate more Americans seemed to come from frustration over not being able to reach high-risk groups. But scientific data to support the changes were often not available, the authors found. "Rather, changes were made at least in part on the basis of expert and organizational professional opinions with the strong belief that such changes would decrease the overall burden of influenza in the United States," the report states.

CCIVI researchers analyzed and compared the studies and documents cited to support each recommendation to expand flu vaccination to more groups. "We found that a number of the new references cited to support the revised recommendations were actually unrelated to specific aspects of the new recommendations and did not present findings from the new studies."

From 2005 to 2008, the ACIP's influenza working group identified several knowledge gaps, including vaccine effectiveness in seniors, but the committee continued to expand the recommendations even though the data to address the working group's concerns weren't available.

"The minutes of the ACIP meeting suggest that the ACIP moved toward a recommendation for universal vaccination on the basis of professional opinions from supporters of the approach, rather than on compelling data . . . consistent with earlier patterns for developing influenza vaccination policy," the report states.

When CCIVI researchers looked at the quality of the studies included in the 2010 ACIP statement, they found that the statement overestimated flu vaccine efficacy and effectiveness.

Even though the ACIP is transitioning to a new evidence-based framework called GRADE (Grading of Recommendations, Assessment, Development, and Evaluation), the GRADE criteria still include studies using serology as an end point, the authors found.

Vaccine-promotion efforts

The researchers also point out scientific flaws underlying recommendations regarding healthcare workers. At today's press conference, Osterholm nonetheless said he supports vaccination for healthcare workers. "We can challenge where we got the current recommendation without challenging that we need to do it [vaccinate workers]," he said.

The team also conducted a detailed review of the government's health promotion activities related to flu vaccination. "We found that materials through mid-2011 consistently reflected the overstatement of vaccine efficacy and effectiveness found in the ACIP statements reviewed above." They also found that promotional messages from other health-related and other nongovernmental groups, such as the National Foundation for Infectious Diseases, mirror the government agency approach.

The report says that overstating flu vaccine efficacy risks loss of public faith in the recommendations, in addition to hindering incentives for developing better vaccines.

The need for next-generation vaccines

The report also provides background on flu immunology to help explain the limitations of existing flu vaccines.

Natural infection stimulates both humoral (antibody) and cellular (T-cell) immune responses, whereas currently licensed TIVs mainly stimulate antibody responses. LAIV was intended to more closely mimic natural infection, leading to broader and more lasting immunity. LAIV works well in young children, who have little preexisting immunity. But it appears that pre-existing immunity blunts the effects of LAIV in older children and adults, in whom no studies clearly demonstrate LAIV effectiveness.

There is little evidence that existing vaccines, which generate antibodies to the often-mutating HA head on the virus's surface, can provide consistent, high-level protection across populations, the report says. Frequent HA mutations enable the virus to evade quick detection by the immune system.

"As long as the vaccine industry and government regulatory agencies remain focused on developing vaccines aimed at the globular head of HA, and to a limited extent NA [neuraminidase], improvement in influenza vaccines will be minimal and incremental," the report states.

The authors conclude that what is really needed is a flu vaccine that stimulates immunity even better than natural infection does—immunity that involves both antibody and cellular responses and works against multiple flu strains. "The goal for new vaccines, therefore, is to stimulate an 'unnatural' immune response to influenza," they write.

One possible approach they suggest is a vaccine containing a combination of antigens, such as ones targeting the HA stalk and the nucleoprotein or matrix 2 (M2) protein. Such a vaccine could generate both antibody and cellular responses, and these antigens contain segments that are the same across different flu strains, raising the possibility of a broadly protective vaccine effective against seasonal flu as well as novel pandemic strains.

Scores of vaccines in trials

Many flu vaccines are currently in clinical trials in the United States, featuring such innovations as recombinant proteins, virus-like particles, non-replicating viruses, viral vectors, and plasmid DNA. But the authors found that only 13 (7%) of 177 vaccines in trials depart from the standard approach of using antigens from the HA head, as opposed to antigens from more conserved parts of the virus, such as the HA stalk or M2 protein.

Many experts told the authors that adjuvants—chemicals added to vaccines to boost the immune response—can be game changers for flu vaccines. But the authors concluded that the data on existing adjuvanted HA-head vaccines are unconvincing, with improved effectiveness seen in only one study, involving children under age 6.

The impact of using adjuvants in seasonal flu vaccines in populations previously exposed to flu or flu vaccine has been "marginal," which suggests that adjuvants are mainly useful in children and during pandemics, where those being vaccinated have little pre-existing immunity, the team writes.

Flu vaccines targeting something other than the HA head face not only difficult technical obstacles, but thorny regulatory barriers as well, the report explains. In licensing flu vaccines, the FDA uses antibodies to the HA head as the evidence of a protective immune response, or "correlate of protection." If a vaccine targets a different viral component, new correlates of protection will have to be developed and assessed.

Moreover, the whole existing regulatory system is a huge obstacle to revolutionary flu vaccines, according to the report. "The regulatory structure as it currently exits will not get us there. A substantial shift in the regulatory paradigm by both government and industry is required."

The major impediment to such a shift is "the pervasive belief that current HA-based vaccines are adequate. As long as this view endures, efforts will remain focused on small, incremental changes to the current vaccines, and we cannot expect any movement toward superior novel-antigen vaccines."

"We found a general perception that we don't need a better flu vaccine, we just need to make more of it faster," Osterholm said in an interview.

FDA, industry criticized
The report charges both the FDA and the vaccine industry with failing to provide leadership in this realm. It says major vaccine manufacturers have little incentive to develop novel-antigen vaccines, because the existing vaccines provide a "reasonably stable source of income."

As a result, the field is left to small, often start-up companies—which can't secure enough public or private money to survive the years of development and testing before a vaccine can actually earn money, according to the report. The process of developing a vaccine and getting it licensed can take 15 years and cost more than $1 billion. And the hurdles will be even greater for a novel-antigen vaccine, because a vaccine that provides protection for several years will need to cost more per dose than do current vaccines, since fewer doses will be sold over time.

At the press conference, Philip K. Russell, MD, who served on a panel of outside experts who advised the CCIVI project, said the barriers to truly innovative flu vaccines boil down to a lack of scientific knowledge, high costs, and regulatory obstacles. Russell is a retired major general with the US Army Medical Corps and an emeritus professor at Johns Hopkins University's School of Hygiene and Public Health.

The authors conclude that what's needed is a "new financially sound pathway supported by the US government, other national governments, and/or private-sector investment."

US government policy on flu vaccines since 2003 has focused mainly on getting more people immunized with existing vaccines and ensuring that capacity is available to quickly produce HA-head vaccines in the event of a flu pandemic, according to the report. There have been steps toward "incremental improvements" in the existing vaccines, but policy makers have not focused on the shortcomings of existing vaccines, and the political will to make better ones has been lacking.

A Manhattan Project needed?
In a chapter on leadership, the authors assert that no US government or international agency has the responsibility or capability to bring about game-changing flu vaccines. Accordingly, they call for a new model for managing the flu vaccine enterprise. As an example of what that might entail, they invoke the Manhattan Project, the Herculean national effort to develop the first atomic bomb during World War II.

"We recognize the current environment of fiscal austerity; however, the economic and political consequences of a severe influenza pandemic in the absence of a readily available and effective vaccine cannot be overstated," they write.

Among their concluding recommendations, the authors call for:

- Developing an international standard for evaluating flu vaccine efficacy and effectiveness, so that scientifically sound estimates can become the basis for policy recommendations about vaccine use
- Declaring game-changing flu vaccines a US government priority
- Providing a financial pathway to overcome the financial disincentives that hinder the advancement of new flu vaccines to market
- Building "a new organizational and leadership structure" for the flu vaccine enterprise to provide "strong science and business leadership and exemplary project management processes"
- Leadership by the US government in global efforts to develop novel-antigen flu vaccines

Positive reactions
The report drew mostly positive early reviews from other experts whose opinions were sought by CIDRAP News. (Most of those cited below were not involved in the CCIVI project, but two of them served on the project's expert advisory group.)

Marc Sprenger, MD, PhD, director of the European Centre for Disease Prevention and Control (ECDC)—which has conducted a number of noteworthy flu-vaccine efficacy studies in recent years—agreed that flu vaccines need improvement.

"From a public health perspective, we can only promote vaccination if we have good, effective vaccines," he said. "While much has been done to improve influenza surveillance in Europe and there is a commitment to improve vaccination coverage, we have seen little progress to improve vaccines over the last two decades. As this report shows, there is clearly a need to develop more effective vaccines. ECDC considers this the highest priority for influenza researchers and vaccine manufacturers."

The US Centers for Disease Control and Prevention (CDC) referred a request for comment to the Department of Health and Human Services (HHS). HHS spokesman Bill Hall said the department welcomes the report and sees the findings as "generally consistent with work published in recent years."

"We agree that influenza places a substantial burden of disease on the United States and globally, which warrants attention and ongoing investments," Hall said. "Public health experts agree that we need better flu vaccines, and HHS is actively supporting multiple avenues of research and development of more effective

influenza vaccine strategies.

"In the meantime, we cannot lose sight of the fact that currently available flu vaccines can help prevent influenza and the serious complications that can result from the disease. Therefore, HHS recommends that—with rare exception—everyone 6 months and older get vaccinated against flu. Influenza vaccination is safe and offers the best protection we currently have against flu."

The report drew warm praise from D. A. Henderson, MD, MPH, who led the fight to eradicate smallpox: "The report is superb and the recommendations reasonable. Like the field in my other two areas of special interest—polio and smallpox—the landscape is littered with reports and committees but once in a while, one emerges which, by review and logic, commands respect and action. I believe that is what this will be seen to have accomplished."

Henderson is a professor of medicine and public health at the University of Pittsburgh and a Johns Hopkins University Distinguished Service Professor.

Concern about public interpretation

Gregory A. Poland, MD, head of the Vaccine Research Group at the Mayo Clinic in Rochester, Minn., said he views the report as "an important report for industry, government, and public policymaking bodies," but he voiced some concern about how it will be interpreted by the news media and the public.

"My concern is that the way the study is being positioned, the way the media will handle it, is to question whether you should get a flu shot, and I think that's the wrong message," he said.

Poland said the message of the report is important, but is generally not new to those in the flu-vaccine field. "We already know the need for better development mechanisms, approval mechanisms, better vaccines for the most vulnerable. It's good that it reinforces that, but it's not necessarily new for investigators."

But he added, "I do like the idea of establishing some standardized definitions that would be used in clinical studies. It would be nice to have a set of definitions common across all studies." Standard definitions for things like correlates of protection, efficacy, and effectiveness would be useful, he said.

Analysis of ACIP work applauded

Peter Sandman, PhD, a member of the CCIVI expert advisory group and risk-communication consultant based in Princeton, N.J., said the most controversial chapter of the report is the researchers' analysis of how ACIP's recommendations led to perceptions that current flu vaccines are more effective than they are, with the overestimation embedded in US public health decisions and public health messages to consumers.

Without the group's detailed documentation of ACIP's decision-making on flu vaccines, the CCIVI report would have been a technical assessment of the inadequacies of the current vaccine and the feasibility of developing a better one, Sandman said.

"The report is that and more. It is also a powerful indictment of the way the public health leadership and particularly the CDC's Advisory Committee on Immunization Practices has impeded progress toward a better vaccine by overestimating and overselling the vaccine we have," he added.

He commented that although the public health community may find it difficult to embrace the themes of the CCIVI report, the *Lancet Infectious Diseases* study paved the way for the topic of flu vaccine efficacy. The next task is for science-based decision-making and science-based flu vaccine public messaging to help build the case for producing a vastly improved vaccine while strongly supporting existing versions, he said.

Al Sommer, MD, MHS, who chaired CCIVI's expert advisory group and is professor and Dean Emeritus of Johns Hopkins Bloomberg School of Public Health, said game-changing flu vaccines won't be easy political or scientific objectives to achieve, but the goal should remain the main focus.

"A second, and perhaps far more achievable objective, is to revisit the rationale for universal flu vaccination, now that we know and are more cognizant of the limitations for existing vaccines," he said.

See also:

Full CCIVI report

Executive summary

Report landing page

Oct 15 CIDRAP News story "A game-changing approach to investigating flu vaccines"

Oct 25, 2011, CIDRAP News story "Strict meta-analysis raises questions about flu vaccine efficacy"