Published in final edited form as:

Vaccine. 2012 February 01; 30(6): 983–984. doi:10.1016/j.vaccine.2011.12.086.

New Influenza Vaccines: Promises, Perils, and Pitfalls

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In no other area of vaccinology are we confronted every year with a recurring dilemma: how best to protect those who respond least well to influenza vaccines during annual influenza epidemics? This includes infants, those immunocompromised by any of a variety of diseases or therapies, and those for whom age has resulted in immunosenescence. The consequences, and economic costs, are considerable — mostly measured as markedly elevated rates of morbidity and mortality due to seasonal and pandemic influenza viruses, as well as lost wages and school time. This is most pronounced in the elderly, in whom we observe the highest mortality and the lowest efficacy of our current vaccines [1]. “Cocooning” efforts to reduce the burden of disease in the elderly by vaccinating children and healthcare workers have been incompletely effective and mired by social and cultural barriers to implementation. Consequently, we are reliant on the development of more effective vaccines to dependably protect populations most vulnerable to this pathogen.

Cognizant of this challenge, new vaccines have become available. Just a handful of years ago, influenza vaccine practice was characterized as a very limited “one size fits all” approach with one vaccine option, and a complicated risk-based immunization approach. The advent of individualized medicine has informed vaccine practice — in just a few years we have seen the licensure (in the U.S.) of live, attenuated influenza virus vaccine (LAIV), high-dose trivalent influenza vaccine (HD-TIV), and intradermal trivalent influenza vaccine (ID-TIV). In other areas of the world, an MF59-adjuvanted influenza vaccine is also available. In addition, the U.S. has moved from a complicated set of 16 high-risk categories for which influenza vaccine was recommended, to a universal recommendation that everyone age six months and older receives seasonal influenza vaccine annually [2].

The aforementioned new vaccines provide the promise of better immunogenicity and efficacy in those most at risk, as well as perhaps increased acceptability and therefore use. Perhaps more importantly, the development pipeline for new influenza vaccines is considerable and includes vaccines with broader immunologic response and wider virologic coverage to capitalize on the breadth of the human immune system and to protect against antigenically drifted and shifted influenza strains. Examples include vaccines targeting highly conserved proteins such as M2e (so-called universal influenza vaccines), DNA vaccines, peptide-based vaccines, vectored approaches, and new adjuvants for use with influenza vaccines, among others.

Perils also exist, as with any new vaccines. While both ID-TIV and HD-TIV vaccines provide superior or non-inferior immunogenicity, improved efficacy has not yet been documented. Such trials are underway, though delayed by the unanticipated H1N1 pandemic. As a result, it is likely that results from such trials will not be available for several more years, and a definitive answer to whether higher antibody levels lead to improved efficacy delayed.

Pitfalls include scientific, economic, and cultural issues. For example, we do not yet understand the basis of immunosenescence, making it difficult to design vaccines or vaccine adjuvants with specific, directed beneficial effects on the immune system. Furthermore, concern exists regarding unintended consequences of non-specific immune system activation, such as autoimmune phenomenon (though no evidence currently exists for triggering of such phenomenon thus far). Other concerns include an inadequate “systems level” understanding of how protective influenza immune responses are generated, maintained, and even what markers (or levels) of immunity are true correlates of protection. For example, compelling work suggests that cell-mediated immunity may result after influenza immunization and plays an important, but unmeasured, role in protection from disease or complications of infection [3; 4]. Further possible scientific pitfalls include the importance of designing highly informative clinical trials that avoid recent concerns of selection and other biases [5].

Economic pitfalls revolve around the generally much higher costs of new vaccines, the lack of an infrastructure for universal reimbursement of adult vaccines, and the necessity of providing such vaccines annually across the population. Cost-benefit and other economic analyses would be both useful and informative to policy makers in this regard.

Cultural pitfalls include generalized vaccine fears among much of the populace, gross misperceptions about vaccine efficacy, safety, and benefit, and a cultural acceptance of “the flu” as a normal and expected consequence of life. Hence, little in the way of urgency or demand for influenza vaccines is evident at the population level. Even in the face of the recent influenza pandemic, otherwise well-educated and (presumably) informed physicians and nurses widely rejected both pandemic and seasonal influenza vaccines [6].

So, how to proceed? Below we offer an agenda for progress that may be useful to policy-makers and funding agencies:

1. Devote resources to more basic and clinical research regarding influenza, influenza immunity, and influenza vaccine delivery to populations. An excellent example of the former is the NIH’s Human Immune Phenotyping Consortium (HIPC)[<http://immuneprofiling.org/hipc/>], where many of the funded projects (including our own laboratory) involve molecular, genetic, and systems biology approaches to understanding the development of vaccine-induced influenza immunity across different ages and medical conditions. Similar programs in basic adjuvant biology, immunosenescence, and the development of novel vaccine candidates are needed. Critical too, and often neglected, are the need for well designed clinical trials to better understand differential efficacy across age

and medical condition(s), and how we might most effectively achieve high rates of vaccine coverage across the population.

2. In a parallel development method, plan for the following new vaccines:
 - a. Introduction of quadrivalent influenza vaccines (bivalent B strains, monovalent H3N2, and monovalent H1N1 strains)
 - b. Licensure of adjuvanted influenza vaccines – a current example might be MF59-adjuvanted vaccines if improved efficacy over TIV can be demonstrated
 - c. Licensure of so-called universal influenza vaccines requiring only intermittent dosing during a lifetime
 - d. Possible licensure of novel vaccine candidates in the future
3. Develop a reliable reimbursement infrastructure for adult vaccines. Such a plan now exists for children (Vaccines for Children), but not for adults. This needs to be fixed and no American, regardless of age, should fail to receive recommended vaccines because of lack of financial resources.
4. Continue the ongoing education about the nature and costs of influenza infection, the role of vaccines in protection, and the safety and efficacy of influenza vaccines among the public, payers, and providers. In particular, a culture of concern about influenza and its prevention must be developed, and providers educated into greater awareness of the tremendous morbidity and mortality—as well as economic costs—of annual influenza epidemics with consequent concern about preventing such infections.
5. Develop convenient and easy access to immunization providers. For example, consider offering some influenza vaccines “over the counter,” or offering vaccines not only at physician and public health offices, but at dental offices, post offices, fire departments, and perhaps other non-traditional venues, with the goal of eliminating access as an obstacle to immunization.

The goal in influenza prevention is straightforward, and explicitly articulated: develop highly immunogenic, safe and efficacious vaccines that prevent influenza infection (or its complications) in nearly all recipients, at low cost, and which can be provided in an extremely convenient manner to the entire population. Achieving that dream is, of course, not straightforward and will require substantial scientific progress over many years. But no progress can come absent defined goals, a well thought out roadmap, and research dollars and support to achieve them. It is hard to imagine a more worthy goal in vaccinology that would benefit everyone alive.

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