EDITORIAL COMMENTARY

Toward Improved Influenza Vaccines

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(See the major article by Carroll et al 24–33.)

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Influenza takes a large toll on human health, particularly in the elderly population. The current unadjuvanted trivalent inactivated influenza vaccines (TIVs) are notorious for modest-to-dismal efficacy among elderly individuals. Protection by TIV is limited largely to the 3 or 4 strains chosen for each influenza season. The drifts in circulating strains mean that annual receipt of TIV is recommended, the only licensed vaccine with such frequent administration. Furthermore, this current strategy provides no cross-protection against highly novel pandemic influenza viruses. There is a delay between identifying a pandemic strain to use in a vaccine and generating a matching vaccine, leaving the population highly vulnerable for some months. A considerable worldwide effort is underway to generate much improved influenza vaccines, particularly for the most vulnerable populations.

The study by Carroll et al in this issue of the *Journal* is timely research in this regard [1]. The group studied a cohort of elderly macaques that were aged >18 years. Similar to elderly humans, these elderly macaques had reduced levels of total T cells, especially naive $CD4^+$ T cells. The addition of a novel adjuvant to 2 doses of a standard TIV dramatically improved the immunogenicity and protective efficacy of the TIV. A liposome/DNA adjuvant, cationic lipid/DNA complex (CLDC), appeared safe and induced higher and more durable levels of protective antibodies, compared with the unadjuvanted TIV. Antibody levels in the elderly macaques that received TIV with the adjuvant approached those seen previously in juvenile macaques given unadjuvanted TIV [2]. There was clear evidence of much better clearance of a challenge influenza virus in the elderly macaques that received the novel adjuvanted TIV, compared with those that received the standard TIV.

Why did the adjuvant work? The levels of influenza virus–neutralizing (hemagglutination-inhibiting) antibodies induced were robust, and the challenge used a strain that closely matched that in the vaccines, as would occur if the seasonal TIV strains matched the circulating infecting strains. However, the adjuvant also induced some $CD4^+$ and $CD8^+$ T-cell immunity that may have assisted the protective efficacy [3]. T-cell immunity is often directed to conserved internal antigens that can provide cross-protection against divergent strains. It is also possible that the CLDC-adjuvanted TIV generated functional nonneutralizing antibodies, such as those involved in antibody-dependent cellular cytotoxicity, that may also have assisted in the protective immunity observed [4]. Such antibodies, like T cells, are often cross-reactive to divergent strains and may provide some cross-protection [5, 6]. These issues could be teased out with passive transfer or heterologous challenge studies in the future.

The translation of these promising macaque results to humans remains to be shown. A key issue in clinical trials will be the reactogenicity of the adjuvant. Although no marked effects were observed in this macaque study, macaques tend not to complain much, and both the general population and regulatory bodies are woefully intolerant of even modest reactogenicity. This is one reason our current TIV remains unadjuvanted. A surprising proportion of humans even fervently believe the current TIV can cause influenza.

A second key issue for clinical trials will be the humoral immunogenicity of CLDC-adjuvanted influenza vaccines. There is reason to be hopeful that results of human studies will be positive. The elderly captive macaques studied (age, 18–22 years) will have had much less prior exposure to influenza viruses than elderly humans (ie, those aged >65 years). It may well be even easier for such vaccines boost low-level preexisting anti–influenza virus immune responses induced by prior infection in humans than it was to generate new responses in macaques. Indeed, recent evidence suggests that even current unadjuvanted TIVs primarily boost low-level preexisting influenza virus antibody responses rather than generate new responses [7]. Interestingly, the

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clear superiority of the CLDC-adjuvanted vaccine was not demonstrated until following the second dose, which may be necessary in future clinical studies.

Where does this CLDC adjuvant approach fit with other efforts at developing better influenza vaccines? Adjuvanted influenza vaccines have now reached the market, particularly the squalene-based oil-in-water adjuvants from GlaxoSmithKline (AS03), Sanofi Pasteur (AF03), and Novartis (MF59). These vaccines generally show important incremental improvements in immunogenicity with modest increases in reactogenicity, compared with unadjuvanted TIVs [8].

There is substantial current research investment in developing influenza vaccines with quantum leaps in efficacy, durability, and cross-protection capacity over the current vaccines. Novel live-attenuated virus approaches look promising in animal models [9]. Lipid-based virus-like particles ("virosomes") [10] and nanoparticle-based approaches show considerable efficacy in early studies [11]. Recent research shows the promise of using vectors to deliver the rare neutralizing antibodies that cross-recognize divergent influenza virus strains [12]. Various viral vector vaccines, designed, in part, to induce T-cell immunity, also show promise [13]. The role of T-cell immunity in controlling immunity will be interesting—it could be argued that T-cell responses may expand too late to be of use in early control of acute influenza virus replication. However, there is solid evidence that T-cell immunity plays a role in primate models [14], and in humans T-cell immunity could play an important role in controlling severe protracted influenza virus infections, which are associated with much of the influenza-associated morbidity and mortality.

Overall, there is a great need to develop better influenza vaccines for the elderly population and other vulnerable groups. The work described by Carroll et al describes another promising approach moving toward human efficacy trials.

Notes

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