Title: On setting expectations for a SARS-CoV-2 Vaccine

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Summary: The experience with influenza and pneumococcal vaccine effectiveness should temper our expectations for early SARS-CoV-2 vaccines. If inadequately protective, better targeted cell mediated immunity may prove critical to improved vaccine performance. Vaccine candidates should be evaluated closely for this capability.

ABSTRACT:

The global coronavirus pandemic is unlike any other since 1918. A century of dramatic medical advances has produced a public expectation that the medical field will rapidly provide solutions to restore normalcy. In under 6 months, since SARS-CoV-2 was identified, the massive international effort to develop a SARS-CoV-2 vaccine has generated more than 140 vaccines in different stages of development with 9 already recruiting into clinical trials posted on clinicaltrials.gov. The long-term strategy to handle COVID-19 will almost certainly rely on vaccines. But, what type of protection can we realistically expect to achieve from vaccines and when?

Key words: COVID-19, SARS-CoV-2, vaccine, T cells

Protection by vaccines against respiratory viral pathogens can help set our expectations for a future SARS-CoV-2 vaccine. Influenza has similarities, in that it also causes respiratory illness and is an RNA virus. The seasonal inactivated influenza vaccine has a modest protective efficacy of 10-60% even in years when the vaccine matches the circulating strains [1]. Vaccines to prevent streptococcal pneumonia, albeit a bacterial target, have similar efficacy reported at 45-64% efficacy [2, 3]. Furthermore, contemporary respiratory syncytial virus (RSV) vaccine trials have yet to demonstrate more than modest protection [4]. Thus, we should expect a modest protective efficacy from vaccines against respiratory pathology in the 60% to 70% range at best and potentially far worse in persons with diminished vaccine response who disproportionately count among the highest risk populations. Also, unlike a vaccine targeting SARS-CoV-2, each of these vaccines operates in a milieu of at least some previous immunity to boost from. Therefore, the expectation that a SARS-CoV-2 vaccine can develop this level of protection from an immune naive state, especially in the setting of immunizing elderly individuals whose naive B and T cells are substantially diminished, needs to be set with caution.

Influenza and pneumococcal vaccines still offer substantial clinical benefit. But, in the context of COVID-19, what should we expect from a vaccine that in older and other high risk groups will likely experience a 40% or higher failure rate? Will the vaccine nevertheless help mitigate disease and prevent hospitalization, mechanical ventilation, or even transmission in those who still get infected? Using the influenza comparison, those who develop influenza despite vaccination still experience reduced morbidity [5]. Current understanding is that influenza antibody titers help prevent infection but cell mediated immunity (CMI) is essential for recovery. Data from several influenza studies suggest that increased CMI, specifically including both CD4+ and CD8+ T cells, helps mitigate influenza severity in older adults when infected despite vaccination [6-8]. An optimal vaccine would protect both by preventing infection and mitigating disease from infection that eludes antibody-derived protection.

Vaccine constructs from Oxford and Moderna have received considerable attention. The former uses the ChAdOx1 construct, a replication-deficient adenovirus platform, which can elicit CD4+ and CD8+ T cell responses and demonstrated antibody responses in a phase 1 *M. tuberculosis* vaccine trial [9]. The latter is an mRNA construct against SARS-CoV-2 which elicited neutralizing antibody in trial volunteers (phase 1); however, in a published phase 1 clinical trial using the same construct technology with 2 influenza viruses they also showed significant antibody responses, but did not demonstrate detectable T cell responses [10]. We should expect all of the existing clinical trial candidates to have incomplete effectiveness, and we need to establish whether those that ineffectively recruit CMI have inferior disease mitigation when COVID-19 develops despite vaccination.

The breathtaking speed of the widespread vaccine development for COVID-19 has leapfrogged the fundamental immunologic work needed for a fuller understanding of the critical components of immunity. The pandemic crisis has necessitated this strategy. Since we are starting without meaningful immunity, generating a robust humoral and CMI response will likely be an iterative process that will benefit from ongoing vaccine development. The most effective vaccines against respiratory-acquired pathogens are all live attenuated virus vaccines (MMR, varicella, and smallpox), while none are primary respiratory pathogens. Logically, none of the current clinical trials use a live attenuated vaccine, as we simply do not know enough about SARS-CoV-2 virology to safely put forward such a candidate. A live attenuated vaccine

could be optimal were it also proven to be safe. Clearly, we must work in parallel, testing vaccine candidates while advancing very robust basic science efforts. We must better understand the immunology to anticipate what is ahead and optimize our current pandemic response while we build the infrastructure that can serve us for the next pandemic crisis.

Potential Conflicts of interest

S.G. and D.C. report investigator initiated grants to the university to study influenza vaccines and consulting of flu vaccines from Seqirus, Sanofi-Pasteur, and Pfizer. S.G. also reports DMC member payments from Janssen and Merck.

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