Editorial

Tortoises, hares, and vaccines: A cautionary note for SARS-CoV-2 vaccine development

In the Aesop fable, "The Hare and the Tortoise," the tortoise unexpectedly beats the hare in a race. The moral of the story is that the race is not always to the swift. This same moral also appears in the wisdom literature of the Old Testament book of Ecclesiastes 9:11, which more generally concerns the limitations of human wisdom—which is nearly always disregarded by humans themselves.

In late December 2019, the world was notified of an unusual cluster of severe respiratory disease occurring in Wuhan, China. Very soon thereafter, the causative agent was identified as the now-named SARS-CoV-2 virus—a betacoronavirus that had crossed the species barrier to infect humans. In the last few months, this virus has circulated worldwide and caused over 3 million identified cases and 200,000 deaths as of this writing, and those numbers are certainly an under-estimate.

Almost immediately, the call went forth that a vaccine was needed. I agree and so does every serious scientist knowledgeable about the issue. There is no question that a vaccine against this virus, and other as-yet-to-come coronaviruses, is imperative to protect human health and to quickly respond to future viral introductions, epidemics, and pandemics. But, alarmingly, scientists began to speak of the promise of a vaccine being available in "months"—promises that began to circulate in the media almost as quickly as the virus.

Vaccine development has a long and documented history. In the US, as is true to greater and lesser degrees around the world, vaccines go through both scientific and regulatory pathways. These pathways, informed by science and the past history of successes and failures, are designed to maximize the chances of efficacy and safety. Further, these pathways are designed to be deliberate, reflective, evidence-based, and peer-reviewed … in short, to maximize the chance that the data generated are robust, interpreted correctly, and lead to safe and effective vaccines when used in the population-at-large. Perhaps the fastest a vaccine has been licensed in response to a new human pathogen of public health concern is the example of Ebola virus. From the first cases to licensure in the US took some 6 years, although work on a vaccine had started in the 1990s. Even the pandemic influenza A/H1N1 vaccine in 2009 took over 6 months to produce and distribute, and this was for a vaccine we had decades of experience in producing and testing with annual strain changes. Even then, many concerns were raised by the public of an "experimental and untested" vaccine being foisted on the public. It turns out that perception is important (at least in terms of vaccine uptake), and that human decision-making under conditions of uncertainty is both biased and flawed, particularly under distorting influences such as economic incentives or perceived losses, peer pressure, and wide-spread fear.

What does history teach us in regard to vaccine development? First, expect the unexpected. Research is non-linear and often presents problems and barriers that are unanticipated. From these we learn (supposedly) and build on both successes and failures for the future. In vaccine development, we need only look back a handful of decades to recall failed vaccines against measles and RSV that used inactivated virus approaches. These vaccines led to antibody enhanced disease (AED) in people who were immunized and later infected with wild virus [1,2]. More recently, despite careful studies through years of preclinical and phase 1–3 clinical trials, AED was detected in post-licensure studies of dengue vaccine [3]. Second, RNA viruses accumulate mutations that can sometimes circumvent vaccine-induced immunity. For example, influenza viruses mutate so fast that nearly annual strain changes are necessary for influenza vaccines. This occurs despite vaccines containing both H and N protein antigens, rather than depending upon single protein/antigen preparations. Third, issues of broad immunogenicity exist. Given that this is an RNA virus, I believe it is critical that more than one viral antigen be included in the vaccine. While the significance remains unknown to date, researchers have already identified at least one mutation in the receptor binding domain of the S gene [4]. Further mutations could conceivably lead to issues of original antigenic sin with resultant disease enhancement after exposure or to vaccines that simply are not effective into the future. "S only" vaccines risk these issues, whereas vaccines that include other relevant SARS-CoV-2 viral antigens considerably reduce this risk. Fourth, decisions must be made regarding how much safety data is needed before initiating first-in-man clinical trials. Of concern is the push for starting clinical trials in the absence of completed animal studies. Novel phase I vaccines should not be administered to humans prior to completion and evaluation of appropriate animal studies for safety, toxicity, and immunogenicity. Rushing through animal studies, using irrelevant or single animal species models, and avoiding non-human primate studies is simply transferring risk from animals to humans in an attempt to rush vaccine development. This may be even more important in studies of novel vaccine antigens, vaccine approaches, and concomitant adjuvants or immunostimulants. Fifth, some are beginning to call for human challenge models as a method for quickly moving through vaccine development. This would require extensive discussion and ethical consultation to consider factors such as the lack of known effective treatment, the balance between

public health need and expediency, what full informed consent would be composed of in a situation like this, and what safeguards would need to be in place if this were even possible. A compelling ethical case must first be made prior to addressing these other issues.

Rushed studies to get quickly to licensure presuppose evidences of safety, efficacy, and benefit. These should not be supposed; rather, the burden of proof lies upon the vaccine developer to demonstrate that those presuppositions are justified. For example, what level of risk are we willing to tolerate to immunize against an infection that may disappear in the next year or two? Or that could diminish in severity in the short- to mid-term? Or to administer to young children whose risk of both serious illness or death is quantifiably very, very low?

This begs the question of how to license a vaccine in the midst of an ongoing pandemic like SARS-CoV-2. Might reasonable "accommodations" be made for such a scenario? Several seem worth immediate discussion:

– Could a vaccine be provided through an EUA mechanism for mentally competent adults who meet certain risk guidelines, and in the context of study enrollment and data collection, and enhanced informed consent?
– Could a vaccine be provided through a revised definition of a compassionate use mechanism in the highest risk subjects after signing waivers of responsibility and enhanced informed-consent procedures? Who should be included—perhaps healthcare providers and first responders who share the highest risk of infection as a starting point?
– What, if any, animal models might be developed that allow the "animal rule" to be utilized in an effort to accelerate research and licensure?
– If phase I and II trials are conducted earlier than normal procedure, could a phased initiation of studies from highest risk to lowest risk subjects be utilized?
– Might one conceive of differential regulatory pathways for vaccine candidates using well-understood antigens, vaccine methodology, adjuvants, manufacture, and routes of administration (TBD) versus those using novel delivery technology and novel antigens or adjuvants?
– As mentioned above, human challenge studies have been advanced as a method to rapidly determine efficacy in discussions I have had with other vaccinologists. Could this be a viable strategy in accelerating licensure? To date, no ethical framework has been advanced to support such an idea.
– What will be the endpoint for determining vaccine efficacy—prevention of infection? Prevention of severe disease? Prevention of viral shedding? Other?

– Will different vaccines and different regulatory pathways be feasible for different members of the population with differing risk:benefit ratios? For example, administering a vaccine to a healthy and robust 18-year-old with no underlying co-morbidities should require an exceptionally high safety and efficacy threshold. Might that safety profile be somewhat different (to be defined) in an exceptionally high risk 80-year-old with multiple co-morbidities? What about for pregnant women or younger but immunocompromised persons?

These and other such questions are raised to consider more carefully and thoughtfully how best to approach the development and distribution of a COVID-19 vaccine. Under current knowledge and disease severity, a vaccine is urgently needed. But such vaccine development must begin and progress cognizant of the many lessons learned from the past. In addition to safety issues, I raise concern over "S-only" vaccine approaches for the mid- to long-term control of this RNA virus. We need a vaccine—and we need it as quickly as one can be developed—that demonstrates safety and efficacy in adequately powered studies. Such an extraordinary event as COVID-19 is an argument for carefully developing a new playbook for how to develop novel vaccines against emerging pathogens in the context of epidemics and pandemics. Modern science has the ability to rapidly develop vaccine candidates, but wisdom lies in attending to the many lessons of the past . . . including that of the tortoise and the hare.

References

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