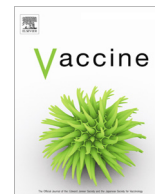




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Commentary

Need for a contingency dimension when planning vaccine development in a pandemic environment

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By any measure, having multiple COVID-19 vaccines studied and tested, manufactured at commercial volumes and ready for distribution in less than a year has been an unprecedented feat. The overall speed of development was all the more remarkable for use of mRNA as a previously untested vaccine platform, for production campaigns at greater than 100 million dose volumes with plans to attain eventual ten-digit volumes for global use, and for collaboration with federal regulators, using less-well known, though nonetheless well-suited, regulatory mechanisms, specifically the Emergency Use Authorization, to gain timely access to waiting patients.

Still, there have been challenges: for example, the long simmering and evolving facets of vaccination hesitations [1]; and the extraordinary loss of 75 million doses' worth of vaccine active pharmaceutical ingredient due to cross-contamination during manufacturing because of inexperienced and inadequately trained workers [2].

There has also been the confusion attributable to unforeseen circumstances. Two are notable. First, in the face of a shortage of BNT162b2 vaccine (Pfizer and BioNTech) in the UK, public health officials chose to allow a gap of up to 12 weeks in the administration of 2nd doses of NBT162b2 in favor of giving available vaccine as first doses to the next cohort of available patients, thus, more rapidly increasing partial protection to a larger proportion of patients [3]. Unfortunately, there were no data available to know how long an interval could be taken without compromising full protection for the patients whose 2nd doses were delayed. Second, when unexpected shortages of one mRNA vaccine occurred, there was interest in knowing whether the second dose could it be replaced with the other available mRNA vaccine. The National Advisory Committee on Immunization (NACI), an External Advisory Body that provides independent public health advice to the Public Health Agency of Canada (PHAC), has prepared an extensive analysis of interchangeability of authorized COVID-19 vaccines in consideration of that potential eventuality [4], while the CDC has not sanctioned interchangeability [5].

Gostin has reported on a resolution from the World Health Assembly [6] that outlines 9 steps that would be needed to prevent

the next pandemic. Step 7, Suspend Intellectual Property Rights and Transfer Technologies, offers strategic guidance through use of a mechanism to share “intellectual property, knowledge and data on health technologies for combating COVID-19.” At the tactical level, there would also be need for statutory and regulatory mechanisms to clear the way for highly specific contingency planning to facilitate responses to the unforeseeable and to encourage collaborations that would not otherwise occur. Examples that could be considered: FDA policy and guidance documents could provide strong direction to manufacturers about seeking opportunities to share control groups when conducting large Phase 3 randomized trials [7]; similarly, manufacturers could be encouraged to collect extended antibody responses beyond what's expected to support a regulatory filing for labeling to inform policy-makers on decisions when considering potential delays in multi-dose regimens; manufacturers could also be encouraged to share active pharmaceutical ingredients with one another to evaluate the potential for cross-over vaccinations of multi-dose regimens; and finally, pregnant women in the last trimester could participate in studies to determine the potential for cross-placental, passive protection of neonates. Tomson and colleagues have developed a “5A taxonomy” of elements as determinants of vaccine uptake, including the following: access, affordability, awareness, acceptance, and activation [8]. Longer term measures are also up for consideration that would begin to address the marked disparities in availability of vaccines across the globe: for example, forward infrastructural development to manufacture vaccines in Low-and-Middle Income Countries and regions. A pharmaceutical company twice undertook this approach in the 1990's: first, for HBV hepatitis in China by building a manufacturing plant in China for recombinant HBV vaccine, and second, for river blindness in Africa by donating ivermectin to the Carter Center [9] which provided the distribution infrastructure.

What must be remembered is that to increase the likelihood that these efforts will be successful, there must be a well-grounded experience of trust: trusted professional relationships are sine qua non when building a network of global, cross-border collaborations for collecting surveillance data, for the transparent sharing of information on outbreaks, for the posting of sequencing results, for practice runs of identifying target candidates, and for manufac-

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turing micro-lots of active pharmaceutical ingredients for testing in animal models. The present epidemiology of emerging COVID-19 variants presents an opportunity to apply these lessons as a try-out for theoretical modeling of responses. This is analogous to what's done when practicing multi-agency mock responses to humanitarian crises. Everything runs more effectively and potentially more efficiently when the collective communities of experts know one another and have learned one another's relative strengths and weaknesses.

Senators Bob Menendez and Susan Collins have called for a bipartisan, bicameral commission to evaluate our response to the COVID-19 pandemic and to make recommendations in preparation for the next one [10].

Two aphorisms aptly capture these efforts in their call for action:

“No one is safe until everyone is safe.” and

“An ounce of prevention is worth a pound of cure.”

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