nature immunology

Lessons learned

Additional work is needed to prepare for the next pandemic viral outbreak.

Largely thanks to lessons learned from previous recent pandemic scares, including the H5N1 'bird flu', governments around the world responded in an efficient manner to the initial outbreak of H1N1. In addition, the good news that one vaccine dose, rather than two doses, is sufficient to protect adults has alleviated some anxiety about H1N1 vaccine availability and has allowed the United States and seven other rich nations to pledge to donate portions of their vaccine supply to poorer countries unable to purchase doses sufficient to protect their vulnerable populations.

However, the fact remains that it will be impossible to produce and administer enough vaccine doses in time to vaccinate the susceptible population—even in some wealthy nations, including the United States—before the anticipated peak of the autumn H1N1 flu pandemic. In addition, not enough is known about several parameters crucial to determining if the available vaccine supplies can be stretched.

Although governments around the globe signed contracts to buy H1N1 vaccine from 20 different companies shortly after the start of the H1N1 outbreak this past summer, vaccine production has been delayed by several factors. Many companies, including all five contracted by the United States, are using the tried-and-true but slow method of growing live virus in chicken eggs. For as-yet-unknown reasons, the reference 'seed strain' of H1N1 has been growing at a pace even slower than anticipated. In addition, companies all over the world were forced to divide their production capacity among vaccines protecting against H1N1 and those designed to combat seasonal flu. Clearly, to circumvent such obstacles during future efforts to combat pandemic viruses, new methods of growing virus must be explored, and efforts to approve and 'scale up' these methods must be expedited.

In an encouraging development, the Belgian vaccine maker Solvay Biologicals just received approval from the Dutch government to produce seasonal and H1N1 influenza vaccines in its cell culture manufacturing facility in the Dutch city of Weesp. In addition, the virus-like particle-based influenza vaccine developed by Novavax has shown promising efficacy results in mid-stage trials. Governmental regulatory agencies should make an effort to expedite the assessment and approval of safe and effective cell culture–based influenza vaccines and to accelerate the construction of facilities needed to produce these vaccines in large quantities. For example, governments should give serious consideration to funding proposals like the University of Pittsburgh Medical Center's 21st Century Biodefense Center, a facility that would augment and speed up vaccine production and development and operate as a public-private partnership.

Even if vaccines are available in abundance, safely and effectively administering them to susceptible people located in developing regions scarce in refrigerators and hypodermic needles can present an enormous challenge. Fortunately, clever researchers are devising ways to circumvent the need for refrigerators and needles while simultaneously boosting the effectiveness of vaccines. For example, although it has been tested only on animals thus far, a steel patch 'decorated' with an array of needles can be coated with a thickened, dry form of a liquid vaccine. In addition to being resistant to high temperatures, this patch can, in theory, be self-administered. Another bonus is that the short length of the needles facilitates delivery of the vaccine to the skin, a site much richer in antigen-presenting cells than the muscle targeted by traditional needles. Public and private funding bodies should target and support this type of research.

More knowledge about strategies for stretching limited vaccine supplies would also increase preparedness for future viral pandemics. For example, adjuvants can boost the amplitude, quality and/or duration of immune responses to many vaccines. However, exactly how adjuvants work is not understood, and some adjuvant-containing vaccines have been associated with deadly, albeit rare, side effects. As a result, some countries, including the United States, have refrained from including adjuvants in influenza vaccines. More research into how adjuvants actually influence the human immune system might help unravel the mystery surrounding these substances, make governments more willing to use them to stretch the supply of vaccines during future viral pandemics and aid efforts to rationally design newer, better adjuvants. In an encouraging turn of events, the US National Institute for Allergy and Infectious Disease has begun soliciting applications for grants aimed at profiling human immune systems at rest and after vaccination and/or infection.

Knowing precisely which susceptible populations to vaccinate first can also help stretch the population-wide effectiveness, if not the actual quantity, of limited vaccine supplies. Fortunately, epidemiology and public health researchers are using new methods, including mathematical modeling, to determine if the existing strategy of first vaccinating the most susceptible people (usually the elderly, infants and pregnant women) is really the most effective way to stop the spread of a virus. For example, data published in *Science* indicate an alternative strategy of prioritizing children (who spread the virus among themselves in school) and their parents (who act as conduits, carrying the virus from their children to the rest of society) for vaccination more efficiently combats viral spread and death due to viral infection. Governments and health providers need to stay abreast of and promote (for example, with more funding and facilities) this research and should rigorously explore the possibility of incorporating these findings into recommended vaccination strategies.

Deficiencies revealed during the worldwide response to the H1N1 outbreak must be remembered by governments, regulatory agencies, health providers and researchers long after this flu season ends. Efforts to remove obstacles to readiness need to be made before the next viral outbreak occurs.