

Future pandemics might be caused by bacteria and not viruses: Recent advances in medical preventive practice

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Most nations have a national security policy for protection in case of a man-made external attack; some nations, for example, base their security policy on the concept of nuclear deterrence. Paradoxically, few modern nations have a national health security policy in case of an attack, not by a human enemy, but by a natural pathogen or a weaponized man-made bio-attack. Only highly developed countries have the resources and policies in place in case of sudden outbreaks of viral or bacterial mutation arising spontaneously outside man-made bioweapons, which could be highly lethal and infectious.

A unique consequence of the COVID-19 pandemic is that it has prompted the scientific community to contemplate the development of healthcare logistics and infrastructures that will tackle possible future pandemics, perhaps in a similar fashion to facing a war or an external attack. Biomedical scientists, armed with new biological techniques, have redirected their efforts to improve the production of new vaccines and drugs to combat the spread of such pathogens.

New pandemics might not be caused by viruses such as the coronavirus SARS-CoV-2, the causative agent of COVID-19, but by other dangerous pathogens, as for example methicillin-resistant *Staphylococcus aureus* or bacteria linked to water and food sanitation. Multi-drug resistance bacteria as well as newly mutated bacteria may infect humans and animals. The infections they may cause would be harder to treat than those caused by non-resistant bacteria. Inevitably, antibiotic resistance will lead to high mortality, expensive medical logistic, infrastructure, and hospitalization. The recent COVID-19 and previously the Ebola and Zika outbreaks have demonstrated how fast infectious diseases can spread, and underline the imperative need for having rapid response vaccine on demand technology in place. At present, we face several pandemic-like scenarios involving viruses such as the common cold; a complex infectious syndrome caused by any of over 200 viral pathogens in four groups, adenoviruses,

coronaviruses, enteroviruses and rhinoviruses. Influenza, which usually occurs in winter outbreaks or epidemics, can become a pandemic, being an ever-present threat to human health. Hepatitis C, hepatitis B, and HIV/AIDS are also a human threat but have been contained by effective medical treatments and targeted pharmacological agents.

Outbreaks of infectious diseases in the past, such as the earlier periodic occurrence of *Yersinia pestis* plagues or the H1N1 “Spanish flu” (1918-1919), can be used to inform present clinical practices and healthcare policies. In the United States, for example, three levels of potential severity, incorporated in influenza pandemic preparedness strategies, correspond to H1N1, H2N2 “Asian flu” (1957-1958), and H3N2 “Hong Kong flu” (1968-1969). These pandemics resulted in an estimated 675,000,^[1] 86,000,^[2] and 56,000,^[3] excess deaths in the United States, respectively. One main contemporary concern in the context of pandemic influenza planning is bacterial pneumonia. Bacterial infection in conjunction with influenza A virus is thought to have led to most of the deaths during the 1918-1919 pandemic.^[4] In current pandemic planning, effective antimicrobial drug measures and immunization are expected to substantially benefit public health. Thus, vaccination with polysaccharide and conjugate pneumococcal vaccines is considered part of a pandemic strategy.^[5]

Infectious pathogens spread rapidly; therefore, containment by public health measures cannot always bring pandemics under control. Instead, global vaccine programs resulting from biotechnological advances can be used to control the spread of the pathogens, induce herd immunity and reduce mortality rates. The best example, a landmark in the history of medicine has been the production of the SARS-CoV-2 specific vaccine, which was developed in less than a year.

In the case of serious infectious disease, the assumption is that the capacity of biotechnology to make novel and effective vaccines

could be used to trigger immunity in the population and hence herd immunity. However, this is not always possible, as in the case of HIV/AIDS, which is at present contained by prophylaxis and effective anti-retroviral drugs, and not by vaccination.

One of the most urgent public health problems is the continuous spread of antimicrobial resistance, in particular antibiotic resistance and the lack of newly developed antibiotics. This threatens to undermine the efficacy of bacterial treatment worldwide. Even the appropriate use of antimicrobials contributes to the development of resistance, and it is compounded by their unnecessary and excessive use.^[6] This is particularly the situation in many developing countries, where unregulated supply chains and the absence of a system for drug prescription^[6,7] facilitate gross misuse. Additionally, the use of antibiotics as growth promoters during food-animal production has contributed to increased prevalence of bacteria resistant to many anti-microbials.^[8]

Despite the advances in vaccinology, vaccines have not been developed against bacterial pathogens such as *Staphylococcus aureus*, *Chlamydia trachomatis*, *Helicobacter pylori* and *Mycobacterium tuberculosis*, to name a few. An example of a successful recent method for creating a vaccine against bacteria is the application of RNA technology, which was used to raise a vaccine against the plague bacterium *Y. pestis*, a gram-negative bacterium related to *Yersinia pseudotuberculosis* and *Yersinia enterocolitica*. This new technology could be applied to other bacterial pathogens, including novel pathogens resulting from the evolution of nonpathogenic bacterial taxa. Advances in nanoparticle-based vaccines offer a new avenue for rapid development of antibacterial vaccines^[9]. For example, several polymer and lipid-based nanocarriers enhance the immunogenicity of oral vaccines enhancing mucosal and systemic immune responses.

In order to prevent the impact of an outbreak mediated by a novel bacterium strain it is imperative to develop new antibiotics able to contain the spread of bacteria into the population and to regulate the use of currently utilised antibiotics. Fewer original class of antibiotic are reaching clinical settings. One reason for this is the high development costs to discover and bring new antibiotics to market with uncertainty in the ability of pharmaceutical companies to recoup those costs. Progress toward the development of new antimicrobials has therefore been slow, with only a limited number available for general use to treat bacterial infections.^[10,11] This is an acknowledged challenge with a number of public and private collaborations working towards finding new solutions to this problem. Encouragingly, the use of antimicrobial growth promoters is presently banned or restricted in many countries during food-animal production.

Recent interest in strategies to combat antibiotic resistance have tended to focus on the use of the CRISPR/Cas system to develop novel antimicrobials and on the activity of outer

membrane-penetrating endolysins (Artilyns). CRISPR/Cas technology entails the application of short CRISPR RNAs (crRNAs) that guide CRISPR-associated (Cas) nucleases to destroy targeted nucleic acids. crRNAs are transcribed from the CRISPR array within which captured pieces of phage DNA are integrated as new spacers. The Cas9 protein is able to cut the chromosome of bacteria and kill them in a sequence-specific manner.^[12,13] To deliver CRISPR/Cas antimicrobials an efficient delivery system is required, with bacteriophage packaging systems as a possible approach.^[14-16] Currently, engineered endolysin-based Artilyns are being developed to combat multidrug resistant Gram-negative pathogens. Artilyns destabilize the cell wall of the bacteria and lyse the cells. This technology can act against both Gram-positive and Gram-negative bacteria.

Linked to the development of novel vaccines, immunotherapy has emerged as a separate branch of medicine in the form of immuno-oncology protocols for the treatment of cancer. This approach mostly, but not entirely, bypasses the use of pharmacological agents and relies exclusively on immunological techniques and the capability of the host immune system to fight diseases. In the time scale of the development of modern medicine, immunotherapy for the treatment of human diseases is a relatively new approach. Today it offers a possible last resort avenue for the treatment of a number of cancer malignancies. There are several distinct protocols and techniques being applied in immunotherapy. These include monoclonal antibodies, the use of immune checkpoint inhibitors, adoptive T-cell transfer, cancer vaccines such as dendritic cell preparations, and the use of modulators of the immune system such as soluble factors, including cytokines. In turn, as the immunotherapeutic techniques evolve it should be possible to use these techniques to boost the immune system to combat microbial infections. The combined use of the above technologies in fighting bacterial infections is still in its infancy, and will most likely find applications in the near future. They could potentially be used in the prevention of an outbreak caused by a lethal pathogenic bacteria and hence, control the advent of future pandemics.

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Conflicts of interest

The author declares no competing financial interests.

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