An introduction to vaccines and immunotherapies

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Abstract
Vaccines and immunotherapies are among the largest categories for pharmaceutical products, meaning that many medical writers will work in this field. For people new to this area, we describe the basics of how vaccines and immunotherapies work.

Vaccines
Vaccines are among the greatest triumphs in public health of recent times and save 2 million to 3 million lives each year.[1] Smallpox, a once deadly disease, was confirmed to be eradicated in 1980 following a worldwide vaccination campaign.[2] Vaccines have also substantially reduced the incidence of several other major diseases in the past few decades, such as polio and measles. Today, licensed vaccines are available for preventing more than 30 different infectious diseases, several of which can be combined or administered at the same vaccination visit.[1]

Because vaccines are given as preventive measures to large populations of healthy individuals, especially infants and children, a highly favourable benefit-risk profile is essential. When adverse events do occur, these are usually mild and transient and are typically centred at the injection site (e.g., injection site pain, redness, swelling). Mild and transient systemic reactions can also occur with some vaccines, such as headache and fever.

Although they are usually considered for individual protection, vaccines can also protect unvaccinated people by reducing person-to-person transmission (Figure 1). This indirect protection, termed "community" or "herd" immunity, usually requires high vaccination coverage (75% to 95% of a target population) but can be essential for successful vaccination campaigns, such as for measles.[3] Similarly, vaccination of pregnant women can also protect infants in their first months of life due to cross-placental transfer of maternal antibodies. Maternal vaccination is currently used to protect mothers and infants against tetanus, influenza, and pertussis.[4]

Immunotherapies
While new vaccines are being continually developed, researchers, clinicians, and pharmaceutical companies have become increasingly interested in immunotherapies. Immunotherapy

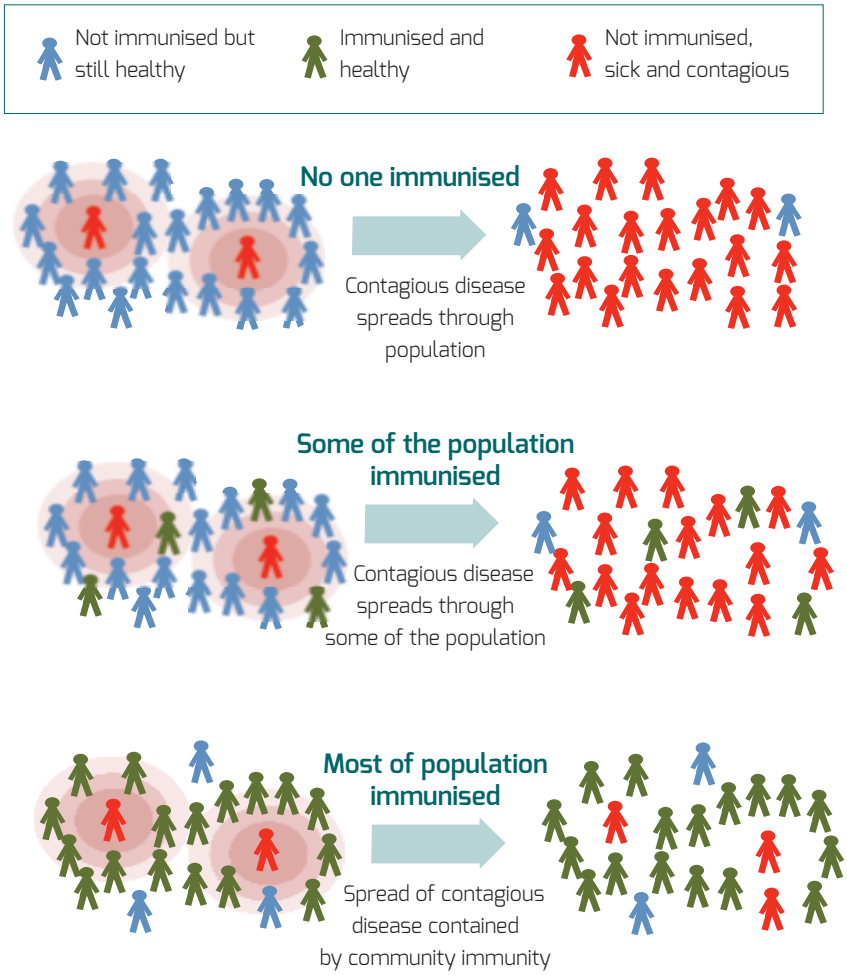

Figure 1. Herd immunity
When a critical portion of a community is immunised against a contagious disease, most of the community are protected against that disease. This is known as "community" or "herd" immunity. The top panel depicts a population in which no one is immunised and an outbreak occurs. In the middle panel, some of the population is immunised but not enough to confer community immunity. In the bottom panel, a critical portion of the population is immunised, which contains the spread of the disease and protects those not immunised. Adapted from Tkarcher – Own work, CC BY-SA4.0, https://commons.wikimedia.org/w/index.php?curid=56760604.

may be defined as the treatment of disease by modulating the immune response. By this definition, it could be argued that some vaccines are a form of immunotherapy, for example therapeutic vaccines.[5]

Many of the drugs approved in recent decades have been immunotherapies, and considerably more are advancing through pharma and biotech drug pipelines. Most immunotherapies are biological agents, for example cytokines, inhibitory or activating monoclonal antibodies, engineered lymphocytes, and allergens. Most notably, immunotherapies have shown unprecedented efficacy against several cancers, including melanoma and lymphoma, and are in clinical trials for many others.[5]

However, the same mechanisms of action that give immunotherapies their efficacy can also cause adverse events. Stimulating immune responses, as in the case of cancer immunotherapy, can result in various immune-related adverse events such as gastrointestinal, hepatic, and skin inflammation, which can range from mild to lethal.[6] Suppressive immunotherapies can also cause adverse events, such as increased susceptibility to infections.[7]

How do vaccines and immunotherapies work?

To understand how vaccines and immunotherapies work, one must first know the basics of how the immune system protects against infection and cancer. The vertebrate immune system can be divided into two categories of defence: innate immunity and adaptive immunity (Figure 2).[8] However, these distinctions are not mutually exclusive.

Innate immunity represents the first line of host defence against pathogenic micro-organisms. Innate immune cells (e.g., macrophages, neutrophils) recognise a limited set of danger signals and microbial molecular determinants shared by different pathogens. On recognising these threats, innate immune cells act within minutes by engulfing pathogens and inducing inflammation and further immune cell recruitment. Another important role of certain innate immune cells is antigen presentation and activation of adaptive immunity.

Adaptive immune cells, notably T and B lymphocytes, provide the second line of defence, generally at a later stage of infection. Unlike innate immunity, adaptive immunity is antigen-specific (i.e., recognises a particular type of pathogen via a specific antigen) and capable of providing the immune "memory" that protects against re-infection with the same pathogen. Every encountered pathogen expresses or contains antigens, each one of which can activate a specific lymphocyte. When a T lymphocyte is activated by an antigen-presenting cell, it proliferates to form clone T cells that go on to recognise and eliminate infected (or malignant) host cells containing the specific antigen. Activated B lymphocytes similarly proliferate to give clones of B cells that differentiate into antibody-producing cells. The antibodies they produce recognise and neutralise pathogens or toxic products expressing the particular antigen. After eliminating the pathogen, the adaptive immune response regresses, but leaves memory lymphocytes that can quickly proliferate to attack or produce antibodies against the same pathogen, even decades later, if it is encountered again.

Vaccines act by initiating innate and adaptive immunity to produce long-term immunological memory against disease-causing pathogens. However, unlike a natural infection, vaccines do not cause the disease because they only contain

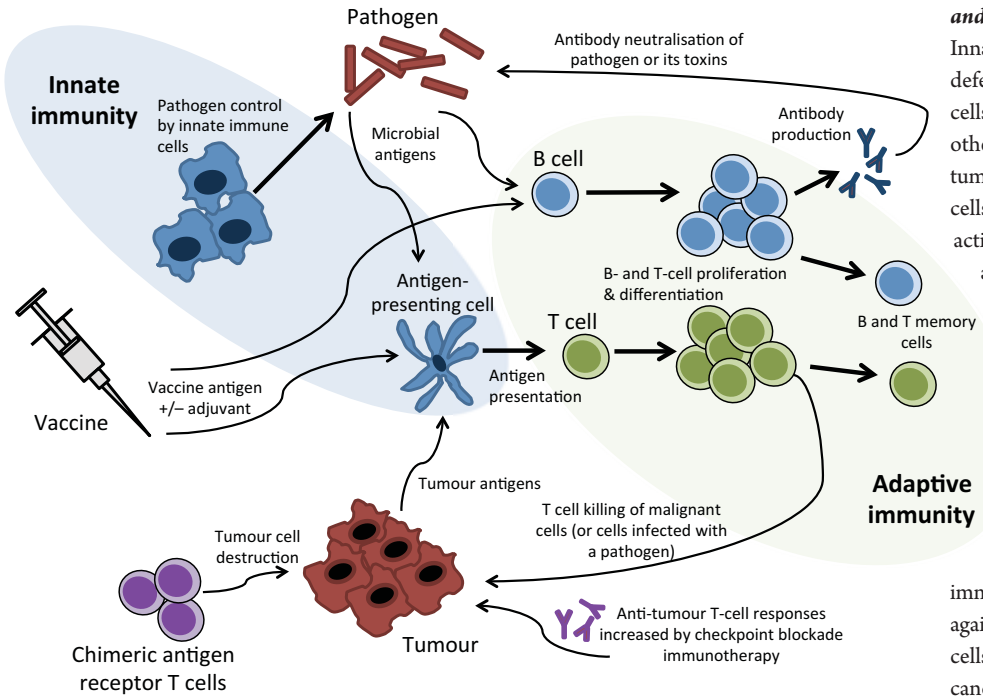

Figure 2. The innate and adaptive immune system and points of interaction with vaccines and immunotherapies

Innate immune cells form the first line of defence against many pathogens. Some innate cells can directly kill certain pathogens, while others take up antigens from pathogens, tumours, and vaccines and present these to T cells to activate adaptive immunity. Antigen-activated T cells proliferate and differentiate, and the resulting T cell clones go on to recognise and eliminate infected host cells or tumour cells expressing the specific antigen. Activated B cells similarly proliferate and differentiate to give clones of antibody-producing cells. Some T and B cells differentiate into memory cells that can quickly attack or produce antibodies if the same pathogen if it is encountered again. Some immunotherapies help adaptive immunity against tumours: chimeric antigen receptor T cells are engineered to recognise and eradicate cancer cells expressing certain tumour antigens; checkpoint blockade immunotherapies consist of antibodies that block molecular regulators of T cell activation, resulting in enhanced anti-tumour immune responses.

inactivated or attenuated micro-organisms, or selected antigenic fragments from pathogens ("subunit vaccines") (Table 1).[9] Vaccine development has made significant progress from the early days of empirical design to today's rational vaccine designs based on the biology of the targeted infection and the disease to be prevented.

Vaccine "adjuvants" – substances that enhance and modulate the immunogenicity of the vaccine's antigens – can be just as important in vaccine design as the vaccine antigen itself. Adjuvants are used to activate innate immunity, improve memory responses, and broaden or extend innate and adaptive immune responses. This can help to reduce the amount of antigen per dose or the number of doses needed for a given vaccine. Subunit vaccines usually require adjuvants because they contain fewer antigens and may lack some molecular components of whole pathogens that trigger innate immune cells.

Immunotherapies, on the other hand, may be designed to amplify an immune response or to reduce it. This can be achieved by targeting various stages in innate and adaptive immunity, for example by neutralising specific inflammatory or immunosuppressive cytokines, or by inhibiting regulatory molecules involved in antigen presentation to T lymphocytes. Cancer immuno-therapy, one of the most active areas of R&D today, usually involves reactivating immune responses against cancer cell antigens, which have been switched off by the immuno-suppressive environment within tumours. In contrast, immunotherapies for autoimmune diseases are usually designed to suppress immune-mediated destruction of host tissues.

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Conclusion

Our improved understanding of the immune system and its interactions with pathogens, allergens, and cancer cells has heralded new vaccine and immunotherapeutic designs along with unprecedented clinical successes. Vaccines and cancer immunotherapies were among the largest categories for pharmaceutical R&D products in 2017.[10] Accordingly, understanding the basic concepts of these agents, and their benefits and risks, is crucial for medical writers who might be involved in such projects.

Conflicts of interest

The authors declare no conflicts of interest related to this article.

Table 1. Examples of different vaccines and immunotherapies

Type	Subtype	Explanation	Examples
Vaccines	Inactivated	Infectious agent (e.g. virus) "killed" by chemicals or heat	Whole-cell pertussis, rabies, and injected polio vaccines
	Live attenuated	Weakened version of the infectious agent (e.g. virus)	Mumps-measles-rubella (MMR), oral polio, and bacille Calmette-Guérin(BCG) vaccines
	Subunit	Only antigenic region of the infectious agent	Tetanus toxoid, influenza, and pneumococcal vaccines
Immunotherapies	Monoclonal antibodies	These neutralise or block certain proteins or may deliver radioisotope or chemicals to mediate targeted cell killing	Anti-tumour necrosis factor (TNF) antibody for treating rheumatoid arthritis, immune checkpoint inhibitors for boosting T-cell responses against tumours
	Cell-based	Injection of modified activated immune cells that fight threats (e.g. malignant cells)	Chimeric antigen receptor (CAR) T cells that eliminate leukemic cells
	Suppression	Suppress the immune system or induce tolerance	Allergen desensitisation, immunosuppressive drugs
	Cytokines	Immune signalling molecules that modulate immune responses	Interleukin-2, interferon-α

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