

In this article...

- How the body produces antibodies and how they protect it from infection
- The history of the use of vaccination, including advances in different types
- The anti-vaccination movement and risks associated with reduced vaccine uptake

The lymphatic system 5: vaccinations and immunological memory



COVID-19

Key points

Foreign materials that elicit a specific immune response and stimulate the production of antibodies when they enter the body are called antigens

Most antibodies are created to recognise and bind to one specific antigen

All vaccines work by priming the immune system against a potential infectious pathogen

Early vaccines used inoculation of a similar but harmless pathogen to develop immunity to deadly pathogens

Modern vaccines use various methods to stimulate immune response, including inactivated or modified pathogens or fragments of the target pathogen

Authors John Knight is associate professor in biomedical science; Yamni Nigam is professor in biomedical science; both at the College of Human and Health Sciences, Swansea University.

Abstract This article, the fifth in a six-part series on the lymphatic system, examines the role of antibodies in developing immunity to infectious viruses and bacteria. It also summarises the history of vaccine development and explains how different vaccines stimulate an immune response.

Citation Knight J, Nigam Y (2021) The lymphatic system 5: vaccinations and immunological memory. *Nursing Times* [online]; 117: 2, 38-42.

Vaccination is very much in the news as the first vaccines to combat SARS-Cov-2, the coronavirus responsible for Covid-19, gain regulatory approval. This article, the fifth in a six-part series on the lymphatic system, examines in greater detail the nature of antibody-mediated immunity discussed in part 3 and explores how vaccines can be used to prime the immune system against infectious diseases.

Antibody-mediated immunity and role of B-lymphocytes

As highlighted in part 3, which discussed the role of the lymphatic system in developing immunity, antibodies are produced by B-lymphocytes when the body is exposed to foreign material. Any foreign material that can elicit a specific immune response and stimulate the production of antibodies is referred to as an antigen (Aryal, 2018). This article focuses on those associated with pathogens that cause infectious diseases. When antibodies are generated during infection their major role is to bind to the infectious agent, 'marking' it for destruction by the immune system; this process is termed opsonisation (see part 3).

The structure of antibodies

Antibodies (also known as immunoglobulins) are soluble globular proteins. The most abundant antibody circulating in the blood is immunoglobulin G (IgG), which accounts for around 10-20% of the total plasma protein content (Vidarsson et al, 2014).

Antibodies have a characteristic molecular configuration, often described as resembling the letter Y. Each molecule consists of four polypeptide (protein) chains, linked by disulphide bonds (Fig 1). Each antibody molecule consists of two heavy chains and two light chains in a Y shape (Fig 1a); the stem region is constant but the terminal ends of the arms are highly variable. These variable portions are the antigen-binding sites and resemble three-dimensional clefts or pockets into which the corresponding antigen will fit.

Antibody molecules are highly specific: each is usually only able to bind to a single antigen (Fig 1b). Just as a key will only fit one particular lock, an antigen will only fit into its complementary antibody by slotting into one of its antigen-binding sites – this is essential to the way antibodies recognise and bind to foreign material.

When antibodies are generated against a pathogen, most bind to that pathogen

Clinical Practice Systems of life

alone, although some can bind to molecules with similar configurations as their original target antigen (Jain and Salunke, 2019). Such cross-reactivity is known to be associated with many autoimmune diseases, such as rheumatic fever.

Clonal selection

The process of clonal selection (Fig 2) is at the heart of antibody-mediated immunity. B-cells (B-lymphocytes), which generate antibodies, circulate in the blood and are also present in lymphoid organs, such as the spleen, bone marrow and lymph nodes. A typical human body has billions of B-cells, with many displaying antibody molecules with unique antigen-binding sites.

The red circle in Fig 2 represents a particle of foreign material such as a bacterium or virus. When pathogens enter the body they typically circulate in the blood and lymph and through the lymphoid organs, and randomly come into contact with B-cells. The antigens on the surface of the pathogen will fit into the antigen-binding site of a complementary antibody molecule just like a key slotting into a lock (Fig 2). Once this occurs, clonal selection is deemed to have taken place; the B-cell will divide repeatedly, producing a large population of clones of the original B-cell (Silverstein, 2002). The majority of newly generated B-cell clones mature and enlarge into antibody-producing plasma cells, which release antibodies (IgG) into the blood (Fig 2). These will circulate throughout the body and bind to and opsonise the pathogen when they encounter it, marking it for destruction.

B-cells and immunological memory

Not all B-cells generated by clonal selection mature into antibody-producing plasma cells. A significant proportion remain in the body for many years as memory cells (Ratajczak et al, 2018). These display the same antibody as the original B-cell clone and effectively hold a long-term 'memory' of the encounter (Fig 2). If the pathogen is encountered again, these memory cells ensure clonal selection can occur quickly, allowing rapid killing of the pathogen before it can cause disease.

B-memory cells and the logic of vaccination

There are many different forms of vaccination, but all work on the same basic principle of priming the immune system against a potential infectious pathogen. This involves introducing a harmless form of the pathogen (or a component derived

Fig 1. Structure of an antibody

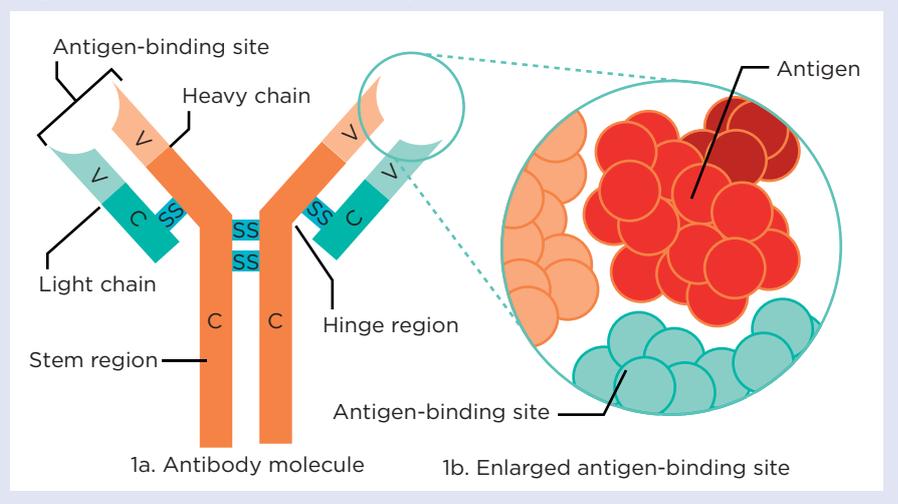
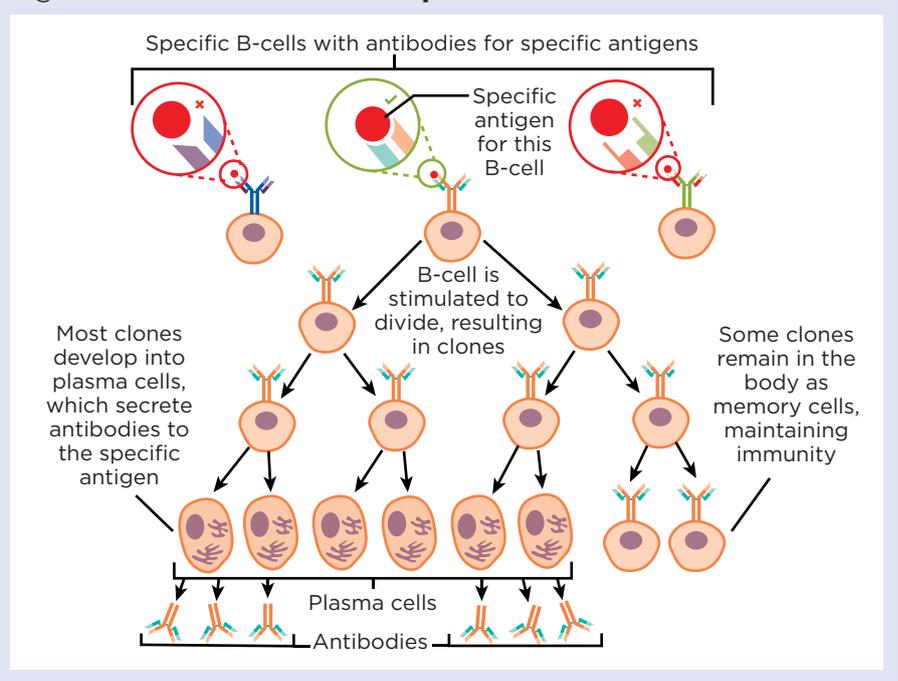


Fig 2. Clonal selection and amplification in B-cells



from it) to initiate clonal selection, antibody production and production of a pool of circulating memory cells.

Early history of vaccination

English physician Edward Jenner's use of a cowpox inoculation to provide immunity against the deadly smallpox virus is recognised as a key foundation in the newly emerging field of immunology and led to the development of the first effective and widely used vaccine. Jenner noted that milkmaids frequently contracted the relatively mild viral infection cowpox, which appeared to protect them against smallpox. He began using cowpox

inoculation in 1796 but it was not until 1840 that widespread vaccination against smallpox using the cowpox vaccine became available (Riedel, 2005). International use of smallpox vaccines led to its global eradication in 1980 and it remains the only infectious disease to be completely eradicated through the use of vaccination. Following Jenner's success, research into vaccines boomed and has continued since with key vaccines developed against some of the most virulent and deadly human pathogens, including those causing typhoid (1896), diphtheria (1942), polio (1956), measles (1968) and rubella (1970).

Clinical Practice

Systems of life

Types of vaccines

Heterologous vaccines

These are the earliest vaccines successfully used to confer immunity. They use micro-organisms that display limited pathogenicity in humans to stimulate the production of antibody and memory cells against highly pathogenic bacteria and viruses; because this is how Jenner's original smallpox vaccine using cowpox functioned, these types of vaccines are often referred to as Jennerian vaccines (Esparza et al, 2018). With more advanced vaccine techniques now available, there are few pure heterologous vaccines that are in general use today, although the Bacillus Calmette-Guérin (BCG) vaccine, which provides protection against tuberculosis (TB), is an example of an attenuated heterologous vaccine.

Attenuated live vaccines

These vaccines use live micro-organisms that have been rendered less pathogenic (attenuated) either by culturing and selecting for less virulent strains or by manipulating the biological properties of the pathogen. Once administered, the constituent micro-organisms replicate freely within the body, generating a natural immune response but without causing the disease. A major advantage of these vaccines is that they elicit a powerful immune response that closely mirrors that seen in people exposed to the disease-causing pathogen. They tend to generate high antibody titres (concentrations) and a large pool of circulating memory cells, meaning booster shots are not usually required.

Attenuated live vaccines are not usually offered to people with a weakened immune system because, in the absence of a normal immune response, the component pathogens can replicate quickly, potentially leading to serious systemic infection. People who are likely to be immunosuppressed include those with congenital immune deficiencies, those undergoing chemotherapy or radiotherapy, transplant recipients and patients using corticosteroids to manage chronic inflammatory or autoimmune disease (Arvas, 2014).

One of the first attenuated vaccines developed was the BCG vaccine, which is used to vaccinate against *Mycobacterium tuberculosis*, the bacterium causing TB. BCG uses the closely related pathogen *M bovis*, which causes TB in cattle and is a zoonotic bacterium (capable of crossing species barriers and infecting a variety of animals). It can also infect humans, causing zoonotic TB, which has symptoms

often indistinguishable from those caused by *M tuberculosis* (World Health Organization, 2017).

In 1908 French microbiologists Albert Calmette and Camille Guérin began culturing *M bovis* isolated from an infected cow. After 11 years and over 230 subcultures, they isolated a strain that failed to cause TB in a variety of experimental animals. This attenuated strain was named Bacillus Calmette-Guérin (BCG) and was first used to vaccinate humans against TB in 1921. Initially the vaccine was given orally, before intradermal administration into the skin became commonplace (Luca and Mihaescu, 2013).

“Just as a key will only fit one particular lock, an antigen will only fit into its complementary antibody”

Early vaccinations proved successful in conferring immunity against TB, and many countries adopted BCG vaccination. However, in 1930 a batch of BCG vaccine contaminated with virulent bacteria caused the deaths of 73 infants in the German city of Lübeck. The so-called ‘Lübeck disaster’ was caused by negligent production of the vaccine. It undermined confidence in the vaccine worldwide (Fox et al, 2016) and is generally recognised as the first major incident to cast global doubt on the safety of vaccines. It was not until the 1940s and 1950s, when TB infections increased significantly, that the BCG vaccine was used again in vaccination programmes and proven to be safe.

Recent evaluations suggest that BCG is 70-80% effective in protecting against severe forms of TB, although it is less effective in adults than in children. Its widespread use has dramatically reduced the incidence of TB in many countries, although infections have started to rise again in many regions, along with antibiotic-resistant strains of *M tuberculosis*. Due to its relatively low incidence in the UK, the BCG vaccine is only given on the NHS to children and adults at increased risk of TB (NHS, 2019a).

BCG remains one of the world's most widely used vaccines and is also used as an immunotherapy to upregulate the immune system in the treatment of bladder cancer (see part 6). Modified forms are also used to enhance immune responses in the treatment of a variety of bacterial, viral and parasitic diseases (Zheng et al, 2015) and it is currently being

evaluated for use in treating Covid-19 (Curtis and Sparrow, 2020).

Other attenuated vaccines used in the UK vaccination schedule include MMR (measles, mumps and rubella), nasal flu, shingles, chickenpox and rotavirus vaccines (Vaccine Knowledge Project, 2019).

Inactivated whole-pathogen vaccines

These vaccines incorporate whole pathogens that have been killed, usually by heating or by exposing them to noxious chemicals or ionising radiation, rendering them unable to infect, replicate and cause disease. The current polio vaccine is an inactivated whole-pathogen vaccine; and is initially given as a component of the 6-in-1 vaccine, which also affords protection against diphtheria, hepatitis B, Haemophilus influenzae type b (Hib), tetanus and pertussis (whooping cough). The 6-in-1 vaccine is given as three doses at eight, 12 and 16 weeks of age (NHS, 2019b). Subsequent boosters are required at the age of:

- Three years and four months, as part of the 4-in-1 (diphtheria, tetanus, whooping cough and polio) preschool booster (NHS, 2019c);
- 14 years, as part of the 3-in-1 (diphtheria, tetanus and polio) teenage booster (NHS, 2019d).

Because inactivated whole-pathogen vaccines cannot replicate, they tend to elicit much weaker and shorter-lived immune responses than live attenuated vaccines. Repeated doses are required to generate an adequate immune response, followed by booster vaccinations to maintain immunity.

To help enhance the immune response to inactivated vaccines, the killed pathogen is usually suspended in a fluid containing irritants such as aluminium salts, which act as an adjuvant. When injected, adjuvants initiate an inflammatory response, increasing blood flow to the site to strengthen and amplify the immune response.

The inflammation initiated by adjuvants can result in tenderness and pain at the injection site, which usually resolves after a few days (Vaccine Knowledge Project, 2019). Because inactivated whole-pathogen vaccines contain no viable pathogen, they can usually be given safely to immunocompromised patients (Arvas, 2014). Other examples of inactivated whole-pathogen vaccines include the annual winter influenza vaccine and the rabies vaccine (Vaccine Knowledge Project, 2019).

Clinical Practice Systems of life

Subunit vaccines

Unlike inactivated whole-pathogen vaccines, subunit vaccines contain no intact bacterial or viral particles but use fragments of material derived from the target micro-organism. The pathogen-derived subunits chosen are typically components of bacterial cell walls and viral envelopes, as these are the natural antigens that would trigger clonal selection and antibody production during infection.

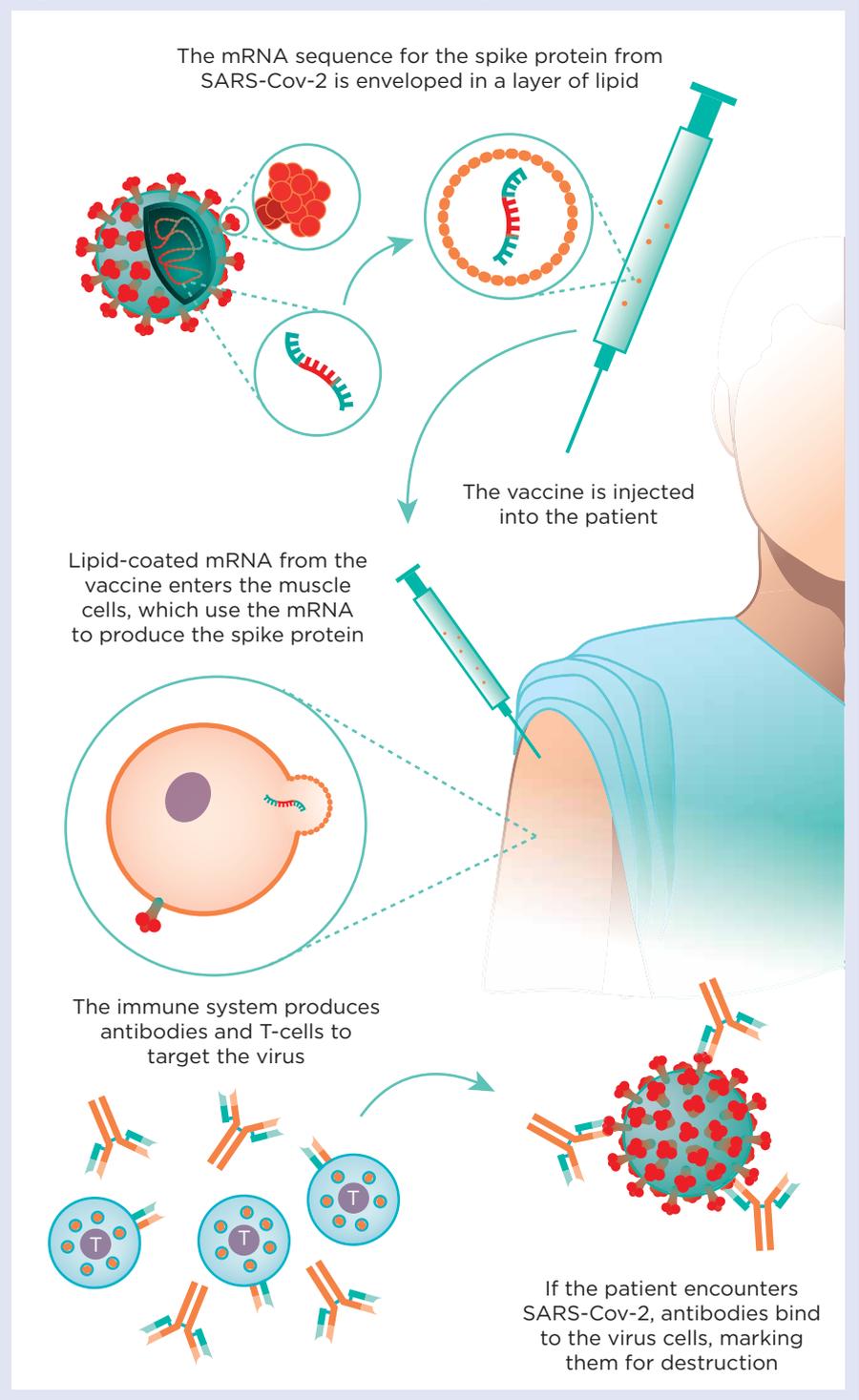
Today most subunit vaccines are made using recombinant DNA techniques. A good example is the vaccine for the hepatitis B virus (HBV); here the gene for an antigen on the HBV surface is inserted into brewer's yeast. This genetically modified yeast can be cultured and will synthesise the HBV surface antigen, which can be harvested and purified for use in the HBV vaccine (Das et al, 2019). Subunit vaccines are particularly useful for highly pathogenic micro-organisms, as the lack of any intact viable pathogen ensures infection is impossible, even in severely immunocompromised patients.

Many of the vaccines currently being developed against SARS-Cov-2 are subunit vaccines using the surface spike protein that allows the virus to enter its target cells. The vaccine developed at the University of Oxford designated ChAdOx1 nCoV-19, which is currently being rolled out, takes the gene for the SARS-Cov-2 spike protein and inserts it into a non-pathogenic chimpanzee adenovirus. Following vaccination, the genetically modified adenovirus will infect target cells, which then synthesise large quantities of the SARS-Cov-2 spike protein, triggering antibody production. If the vaccinated patient comes into contact with SARS-Cov-2, their immune system will be able to target the virus and prevent infection (Mahase, 2020a).

Toxoid vaccines

The symptoms associated with many bacterial infections are caused by toxins produced by the pathogen. For example, *Corynebacterium diphtheria* (responsible for diphtheria) generates a powerful toxin that inhibits protein synthesis in the body, damaging the respiratory tract, nerves and heart (Murtaza et al, 2016). The diphtheria vaccine uses a modified version of this toxin, which has been inactivated with a chemical (usually formalin). The modified toxin is referred to as a toxoid (toxin-like molecule); because it is structurally almost identical to the original diphtheria toxin, it elicits antibody

Fig 3. How an RNA vaccine works against SARS-Cov-2



production when used in a vaccine. If a vaccine recipient becomes infected with diphtheria, these antibodies bind to and neutralise the diphtheria toxin – reducing or eliminating symptoms. Although the pathogen itself is not being targeted, eventually the person's immune system can target and eliminate the *C diphtheria bacterium* itself.

Conjugated vaccines

Some antigens on the surface of pathogens do not naturally elicit a strong immune response when used in vaccines. Conjugated vaccines can improve immune responses to these relatively weak antigens by linking (conjugating) them to other molecules, such as bacterial toxoids, which generate more robust immune

Clinical Practice Systems of life

reactions. The Hib vaccine is a good example of a conjugated vaccine. Hib is unrelated to viral influenza; it is a bacterial infection that typically infects babies and young children, causing potentially life-threatening septicaemia and bacterial meningitis. The Hib vaccine takes portions of the bacterial cell wall and conjugates them to toxoids (commonly tetanus or diphtheria toxoids) to render them more powerful elicitors of antibody production (Heath and McVernon, 2002).



1796 Year Edward Jenner began using cowpox inoculation to provide immunity to smallpox

DNA and RNA vaccines

With recent advances in molecular biology allowing the rapid sequencing and manipulation of DNA, attention has turned to using this technology to design and produce a new generation of vaccines. DNA and RNA vaccines use the body's own cells to make antigenic components of bacteria and viruses to trigger an immune response. For example, a DNA vaccine can be created by inserting the sequence of a viral protein into a small, ring-shaped piece of DNA called a plasmid, which is then injected into a muscle. The muscle cells take up the plasmid and use the information encoded in its sequences to make the viral protein; this stimulates the production of antibodies via normal clonal selection.

Although DNA vaccines are already licensed for veterinary use, none are yet licensed for use in humans. However, clinical trials are exploring their use against a variety of human pathogens, including the Ebola, Marburg and Zika viruses. Early results have been encouraging, with boostable antibody production reported (Liu, 2019).

The current coronavirus pandemic has advanced novel vaccine development: one of the first SARS-Cov-2 vaccines to undergo clinical trials was an RNA-based vaccine developed in the US. This uses messenger RNA (mRNA) sequences that code for the SARS-Cov-2 spike protein (Fig 3); these are enveloped in a lipid coating and injected into the deltoid muscle. The mRNA will then initiate production of the spike protein in human cells, stimulating production of antibodies against the virus. Initial findings reported in July 2020 indicated the vaccine is effective in producing specific immune responses against SARS-Cov-2 without

any trial-limiting safety concerns (Jackson et al, 2020). The vaccine, now known as the Moderna vaccine, was approved for use in the US in December 2020; earlier that month a similar RNA vaccine, developed by Pfizer and BioNTech, became the first SARS-Cov-2 vaccine to receive regulatory approval in the UK (Mahase, 2020b).

Risks associated with reduced vaccine uptake

The anti-vaccination movement is as old as modern vaccination itself. When the effectiveness of Jenner's smallpox vaccine became apparent, the Vaccination Act in 1840 made it mandatory for parents in the UK to vaccinate their children. This led to significant public opposition and the formation of the Anti-Vaccination League, which successfully campaigned for removal of penalties and for parents' right to conscientiously object to vaccination (Hussain et al, 2018). Although the contaminated BCG vaccine that led to the Lübeck disaster shook public confidence in early TB vaccination programmes, the effectiveness of successive new vaccines against a variety of deadly diseases ensured that vaccine uptake was maintained at a high level.

The modern anti-vaccination movement was given great impetus by a paper published in *The Lancet* that linked the MMR vaccine with the development of autism in young children (Wakefield et al, 1998). Despite being widely criticised in the scientific community, and later retracted by *The Lancet*, there was widespread loss of public confidence in the vaccine. In the UK, uptake of the MMR vaccine dropped from 92% in 1996 to 84% in 2002 – and in parts of London to as low as 61% – which is far below the threshold required for herd immunity against measles. Unsurprisingly, cases increased significantly and in 2008 measles was declared endemic in the UK for the first time in 14 years (Hussain et al, 2018).

MMR vaccination has recovered in recent years and, currently, scheduled childhood vaccine uptake in the UK remains high. However, there is a major concern that increased use of the internet and social media to promote anti-vaccination messages will further undermine confidence in the safety of vaccines and reduce uptake (Gilroy, 2019).**NT**

References

Arvas A (2014) Vaccination in patients with immunosuppression. *Turkish Archives of Pediatrics*; 49: 3, 181-185.

Aryal S (2018) *Antigen Properties, Types and Determinants of Antigenicity*. Microbiologyinfo.com

Curtis N, Sparrow A (2020) Considering BCG vaccination to reduce the impact of COVID-19. *The Lancet*; 395: 1545-1546.

Das S et al (2019) Hepatitis B vaccine and immunoglobulin: key concepts. *Journal of Clinical and Translational Hepatology*; 7: 2, 165-171.

Esparza J et al (2018) Beyond the myths: novel findings for old paradigms in the history of the smallpox vaccine. *PLoS Pathogens*; 14: 7, e1007082.

Fox GJ et al (2016) Tuberculosis in newborns: the lessons of the "Lübeck Disaster" (1929-1933). *PLoS Pathog*; 12: 1, e1005271.

Gilroy R (2019) The anti-vaccination movement: a concern for public health. *Practice Nursing*; 30: 5, 248-249.

Heath P, McVernon J (2002) The UK Hib vaccine experience. *Archives of Disease in Childhood*; 86: 396-399.

Hussain A et al (2018) The anti-vaccination movement: a regression in modern medicine. *Cureus*; 10: 7, e2919.

Jackson LA et al (2020) A SARS-CoV-2 mRNA vaccine – preliminary report. *New England Journal of Medicine*; 383: 20, 1920-1931.

Jain D, Salunke DM (2019) Antibody specificity and promiscuity. *Biochemical Journal*; 476: 3, 433-447.

Liu MA (2019) A comparison of plasmid DNA and mRNA as vaccine technologies. *Vaccines*; 7: 2, 37.

Luca S, Mihaescu T (2013) History of BCG vaccine. *Maedica*; 8: 1, 53-58.

Mahase E (2020a) Covid-19: Oxford team begins vaccine trials in Brazil and South Africa to determine efficacy. *British Medical Journal*; 369: m2612.

Mahase E (2020b) Covid-19: UK approves Pfizer and BioNTech vaccine with rollout due to start next week. *British Medical Journal*; 371: m4714.

Murtaza M et al (2016) Diphtheria: clinical manifestations, diagnosis, and role of immunization in prevention. *JOSR Journal of Dental and Medical Sciences*; 15: 10, 9790/0853-1508037176.

NHS (2019a) *BCG Tuberculosis (TB) Vaccine Overview*. NHS.

NHS (2019b) *6-in-1 Vaccine Overview*. NHS.

NHS (2019c) *4-in-1 Pre-school Booster Overview*. NHS.

NHS (2019d) *3-in-1 Teenage Booster Overview*. NHS.

Ratajczak W et al (2018) Immunological memory cells. *Central-European Journal of Immunology*; 43: 2, 194-203.

Riedel S (2005) Edward Jenner and the history of smallpox and vaccination. *Proceedings (Baylor University Medical Center)*; 18: 1, 21-25.

Silverstein A (2002) The Clonal Selection Theory: what it really is and why modern challenges are misplaced. *Nature Immunology*; 3: 793-796.

Vaccine Knowledge Project (2019) *The UK Immunisation Schedule*. Oxford Vaccine Group.

Vidarsson G et al (2014) IgG subclasses and allotypes: from structure to effector functions. *Frontiers in Immunology*; 5: 520.

Wakefield AJ et al (1998) Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *The Lancet*; 1998: 351, 637-641.

World Health Organization (2017) *Zoonotic Tuberculosis Factsheet*. WHO.

Zheng YQ et al (2015) Applications of bacillus Calmette-Guerin and recombinant bacillus Calmette-Guerin in vaccine development and tumor immunotherapy. *Expert Review of Vaccines*; 14: 9, 1255-1275.