From Bench to Bedside: Monoclonal Antibodies as Next-Generation Antimicrobials

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Abstract:

Monoclonal antibodies (mAbs) represent the future of infectious disease management amid rising antimicrobial resistance and emerging pathogens. Evolving from early serum therapies, mAbs now offer targeted and highly specific immune responses through multiple mechanisms, including neutralisation, complement, and cellular cytotoxicity. Several mAbs are approved for infections, including Coronavirus Disease 2019 (COVID-19), respiratory syncytial virus (RSV), Ebola, human immunodeficiency virus (HIV), and anthrax, with many more in various phases of development. This review explores the structure, types, and clinical applications of mAbs, including newer formats like bispecific antibodies, mimetics, and antibody-drug conjugates. mAbs also show promise in travel medicine and vaccine development. Their rapid deployment during the COVID-19 pandemic underscores their potential in responding to future public health emergencies.

Key words: Monoclonal Antibodies, Antimicrobial Resistance, Passive Immunotherapy, Infectious Diseases, COVID-19, Ebola, RSV, Bi-Specific Antibodies, Antibody Mimetics, Antibody-Drug Conjugates, Vaccine Development, Travel Medicine, Emerging Pathogens.

Historical Perspective[1]

Antibodies were first used in the late 19th century to treat toxin-producing bacterial infections such as diphtheria and tetanus. Von Behring won the Nobel Prize in medicine for his revolutionary work in diphtheria treatment. This ushered the beginning of the serum therapy era, where animal sera were used against other organisms like *Neisseria meningitidis* and Group A *Streptococcus*, though this often resulted in serum sickness. Human sera offered some improvement, but impurities still caused immune complex-mediated fever, rash, and hypotension.

In 1891, Klemperer demonstrated the benefits of serum therapy for *Streptococcus pneumoniae* when properly administered. However, because the bacterium had multiple serotypes, trials showed that mixing sera targeting various serotypes was better, and this became the standard therapy for pneumonia. However, serum therapy failed during the meningitis outbreaks in the United States of America (USA) and Europe.

The discovery of penicillin by Alexander Fleming in 1928 marked the beginning of the antibiotic era for fighting infections, leading to the abandonment of serum therapy. Nevertheless, sera continued to be used for specific indications, such as snake bites. However, the indiscriminate use of antibiotics opened the Pandora's box, resulting in the emergence of multi-drug-resistant (MDR) organisms such as Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant *Enterococcus* (VRE). As per the World Health Organisation (WHO) and Centres for Disease Control and Prevention (CDC), antibiotic-resistant infections are estimated to cause 10 million

deaths annually by 2050, along with a 2%–3.5% reduction in global gross domestic product (GDP). An additional challenge is the emergence of new pathogens such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), along with the re-emergence of others like Ebola. Ebola has a mortality rate exceeding 50%, with no successful treatment options or vaccines. Antibody-based therapies have remained largely experimental, although convalescent sera and monoclonal antibodies (mAbs) were used during the Coronavirus Disease 2019 (COVID-19) pandemic under emergency use approvals. These recent outbreaks of Ebola and COVID-19, together with the grim scenario of antibiotic resistance, have catalysed renewed interest in mAbs as the next generation of antimicrobial agents. were used during the COVID-19 pandemic under emergency use approvals. These recent outbreaks of Ebola and COVID-19, together with the grim scenario of antibiotic resistance, have catalysed renewed interest in mAbs as the next generation of antimicrobial agents.

Today, antibody treatments are used for diseases like hepatitis B, rabies, respiratory syncytial virus (RSV) infection, tetanus, botulism, vaccinia virus infection, and certain enteroviral infections. These therapies generally involve pooled immunoglobulin (intravenous immunoglobulin, [IVIG] from multiple donors, leading to batch-to-batch variability, the need for large quantities due to low specificity, and limited supply dependent on donor availability. The potential of antibodies to treat infections like *Plasmodium falciparum, Pseudomonas aeruginosa, Mycobacterium tuberculosis,* and *Staphylococcus aureus* has been under-explored, under-estimated, and under-appreciated.[2]

In 1975, Cesar Milstein and Georges Köhler developed the first mAbs via fusion of B lymphocytes (B cells) with immortal myeloma cells, an innovation that earned them the Nobel Prize in 1984.

Introduction to Antibodies[3,4]

Antibodies, or immunoglobulins (Ig), are produced by B cells and play a crucial role in adaptive immunity by neutralising toxins and eliminating pathogens. Ig are found in blood, plasma, and other extracellular fluids (historically called "humors"); hence, their action is referred to as the 'humoral' immune response.

An antibody is a Y-shaped molecule, composed of 2 pairs of polypeptide chains: two heavy chains and two light chains. Each chain has a variable region and a constant region. The variable regions of the heavy and light chains together form the antigen-binding site, which determines the antibody specificity. The constant regions are linked by disulfide bonds, providing structural stability to the molecule. The lower part of the Y, known as the fragment crystallisable (Fc) region, consists of constant segments of the heavy chains (Figure 1).

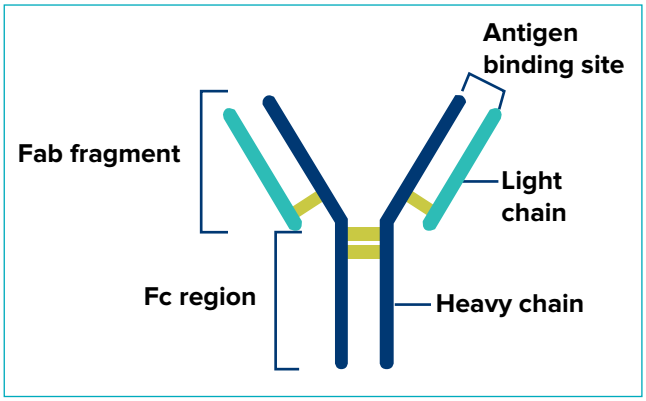

Figure 1: Structure of an antibody.[3] The heavy chains (blue), the light chains (green), the disulfide bonds (yellow).

Abbreviations: Fab: Fragment Antigen Binding; Fc: Fragment Crystallisable.

Function of antibodies

1. **Neutralising function of antibodies:** The antigen-binding site binds to bacterial toxins or viruses, preventing their attachment to and entry into host cells, thereby neutralising the toxins and their harmful effects.

2. **Effector functions of antibodies:** Effector functions are triggered when the Fc region of an antibody binds to Fc receptors on immune cells after the antibody has attached to an infectious agent or an infected cell. The major effector functions include:

    - **Complement activation:** Activation of the complement system leads to the lysis of pathogens, a process referred to as complement-dependent cellular cytotoxicity (CDCC).
    - **Phagocytosis:** Antibodies bound to pathogens enhance their uptake and destruction by phagocytic cells through Fc receptor interactions.
    - **ADCC:** Antibodies recruit immune cells like macrophages, eosinophils, neutrophils, and natural killer (NK) cells to destroy infected cells via Fc receptor binding.

The various mechanisms through which antibodies exert their effects are summarised in Figure 2.

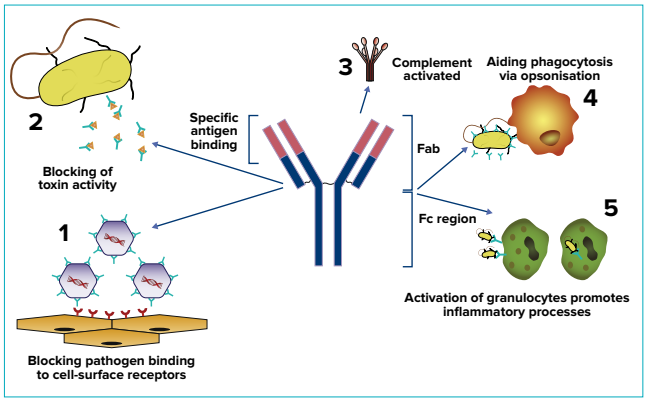

Figure 2: Functions of antibodies.[5]

Abbreviations: Fab: Fragment Antigen Binding; Fc: Fragment Crystallisable.

Monoclonal Antibodies (mAbs)

Definition: highly purified antibodies produced from a single parent cell, ensuring specificity to one particular target for a disease.

Types of mAbs in clinical use

These antibody types differ in structure and function (Table 1). Over time, the human protein percentage has increased (Table 2).

Stage	Description	Example
Murine antibodies	Entirely mouse-derived immunoglobulin G (IgG)	OKT3 (Muramonab-CD3, 1986)
Chimeric antibodies	Human constant regions + murine variable regions	Rituxan (rituximab)
Humanised antibodies	Human antibody structure with only murine antigen–binding complementarity-determining regions (CDRs)	Xolair (omalizumab)
Fully human antibodies	100% human sequence	Humira (adalimumab, 2002)

Table 1: Types of monoclonal antibodies in use.

Type	Composition	Human protein %
Murine	100% mouse protein	0%
Chimeric	Human constant + mouse variable regions	~65%
Humanised	Mostly human with mouse complementarity-determining regions (CDRs)	~95%
Fully human	100% human protein	100%

Table 2: Evolution of monoclonal antibodies to fully humanised form.

Nomenclature of mAbs

Pre-2021

Prior to 2021, all mAb names ended with the stem-mab. This naming scheme was replaced in 2021 by the World Health Organisation (WHO) International Nonproprietary Names (INN) nomenclature system, which classifies antibodies based on their structure and target. Examples of pre-2021 nomenclature: Altumomab: "-al-" (prefix) + "-tum-" (tumour target) + "-o-" (mouse origin) + "-mab" (suffix) (Table 3).

-mAb	Monoclonal antibody
-mo-mab	Mouse mab
-xi-mab	Chimeric mab
-zu-mab	Humanised mab
-mu-mab	Human mab
-tu-xx-mab	Tumour-directed xx mab
-ll-xx-mab	Immune-directed xx mab
-ci-xx-mab	Cardiovascular–directed xx mab
-vi-xx-mab	Virus–directed xx mab

Table 3: Nomenclature of monoclonal antibodies (pre-2021).

Post-2021[6]

The INN nomenclature for mAbs is a combination of a unique prefix, one or more infixes (sub-stems), and a suffix.

- **Prefix:** The prefix is random and decided by the manufacturer to ensure distinctiveness.
- **Infix(es):** One or more infixes or sub-stems indicate the target and source or purpose.
  - **Target (Infix A):** Indicates disease or target system.
  - **Source/Type (Infix B):** Previously indicated the origin (e.g., -o- for mouse) but is largely being phased out to avoid confusion with the new suffix system.
  - **Veterinary use:** The pre-substem "-vet-" can be used for veterinary products.
- **Suffix:** A new suffix system has replaced the outdated '-mab stem'. As per the 2021 WHO recommendations, the new suffixes for monospecific Ig are as follows:
  - -tug (anti-tumour)
  - -bart (anti-tumour)
  - -mig (multi-specific immunoglobulins)
  - -ment (anti-target for infectious diseases)

Thus, under the new system, the suffix indicates the drug's target or function, while the infixes specify the target class (e.g., -ta- for tumour) and where relevant the source of the antibody (e.g., -xi- for chimeric, -zu- for humanised).

Example of post-2021 nomenclature for mAbs

Rituximab is a chimeric mAb targeting tumours. Chimeric is denoted by -xi- in the name. If this drug were to be renamed as per INN nomenclature, it would not have -xi-, nor -mab. Also -tu- is no longer used to indicate the target tumour and has been replaced by -ta-. So, ri-tu-xi-mab would be renamed Ri-ta-tug (Ritatug) if it had been named after 2021.

Therapeutic applications of mAbs[7]

mAbs have both diagnostic as well as therapeutic indications. Diagnostic role includes immunoassays, cancer and disease detection, tissue typing and radio-labelling for imaging purposes. The therapeutic uses are vast and some of these are listed below (Table 4) (Figure 3).

Therapy area	Mechanism of action	Examples and key indications
Oncology	Targeted therapy by attaching to tumour cells, enhancing destruction	Trastuzumab (Herceptin): Blocks human epidermal growth factor receptor 2 (HER2) protein in breast and stomach cancer Rituximab: Binds to the cluster of differentiation 20 (CD20) protein on B-cells, in lymphomas and leukaemias
Oncology	Targeting tumour microenvironment and vascular supply	Bevacizumab (Avastin): Blocks vascular endothelial growth factor (VEGF) to inhibit neo-vascularisation
Oncology	Conjugated mAbs 'smart bombs' for delivering cytotoxic drugs and radioisotopes	Brentuximab vedotin (Adcetris): antibody-drug conjugate (ADC) linking antibody targeting the cluster of differentiation 30 (CD30) antigen to a chemotherapy drug for Hodgkin lymphoma
Oncology	Immune check point inhibitors block immune checkpoint proteins (like PD-1 or CTLA-4) that help cancer cells to hide from the immune attack. This "releases the brakes" permitting immune response	Pembrolizumab (Keytruda) and nivolumab (Opdivo): Target PD-1 to boost the T-cell immune response in melanoma and lung cancer
Oncology	Bispecific antibodies to bind to two different targets simultaneously, bringing a cancer cell and an immune cell closer to trigger an attack	Blinatumomab (Blincyto): Connects leukaemia cells expressing cluster of differentiation 19 (CD19) to T-cells expressing cluster of differentiation 3 (CD3), triggering the T-cells to kill the mitotic cells

Therapy area	Mechanism of action	Examples and key indications
Autoimmune disorders	Cytokine or tumour necrosis factor-α (TNF-α) inhibitors reduce inflammation	Adalimumab (Humira), infliximab (Remicade): rheumatoid arthritis (RA), Crohn's disease
Autoimmune disorders	Targeting specific immune cells. mAbs can target and depleting specific immune cells	Rituximab (Rituxan): Depletes B-cells in RA, multiple sclerosis
Autoimmune disorders	Immuno-modulators for signalling pathways	Belimumab (Benlysta): Inhibits B-cell activating factor (BAFF or BLyS) to reduce harmful B-cells in systemic lupus erythematosus (SLE)
Infectious diseases	Neutralising viruses, binding to viral proteins, preventing host cell entry	Several mAbs used in COVID-19 treatment
Infectious diseases	Passive immunity	Palivizumab (Synagis): as prevention of serious respiratory syncytial virus (RSV) in infants.
Infectious diseases	Neutralise bacterial toxins	Sepsis treatment for diseases like anthrax (e.g., Raxibacumab).
Cardiovascular disease	Lowering low-density lipoprotein cholesterol (LDL-C) levels	Evolocumab and alirocumab.

Table 4: Therapeutic applications of monoclonal antibodies (mAbs).

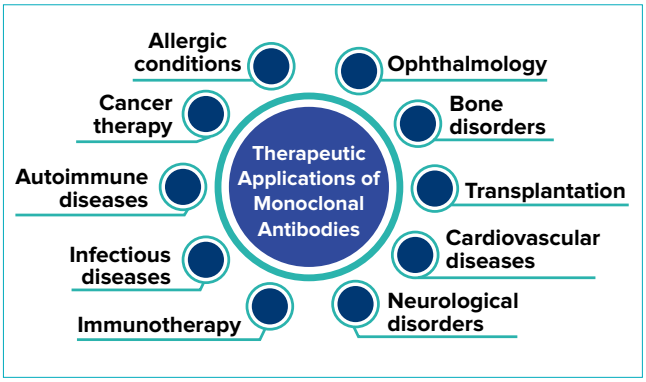

Figure 3: Therapeutic applications of monoclonal antibodies.[8]

Production of mAbs

Hybridoma technique

In this technique, specific mAbs are produced by fusing antibody-producing B-cells with immortal myeloma cells to create hybridomas, which can continuously secrete large quantities of highly specific identical, highly specific mAbs. The steps in the hybridoma technique include (Figure 4):

- **Step 1 -** A mouse is immunised with a specific antigen to elicit an immune response
- **Step 2 -** Antibody-producing B cells are harvested from the mouse spleen
- **Step 3 -** Harvested B cells are fused with immortal myeloma cells (cancerous B cells) using chemical or electrical techniques
- **Step 4 -** Fused cell hybridomas combine B cell's capacity for specified antibody production with the immortality of myeloma cells
- **Step 5 -** Selection of hybridomas and culture to produce massive quantities of a specific mAb

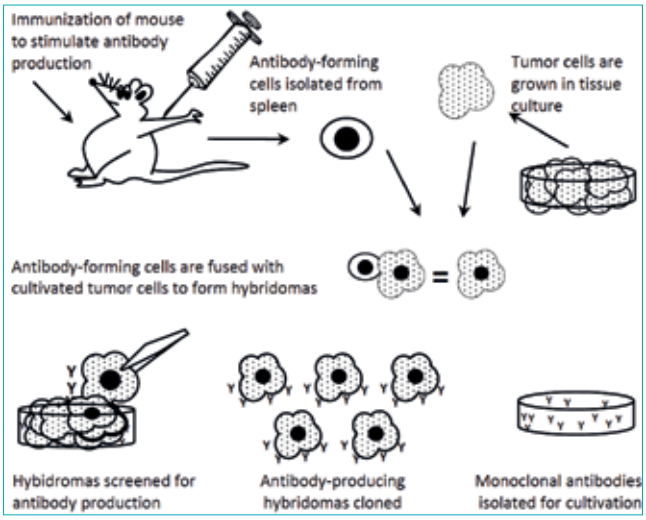

Figure 4: Monoclonal antibody production with hybridoma technology.[9]

Some of the recent advances in hybridoma technology include the development of technologies for humanised antibody and bispecific antibody production (Figure 5); the use of genetically engineered yeast and mammalian cell lines for large-scale fermentation (up to 5,000 Litres); and improved cell line design and fermentation processes, which have improved specificity and reduced impurities. Additionally, the upscaling production has reduced mAb costs. Currently,

mAbs represent the fastest growing segment in the biopharma sector (> 100 billion dollars annually). Moreover, focus has expanded beyond cancer and autoimmune disorders to include infectious diseases.[2,11,12]

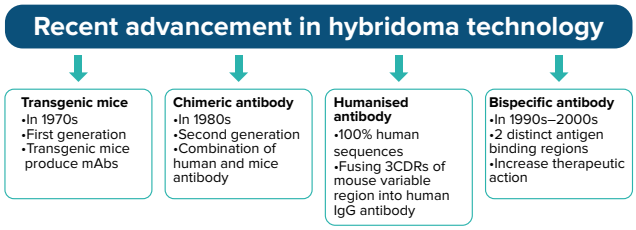

Figure 5: Advances in hybridoma technology.[10]

Abbreviations: mAbs: Monoclonal Antibodies; CDR: Complementarity-Determining Region.

Advantages of mAbs over traditional anti-microbial therapy

With the emergence of MDR bacteria, mAbs are going to play a crucial role in the fight against infections in the near future (Table 5).

Feature	Serum therapy	Antibiotics	mAbs
Source	Animal or human sera	Chemical processes/ fermentation	Tissue culture, hybridomas
Variation in each lot	Significant	Low	Low
Disease specificity	Narrow spectrum	Broad spectrum	Narrow spectrum
Side-effects	Poor tolerance, newer immu-noglobulins safer	Low toxicity	Low toxicity
Pharma-cokinetics	Variable	Consistent	Consistent
Route of administration	SC, IM or IV	Oral, IM, IV	SC, IM, IV

Table 5: Comparison of serum therapy, antibiotics, and monoclonal antibodies (mABs) as anti-microbial therapy.

Abbreviations: IM: Intramuscular; IV: Intravenous; SC: Subcutaneous.

Role of mAbs in viral infections (Table 6)

RSV: mAbs including nirsevimab and pallivizumab offer key advantages over vaccines by providing immediate, long-lasting passive immunisation and preventing severe RSV infection in infants and vulnerable young children. Both target the fusion 'F' protein of the virus. Nirsevimab, with its extended half-life offers protection for an entire RSV season, whereas pallivizumab requires monthly injections. Notably, plant-based expression platforms have been successfully used for production of recombinant RSV mAbs, which will reduce manufacturing costs compared to traditional mammalian platforms.[13]

Human immunodeficiency virus (HIV): mAbs can be potentially used in prophylaxis and treatment of multidrug-resistant (MDR) HIV in treatment-experienced patients. Ibalizumab has received approval for resistant HIV infection, while broadly neutralising antibodies (bNAbs) such as VRC01 are being tested for long acting pre-exposure prophylaxis (PrEP) and for immune enhancement in long-term treatment. The fact that HIV mutates rapidly remains a challenge.[14,15]

Rabies: Conventional post-exposure prophylaxis using equine or human rabies immunoglobulin (HRIG) faces limitations due to cost, availability and potential side-effects. mAbs produced by recombinant DNA technology, now offer a safer and more accessible alternative for immediate passive immunity after a potential exposure to the virus following an animal bite. Rabishield and Twinrab are approved for use and are administered by infiltration majorly around the wound site, with the remainder given intramuscularly.[16]

	Action	Effect/ Efficacy	Indications	Dose	Half-life ($t_{1/2}$)	Cost	Potential use
RSV prevention							
Palivizumab (RSV prevention)	Humanised mAB Target RSV F protein site II	45.82% against RSV related hospitalisation in high-risk infants	Infants < 29 weeks of gestational age; chronic lung disease of prematurity; haemody-namically significant congenital heart defect; select cases of pulmonary abnormalities, neuromuscular disorders, and severe immunodeficiency	15 mg/kg administered monthly up to a maximum of 5 doses during RSV season	Short half-life of approximately 17–26 days	Expensive	Recomm-ended in high-risk population only
Nirsevimab (RSV prevention)	Humanised mAB Target RSV prefusion F protein site	Preterms: 70.1% reduction on RSV associated MALRTIs, 2.6% vs 9.5% on RSV disease compared to placebo	Universal indication (potential) on infants	Single dose 50 mg IM in infants weighing < 5 kg and 100 mg IM in those weighing > 5 kg	Long half-life of approximately 150 days due to modified Fc region	Relatively better cost to effec-tiveness ratio	Universal prophylaxis in children against RSV
HIV therapy							
Ibalizumab	Humanised mAB Target CD4 T cell extracellular domain 1 and 2	In vitro neutralising activity against approximately 90% of a diverse panel of HIV strains Rapid reduction of HIV-ribonucleic acid (RNA) levels, 43% of participants achieve HIV RNA suppression after 24 weeks therapy	Used in combination therapy in heavily treatment experienced MDR HIV-1 patients unresponsive to the current antiretroviral regimen	Initial dose: 2000 mg IV and maintenance dose 800 mg every fortnight	Extended$_{t1/2}$ with high dose due to saturable elimination	Very expensive	Only in patients with MDR HIV.
Rabies prevention							
Rabies Human mAb (rDNA) Rabishield	Target a confo-rmational epitope of the rabies G protein	It is as effective as serum derived hyper-immune IgG It can fail against virus variants that circulate in Africa and North America	It must be given together with vaccine within 7 days after a bite for rabies post-exposure prophylaxis	3.33 IU/kg body weight		Cheaper than hyper-immune rabies IgG	Largely replaced by two mABs combination below
Miromavimab plus docaravimab (Twinrab)	Target the antigenic sites I and III of the rabies G protein	Combination is as effective as serum derived hyperimmune IgG	It must be given together with vaccine within 7 days after a bite	40 IU/kg body weight		Cheaper than hyper-immune rabies IgG	Highly recomm-ended

Table 6: Currently approved mABs for RSV, HIV and Rabies virus.[17]

Abbreviations: Fc: Fragment Crystallisable; HIV: Human Immunodeficiency Virus; HRIG: Human Rabies Immunoglobulin; IgG: Immunoglobulin G; IM: Intramuscular; IV: Intravenous; MALRTI: Medically Attended Lower Respiratory Tract Infection; MDR: Multidrug-Resistant; mAb: Monoclonal Antibody; rDNA: Recombinant Deoxyribonucleic Acid; RSV: Respiratory Syncytial Virus; $t_1/_2$: Half-Life.

Ebola virus (Table 7): The WHO has approved two mAbs as approved therapies for the treatment of infections caused by the Zaire strain of the Ebola virus. Inmazeb (REGN-EB3) is a cocktail of three mAbs — atoltivimab, maftivimab, and odesivimab — that bind to different, non-overlapping parts of the Ebola virus glycoprotein. Ebanga (mAb114), also known as ansuvimab is a single humanised mAb. These antibodies neutralise the virus by binding to its surface glycoprotein and prevent its entry into host cells. In randomised clinical trials conducted during the 2018–2020 Ebola outbreak in the Democratic Republic of the Congo (PALM Trial), both mAbs demonstrated significant efficacy when administered early in the course of infection. These mAbs are not effective against the Sudan strain of the Ebola virus. Furthermore, they cannot be administered along with the live Ebola vaccine, as it reduces the vaccine's efficacy.[18,19]

Drug (Brand name; Company)	Target	Format	Technology	Indication	Year of FDA approval
Ansuvimab (Ebanga)	Ebola glycoprotein	Human IgG1	Human	Prevention and treatment of Ebola	2020
Atoltivimab, maftivimab and odesivimab (Inmazeb)	Ebola glycoprotein	Human IgG1	Transgenic mice	Prevention and treatment of Ebola	2020

Table 7: Monoclonal antibodies for Ebola.
Abbreviations: FDA: Food and Drug Administration; IgG1: Immunoglobulin G1.

COVID-19 infection: mAbs were developed on a war-footing during the COVID-19 pandemic for the treatment of the SARS-CoV-2 infection. Examples include REGEN-COV (combination of casirivimab and imdevimab) targeting the virus spike protein, approved by the United States Food and Drug Administration (US FDA) and the European Union (EU) for both treatment and prevention. Other mAbs included bamlanivimab and etesevimab, tixagevimab and cilgavimab, bebtelovimab, and sotrovimab However, the emergence of new SARS-CoV-2 variants posed a major challenge, limiting the continued usefulness of these antibody cocktails. Moreover, multiple studies including a randomised control trial comparing COVID-19 convalescent plasma with mAbs found no difference in efficacy in preventing the need for hospitalisation.[20]

Role of mAbs in bacterial infections[21]

With the emergence of MDR pathogens and indiscriminate use of antibiotics, extensive research is underway to explore the use mAbs as anti-microbials. This approach offers greater specificity towards individual targets, unlike broad-spectrum antibiotics, thereby reducing the likelihood of developing antimicrobial resistance. The proposed mechanisms of action of mAbs against bacteria include the following (Figure 6):

- **Neutralisation of bacterial toxins –** e.g., bezlotoxumab for *Clostridium difficile*
- **Inhibition of bacterial adhesion to host cells –** e.g., mAbs targeting the Type III secretion system (TTSS) of *Pseudomonas aeruginosa*
- **Interference with bacterial communication system (quorum sensing) –** by blocking quorum sensing (QS) molecules, thereby reducing bacterial virulence
- **Opsono-phagocytosis –** by functioning as opsonins, to mark pathogens for enhanced destruction by macrophages and neutrophils
- **Complement-dependent cytotoxicity –** by activating the complement cascade
- **Disruption of biofilm –** by binding to the scaffolding matrix proteins within the biofilm

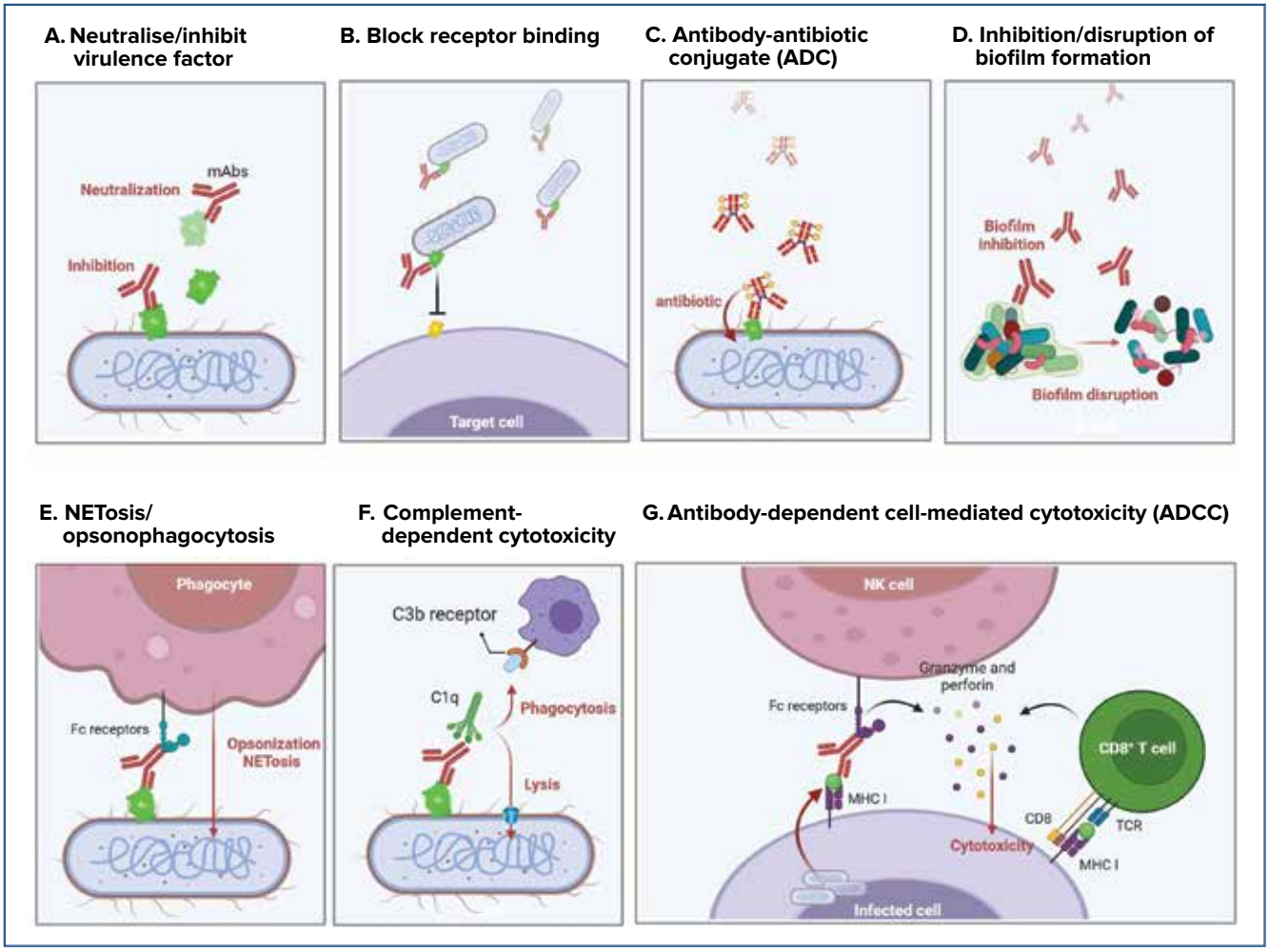

Figure 6: Mechanisms of monoclonal antibodies against bacterial infections.[21]

Abbreviation: NET: Neutrophil Extracellular Trap.

US FDA-approved antibacterial mAbs[18,19]

To date, only three antibacterial mAbs had received FDA approval, as follows:

1. **Bezlotoxumab (Zinplava®):** For adults at high risk of recurrent of *Clostridium difficile* infection. It works by binding to and neutralising the *C. difficile* toxin B.
2. **Raxibacumab (Abthrax®):** For the treatment and prophylaxis of inhalational anthrax caused by *Bacillus anthracis*. It works by neutralising the protective antigen (PA) component of the anthrax toxin.
3. **Obiltoxaximab (Anthim®):** For inhalational anthrax. Similar to raxibacumab, it also targets and neutralises the PA component of the anthrax toxin.

Challenges in development of anti-bacterial mAbs:

1. **Pathogen diversity:** Unlike viruses, bacteria possess hundreds of potential surface antigens and multiple serotypes. Consequently, a single mAb may not provide broad protection, necessitating the development of antibody cocktails targeting multiple epitopes.
2. **Target accessibility:** A potential target may be masked by the polysaccharide capsule, making it difficult for mAb to bind.
3. **Clinical trial failures:** Many candidate mAbs have failed in human trials after being found useful in animal models. Moreover, co-administration with antibiotics during studies can confound results.
4. **Cost and market size:** The research and development of mAbs is very expensive, and the relatively small market size can limit commercial viability.
5. **Dependence on rapid diagnostics:** As mAbs are highly specific, effective treatment may depend on rapid and accurate diagnosis of the infective pathogen.

The key viral and bacterial targets currently under investigation for mAb development are summarised in Table 8.

Infection	Target site
SARS-CoV2	S1 receptor binding domain (SBD) for binding spike protein S to ACE2
Influenza	Haemagglutinin (HA) and neuraminidase (NA) receptors
Ebola	Viral glycoprotein
Hepatitis C	E1-E2 complex
Zika and dengue	E protein
Bacterial infections	Toxin, lipopolysaccharide

Table 8: Targets for monoclonal antibodies (mAbs) against infectious diseases.

Abbreviations: ACE2: Angiotensin-Converting Enzyme 2; E: Envelope; E1-E2: Envelope Glycoprotein Complex; HA: Haemagglutinin; NA: Neuraminidase; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SBD: Spike Binding Domain.

Side-effects of mAbs

When evaluating mAb therapies, it is important to recognise that each mAb is a unique protein, and treatment involves administering a significant quantity of protein through IV, intramuscular, or subcutaneous routes. While mAbs generally have an excellent safety profile in both randomised controlled trials (RCTs) and observational studies, some have been linked to adverse events, which may be related to the specific characteristics of individual formulations. Side effects can include infusion-related reactions, fever, nausea, rash, diarrhoea, and hypotension. For instance, the combination of tixagevimab and cilgavimab was associated with a higher incidence of thromboembolic events compared with other mAbs, while the combination of casirivimab and imdevimab, and bamlanivimab alone, have shown a higher incidence of ischaemic heart disease events. Bevacizumab (Avastin), which targets a protein called vascular endothelial growth factor (VEGF), can cause hypertension, bleeding, thrombotic events, and kidney damage. Similarly, cetuximab (Erbitux), which targets the epidermal growth factor receptor (EGFR), may cause severe skin rashes in some people as EGFR is also present in normal skin cells.

Application of mAbs in travel medicine[22]

mAbs may be used in travel medicine in the following scenarios in the future:

- **Pre-travel prophylaxis:** Passive immunisation using mAbs could prevent diseases such as malaria.
- **Post-exposure prophylaxis:** mAbs can prevent disease onset after exposure, as already demonstrated in rabies management.
- **Treatment of travel-acquired infections:** mAbs may be developed for infections like dengue fever and yellow fever.

Hypothetically, mAbs may offer advantages in certain situations over standard vaccines and prophylaxis methods. For example, using mAbs to prevent *Plasmodium falciparum* malaria could involve a single injectable dose administered before departure, providing protection without significant side effects, compared to daily or weekly oral anti-malarial prophylaxis. Other examples include single-dose mAb prophylaxis for hepatitis A or yellow fever in immunocompromised travellers who may not be able to produce a sufficient antibody response or where live attenuated vaccines, such as the yellow fever vaccine is contraindicated.

mAbs have also shown promise in treating diseases with high mortality, such as Ebola and yellow fever, and research is ongoing for diseases like rabies and dengue fever.

Emerging mAbs against infectious diseases

Nipah virus: A human clinical trial to test the safety and efficacy of a novel monoclonal antibody, MBP1F5, is expected to begin in India and Bangladesh soon. Nipah virus has a high mortality rate (45%–75%), and currently lacks an approved vaccine.[23,24]

Dengue: Phase II clinical trials are underway for AV-1, an investigational human mAb developed by AbViro (USA), to mitigate clinical symptoms when administered before or after dengue infection.[25]

Influenza: mAbs in clinical development for influenza are aimed at treating active infections. Due to the annual variation in circulating strains, most mAbs under development target the highly conserved stem region of the hemagglutinin (HA) protein.

Malaria: Based on promising preclinical results from two mouse models of *Plasmodium falciparum* infection, the mAb CIS43LS is being developed as a long-acting immune prophylactic against malaria.

Next generation antibodies[26]

The different formats and types of next-generation antibodies are illustrated in Figure 7.

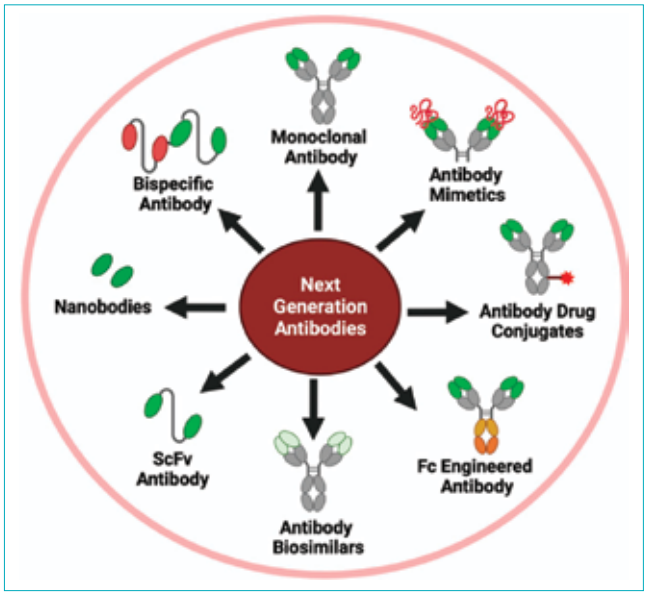

Figure 7: Next generation antibodies.[26]

Abbreviations: Fc: Fragment Crystallisable; ScFv: Single-Chain Variable Fragment.

Single-chain variable fragment (scFv) antibodies

mAbs have limitations in treating diseases because of their relatively large molecular size. To address this, smaller scFv recombinant antibodies have been developed. They consist of the variable heavy (VH) and variable light (VL) chains connected by a flexible poly-linker peptide (15–20 amino acids). The bacterial expression system, particularly *Escherichia coli*, is commonly used for scFv production. The size of scFvs (27 kDa) is roughly one-fifth that of a complete antibody, allowing easier penetration into tumours and accessibility to cryptic epitopes. Moreover, scFvs are cleared more easily from non-target healthy tissues causing lesser side-effects.

An scFv is thus a recombinant antibody format composed of a single polypeptide chain that retains the antigen-binding properties inherent in the intact antibody, while offering advantages in size, penetration, and manufacturability.

Bispecific antibodies

mAbs have two arms that each recognises the same target antigen. Bispecific antibodies (bsAbs) have two unique binding domains simultaneously binding to two different antigens, offering an improved therapeutic approach. Early bsAbs were created by chemically combining two mAbs or fusing together two hybridoma cell lines, resulting in ‘quadroma’ cell lines. Recently, genetic engineering advancements have led to the development of more than 50 recombinant bsAbs. Removab (catumaxomab) and Blincyto (blinatumomab) were amongst the first clinically approved bsAbs, used for treating malignant ascites intraperitoneally and for relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) respectively.

Antibody biosimilars

Antibody biosimilars are biologic drugs that closely resemble approved therapeutic mAbs (reference or originator mAbs) in structure, function, and efficacy. These have to replicate the safety, efficacy, and quality of the original mAbs, they are not identical to the originator molecule. Several biosimilars for including infliximab, rituximab, trastuzumab, and bevacizumab have been approved. These are more affordable although efficacy maybe lower.

Antibody mimetics

Antibody mimetics, or "synthetic antibodies," are designed to mimic the functions of natural antibodies by replicating their antigen-binding segments, minus the Fc region and associated issues. These are more stable and cost-effective.

Antibody drug conjugates (ADCs)

ADCs combine the specificity of mAbs with the potent cytotoxic effects of small-molecule drugs. ADCs selectively deliver powerful anticancer agents directly to tumour cells, minimising the systemic toxicity that typically accompanies chemotherapy eg. ado-trastuzumab emtansine (Kadcyla) for human epidermal growth factor receptor 2 (HER2) positive breast cancer. ADCs can be used in combination with other oncology treatments to enhance overall anti-tumour effects.

mAbs as vaccines[27]

Although vaccines remain the most effective preventive measure against infections, effective vaccines have not yet been developed for pathogens such as HIV, RSV, Hepatitis C, and Ebola virus. For a vaccine to be effective, it must elicit a robust and durable antibody response. Identifying antibodies capable of effectively neutralising a pathogen is a key step in hastening vaccine development.

Pathogen-neutralising mAbs are used to identify antigenic structures on the pathogen's surface. These antigen-antibody complexes are then analysed to select antigenic structures suitable for vaccine design (Figure 8).

The concept of reverse vaccinology 2.0, also known as antibody-based vaccinology, aims to overcome the limitations of traditional vaccine development methods by creating novel vaccines through the use of structural information derived from mAb-antigen complexes. The process starts with single-cell cultures of plasma or memory B cells derived from convalescent patients or vaccinated donors. These cultures are screened to identify mAbs with neutralising activity against the target pathogen. The recombinant mAbs are then used to identify the antigen and analyse the three-dimensional (3D) structure of the antigen-mAb complex. This structural data is crucial for designing and optimising stabilised antigens for next-generation vaccine development.

Roadmap for mAb use in infection outbreaks

Humanity has faced at least seven major viral outbreaks in the 21st century — SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), influenza A (H1N1), Zika virus, Ebola virus, SARS-CoV-2,

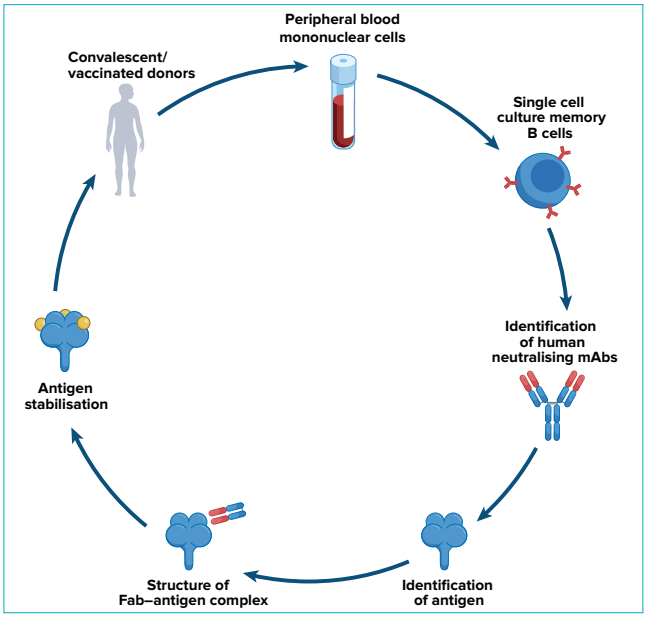

Figure 8: Schematic representation of reverse vaccinology 2.0.[27]

and monkey pox (Mpox) — and must brace ourselves for further outbreaks. The war-paced development and deployment of mAbs for COVID-19 pandemic stands out as a scientific success story. This accomplishment saved countless lives and established a blueprint for contingency planning in future infectious disease emergencies. To further enhance mAb effectiveness, they could be combined with small-molecule antiviral drugs, which may lower viral loads and minimise the selection of mutant strains. Given the importance of early intervention, widespread use of mAbs will require the establishment of dedicated infusion centres and physician education, so that mAb therapy can be promptly administered to high-risk individuals during future outbreaks.

Conclusion

mAbs have evolved from experimental immunotherapies to essential tools in infectious disease management. Their precision, adaptability, and safety make them promising alternatives to conventional antimicrobials, particularly in an era of rising MDR. Recent advances — including bispecific antibodies, antibody–drug conjugates, and mimetics — have expanded their clinical utility beyond oncology to encompass viral, bacterial, and parasitic infections. The rapid development of mAbs during the COVID-19 pandemic demonstrated their scalability and global relevance. Future priorities include cost-effective production, improved delivery systems, and equitable access to ensure mAbs become integral components of modern antimicrobial therapy.

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