Monoclonal Antibodies for Pediatric Viral Disease Prevention and Treatment

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Medical advancements over the last century have improved our ability to treat pediatric infectious diseases, significantly reducing associated morbidity and mortality worldwide. Although vaccines have been pivotal in this progress, many viral pathogens still do not currently have effective vaccines. The COVID-19 pandemic highlighted the need for rapid responses to emerging viral pathogens and introduced new tools to combat them. This review addresses human monoclonal antibodies (mAbs) as a strategy for treating and preventing viral infections in pediatric populations. We discuss previously used and currently available mAbs and advancements in mAb discovery. We address the future of mAb therapy by describing novel approaches in drug production and delivery platforms in addition to alternative antibody classes. Finally, we review the challenges and limitations of mAb therapy development for newborns and children.

INTRODUCTION

Until the mid-20th century, viral infectious diseases were a major cause of mortality for newborns and children. Currently, many diseases caused by viral infection can be prevented or attenuated by specific vaccines: examples include polio, hepatitis B, measles, rubella, influenza, and SARS-CoV-2. For other viruses, particularly those characterized by persistent infection such as cytomegalovirus (CMV), HIV, and Zika virus, no effective vaccine exists.

Human monoclonal antibodies (mAbs) have favorable safety profiles and may be an alternative to antivirals for many viral diseases. Historically, both the discovery and production of mAb therapeutics were limited by the time- and labor-intensive approaches needed to produce these agents. High throughput screening and manufacturing protocols have overcome many of these hurdles.[1] Advancements in large-scale cell culture and rapid purification, spurred by developments in cancer mAb products, have made antibodies more feasible products.[2] Newer mAbs exhibit remarkable precision in their binding and can function through multiple mechanisms of action. Neutralizing antibodies block viral entry, whereas others employ effector mechanisms to mark infected cells for targeted destruction. Additionally, mAbs can be engineered to introduce amino acid mutations that extend their half-life in vivo, enhance or ablate effector functions, and minimize antidrug antibody (ADA) responses. With the identification of mAbs that can bind sites on the same virus protein, it is possible to combine mAbs into a synergistic mixture that can both increase potency and decrease the chances of viral escape by single-site mutation. Ideally, expanded mAb research will lead to the discovery of mAbs that are cross- and pan-reactive within viral families.

abstract

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In this review, we address the current status of human mAbs as preventive or therapeutic interventions for important pediatric viral pathogens. We also discuss novel production and delivery platforms and the potential for different classes of mAbs and engineered mAbs. Finally, we review recommendations and challenges for using passive mAbs in early life to complement current clinical practices and improve the survival and health of infants and children.

Antibodies Across the Early Childhood Development Timeline

Antibodies not only protect individuals from viral infections, but their study enhances our understanding of protective responses. Immunoglobulin G (IgG) is the primary antibody responsible for neutralizing viruses and is the dominant immunoglobulin in serum, whereas immunoglobulin A (IgA) is the most abundant isotype in mucosal secretions. Figure 1 illustrates the relative levels and variations of antibody titers in newborns and children from birth through their teenage years. Maternal immunoglobulin (primarily IgG) is transferred across the placenta and through colostrum and breast milk, providing essential protection to newborns and infants (Figure 1A).[3,4] Mucosal surfaces in humans are predominantly protected against infectious pathogens by secretory IgA (sIgA), which comprises 80% to 90% of antibodies in breast milk.[5] As a critical component of early-life immunity, breast milk provides infants with postnatal maternal immunization via high levels of sIgA.[6] Trans-placentally acquired antibodies, principally IgG, reflect the repertoire present in the mother's blood during gestation and delivery. This principle underlies the strategy of vaccinating pregnant women, ensuring that the infant is protected through these vertically transmitted antibodies.[7,8] The effectiveness of maternal antibodies provides strong proof that passive immunization of infants with mAbs can protect against infections.

Because maternally acquired antibodies wane with time and eventually leave the growing infant increasingly vulnerable to infection,[9] there is a compelling rationale for initiating infant immunizations early in life to induce a response before this occurs.[10] In newborns and infants, effective and safe vaccines administered early after birth and in childhood can provide protective immunity against vaccine-specific pathogens once levels reach the protective threshold, but this can take weeks to months (Figure 1B). The

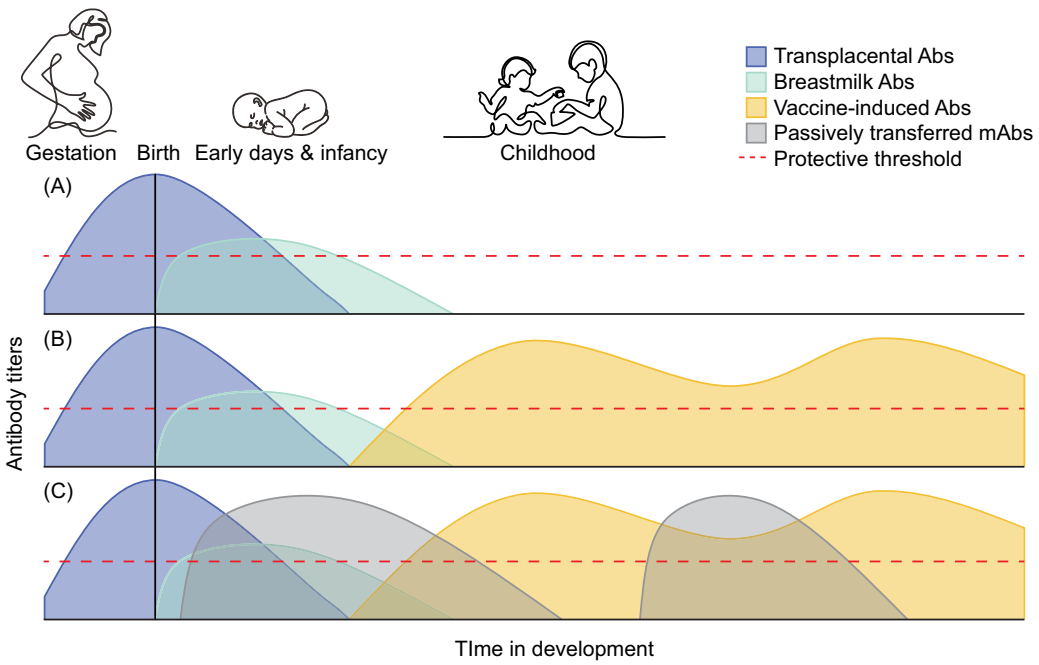

FIGURE 1.
Sources and levels of antibodies in early life. Schematic diagram of Ab titers in arbitrary units (y-axis) as they ebb and flow as a function of time in development (x-axis) with various treatments. A protective threshold in the graphs is shown as a red dotted line in newborns, infants, toddlers, and children, depicted at the top of the figure. (A) Maternal Abs are transferred by the placenta during gestation prior to birth (blue) and by maternal breast milk (aqua) via breastfeeding. Following decay of these Abs, the infant is highly susceptible in the absence of vaccination or if vaccines are not available. (B) The introduction of vaccines (ochre) in newborns, infants, and children can reestablish a threshold of protective Abs that are specific to each vaccine. A gap of limited or no protection can occur for diseases with no vaccines or for vaccines that are not given. (C) The use of passive mAbs (gray shading near birth and later in childhood, as examples) increases Abs against a specific agent either prior to vaccination or when needed if an outbreak occurs, leaving no gap in protection.
Abbreviations: Ab, antibody; mAb, monoclonal antibody.

expanded program for immunization was implemented to maintain and strengthen early-life immunity by vaccinating children in their first year of life, with continued vaccinations scheduled through their 18th year.[11] However, infants and children will only be protected against diseases for which we have vaccines, and, unfortunately, some vaccines are less efficacious than others.

Gaps in vaccine coverage and limited availability provide an opportunity to use human mAbs as rapid and effective antivirals for newborns and children who are either unvaccinated or partially vaccinated. As illustrated in Figure 1C, passive mAbs targeting specific viral pathogens can supplement maternal antibodies, preventing infection or disease in both vaccinated and unvaccinated newborns and children. In outbreaks caused by newly emerging pathogens, administering passive antibodies as drugs could significantly reduce the severity of or prevent infections in infants and children.[12]

Human mAb Mixtures for Viral Infections

Although the number of human mAb antiviral therapeutics currently approved or in clinical testing has increased (Table 1), most are not yet available for newborns and children owing to the US Food and Drug Administration (FDA) requirement for prior safety studies in adults. Large disease outbreaks such as the recent Ebola, Zika, and SARS-CoV-2 pandemics have demonstrated the need for mAbs,[13] as well as alternative delivery routes. Human mAb therapeutics are approved for Ebola, SARS-CoV-2, and respiratory syncytial virus (RSV), whereas mAbs are still in development for the other examples that we cite.

Ebola

Four viruses in the *Ebolavirus* genus cause Ebola virus disease (EVD), with mortality ranging from 25% to 90%. In 2020, the FDA approved the use of 2 different mAb therapies for the treatment of Ebola virus species, *Zaire ebolavirus*. One of them is Ebanga,[14] Ansuvimab-zykl (mAb114), a human mAb against the Ebola envelope (Env) glycoprotein inhibiting viral entry. The Pamoja Tulinde Maisha (PALM) trial evaluated the efficacy and safety of mAb114 in pediatric patients,[15] with 55 in the treatment arm and 34 in the control arm, and efficacy was 64.9%.[16] The other mAb therapy is Inmazeb (ie, REGN-EB3, a combination of Atolivimab, Maftimimab, and Odesivimab-ebgn),[17] which was tested in the PALM trial in 42 pediatric patients and showed similar efficacy. Despite the 2022 recommendations by the World Health Organization to treat patients with EVD or neonates born to infected mothers with mAb114 or REGN-EB3,[17] there are still notable availability and equity challenges globally.

SARS-CoV-2

The SARS-CoV-2 pandemic led to COVID-19 disease and approximately 14.9 million deaths globally. Five different anti-SARS-CoV-2 mAbs were tested to limit viral

TABLE 1. An Overview of Clinically Evaluated Human mAb Therapies for Viral Diseases

Virus	mAbs	Mechanism of Action	Study Types	Study Participant Ages
Ebola	mAb113, REGN-EB3	Targets Ebola glycoprotein to inhibit viral entry	Phase 3 clinical trial[16]	Any age, including neonates[16]
SARS-CoV-2	Bamlanivimab-Etesivimab,[103] Casirivimab-Imdevimab,[19] Sotrovimab,[20] Bebtelovimab, Tixagevimab/Cilgavimab,[22] Pemvivibart[24]	Binding to the viral surface spike glycoprotein to inhibit cell entry	Phase 3 clinical trial	>12 years
RSV	Palivizumab,[25] Nirsevimab[26]	Binds to the RSV fusion protein to inhibit viral entry	Phase 3 clinical trial	<2 years
HIV	3BNC117 + 10–1074,[34] VRC01[30]	Each mAb neutralizes the virus by targeted nonoverlapping epitopes on the HIV Env protein[104]	Phase 3 clinical trial; Phase 2 clinical trial; Phase 1 trial in infants[30]	>18 years; infants >36 weeks' gestation at birth
CMV	MCMV3068A + MCMV5322A[37]	Binds to CMV surfactant glycoproteins	Phase 2 clinical trial	>18 y[37]
HSV	HDIT101[105]	Binds to glycoprotein B (found on viruses and infected cells), inhibiting the virus's ability to enter cells or spread via cell-to-cell transmission	Phase 1 clinical trial[105]	Ages 21–56 years
Hepatitis B and D	Myrcludex B (Bulevirtide)[106]	Blocks HBV/HDV host receptor	Phase 2 and 3 trials for compensated patients with chronic hepatitis D	>18 years
Chikungunya virus	mRNA-1994[107]	mRNA coding for Chikungunya-specific neutralizing mAb	Phase 1 trial	18–50 years

Note: "+" indicates a combined mAb therapy.
Abbreviations: CMV, cytomegalovirus; Env, envelope; HBV, heptatis B virus; HDV, heptatis D virus; HSV, herpes simplex virus; mAb, monoclonal antibody; mRNA, messenger RNA; RSV, respiratory syncytial virus.

dissemination by binding to the viral Env (spike): (1) The combination Bamlanivimab and Etesivimab was tested for mild-or-moderate COVID-19 in 518 patients (including 4 who were aged 12–17 years) vs placebo in 517 patients (including 7 who were agesd12–17 years). Only 2.1% of patients in the mAb group required hospitalization, with no patient deaths, whereas 7.0% of placebo group patients were hospitalized owing to COVID-19 complications, with 9 COVID-19 related deaths. (2) A combination of Casirivimab and Imdevimab was evaluated for its impact on viral load and progression to symptomatic infection.[18] Patients received mAbs (39 patients, of which 15 were aged 12–17 years) or placebo (42 participants, of which 11 were aged 12–17 years). At 28 days, treated patients had a 13.3% decreased risk of becoming symptomatic, significantly decreased symptoms,[19] and significant decreases in viral load. (3) Bebtelovimab treatment decreased viral load compared to placebo but did not have significant results in low-risk groups. (4) Sotrovimab (VIR-7831) was tested in a phase 3 trial in which the primary outcome was determined based on hospitalization for more than 1 day and on survival at 29 days after beginning the therapy. Only 1% of patients receiving mAbs were hospitalized for over 1 day or died compared with 7% of those in the placebo group.[20] (5) Evusheld (Tixagevimab/Cilgavimab)[21] was compared to the standard of care (Remdesivir) in a phase 3 multisite trial and decreased recovery time relative to the control.[22] When given as preexposure prophylaxis and evaluating the infection rate over 49 to 73 days, only 4.4% of immunocompromised patients developed COVID-19.[23] Use of these mAbs was discontinued owing to viral escape. In 2024, a new mAb called Pemivibart (Pemgarda) was approved for prophylaxis for immunocompromised individuals under an Emergency Use Authorization.[24]

RSV

RSV is more likely to significantly affect infants and adults over age 60 years. In 2022 and 2023, there were significant spikes in RSV infection in children, with hospitalization rates going up from 13.3 to 61.5 per 100 000 from 2021 to 2022, respectively. Palivizumab (marketed as Synagis), an IgG1 mAb that targets RSV's fusion protein, became the first FDA-approved mAb for RSV in 1998. Study participants were children under the age of 6 months, born before 35 weeks, or those under the age of 2 years being treated for bronchopulmonary dysplasia. Following 5 monthly Palivizumab injections or placebo, RSV-related hospitalizations over 150 days were decreased by 55% relative to the placebo.[12,25] Nirsevimab is a more potent IgG1 human mAb modified for extended durability. In a 2022 phase 3 trial, the efficacy of Nirsevimab vs placebo was evaluated in patients younger than age 1 year who had been born at a minimum of 35 weeks' gestation to assess the rate of developing RSV and of hospitalization over 150 days after mAb injection. Nirsevimab efficacy was 74.5% and significantly better at preventing medically attended, RSV-associated lower respiratory tract infection than placebo,[26] although hospitalization rates were not significantly different. In August 2023, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices determined that Nirsevimab should be the preferred therapy for all infants and children.[27]

HIV

Transmission of HIV to children who are born to mothers living with the virus can occur in utero, intrapartum, and during breastfeeding. Antiretroviral therapy (ART) regimens are very effective in limiting transmission and controlling viremia, but more than 100 000 children acquire HIV every year. Moreover, children living with HIV must adhere to ART for their entire lives to prevent viral rebound, and ART availability, adherence, and inherent toxicity all limit effectiveness. Human broadly neutralizing antibodies (bNAbs) directed to the Env potently neutralize many divergent HIV variants, and their therapeutic potential is under evaluation. Two parallel randomized, placebo-controlled, double-blinded, multicenter, phase 2b trials in men and women tested the preventive efficacy of the moderately potent bNAb VRC01. Although VRC01 did not significantly decrease acquisition of HIV relative to placebo, this single bNAb limited the acquisition of viruses that were sensitive to VRC01, thereby demonstrating antibody efficacy against HIV. The study also suggested that 2 or 3 bNAbs directed against different epitopes on the Env may be necessary to prevent infection owing to the extreme global diversity of HIV.[28,29] A phase 1 study of VRC01 in infants living with HIV and receiving ART showed that subcutaneous (SC) delivery is safe and well tolerated, achieving therapeutic doses and opening the door to efficacy studies.[30] In infant primate studies using the chimeric virus simian HIV (SHIV), a mixture of 2 bNAbs delivered as postexposure prophylaxis cleared infection when given as late as 30 hours following oral exposure to the virus.[31,32] Combination bNAb trials are currently in the planning phase, with the goal of preventing HIV infection in newborns and breastfeeding infants.[33] The therapeutic potential of bNAbs has also been evaluated in individuals living with HIV. In the absence of ART, 2 human bNAbs temporarily suppressed HIV in the plasma of adults who had a neutralization-sensitive virus, and viral suppression lasted 30 weeks longer than in those who received the placebo.[34] In children, a recent proof-of-concept trial showed that a 2-bNAb mixture of antibodies could replace ART when given during treatment interruption, resulting in sustained suppression in 44% of those in the study.[35]

CMV

CMV is a common virus that can infect people of all ages, with over 50% of adults infected by age 40 years.

Although most individuals are unaware of their CMV status, the virus can lead to severe complications in immunocompromised individuals, including neonates and older adults. RG7667, a mAb mixture therapy, comprises 2 mAbs, MCMV3068A and MCMV5322A, that inhibit viral transmission by binding to CMV surface glycoproteins.[36] In a phase 2 trial involving renal transplant patients receiving either the mAb or placebo at 1, 4, and 8 weeks after kidney transplant, the rate of CMV viremia in the mAb group was only 15.3% less than that in the control group.[37] Currently, no FDA-approved CMV mAb exists.[38]

Lassa Virus

Lassa virus, which poses a high fatality risk to pregnant women and their fetuses, is ranked as the top threat among 50 zoonotic viruses and is thereby an important target for developing mAb therapies.[39] In primate studies, low doses of Arevirumab, a mixture of 3 potent mAbs directed to the Lassa glycoprotein C complex, uniformly prevented lethal disease against the major lineages of Lassa.[40]

Novel Antibody Production Platforms

The production of antibodies in mammalian cells, principally Chinese hamster ovary cells, remains a standard practice owing to the requirement for posttranslational modifications that closely resemble human proteins. These cells offer high yields and the ability to perform complex glycosylation. However, the complexity, cost, and risk of contamination associated with mammalian cell cultures is driving the exploration of alternative production systems.

Plant-Produced mAbs

Using plants as bioreactors for mAb production has several advantages, including decreased animal pathogenic contaminants, rapid expression and evaluation, low production costs, and easy agricultural scalability compared to existing production systems.[41] mAbs generated using plant platforms include those directed to anthrax, *Clostridium perfringens*, Ebola virus, HIV, herpes simplex, rabies, RSV, staphylococcal enterotoxin, and West Nile virus.[41] During the 2014 Ebola outbreak, a combination of 3 tobacco-derived, IgG-based chimeric mAbs was used as an emergency treatment for 7 patients, 5 of whom recovered.[42] Repeated delivery of the plant-produced HIV-1 bNAb PGT121 protected infant macaques from repeated oral SHIV challenge, suggesting that plant-produced bNAbs hold promise as passive immunoprophylaxis to prevent breast milk transmission of HIV-1.[43] Glycan engineering of plant systems has enabled the production of mAb glycovariants with enhanced functional capacity.[44] Notably, plant-derived afucosylated mAb PGT121 demonstrated increased binding to FcγRIIIa and enhanced antibody-dependent, cell-mediated cytotoxicity in vitro and in vivo.[45] However, plant-derived recombinant HIV-specific mAbs, including engineered variants with higher neonatal Fc receptor (FcRn) affinity, demonstrated poor placental transfer in rhesus macaques compared to mammalian-derived versions of the same mAbs.[46,47] This difference could have important therapeutic implications and requires further investigation.

Expression of mAbs Using Viral Vectors

Adeno-associated viruses (AAVs) have been engineered for gene therapy applications owing to their lack of pathogenicity and toxicity, excellent safety profiles, and ability to infect both dividing and nondividing cells and long-term transgene expression profile after a single administration.[48] Some examples include an AAV-based mAb against RSV in murine and ovine models, resulting in robust and sustained placental transfer,[49] and an antihuman angiotensin-converting enzyme 2 (hACE2) mAb that showed potent inhibitory activity against multiple SARS-CoV-2 variants such as Omicron.[50] Originally modeled with simian immunodeficiency virus in rhesus macaques, long-term expression of mAbs prevented infection. This approach has been applied with bNAbs to HIV,[51] as has been reviewed recently.[52] ADA directed to both AAV and the encoded bNAbs are common. Strategies to limit ADA include the development of synthetic AAV capsids not recognized by the anti-AAV antibodies, blockade of the FcRn to reduce host anti-AAV antibodies transiently, and induction of tolerance to the AAV-encoded immunoglobulin.[53]

Expression of mAbs Using Messenger RNA

Messenger RNA (mRNA)-based therapeutics have emerged as a promising new class of biologics capable of encoding proteins for direct in vivo expression.[54] Because mAbs acquire various posttranslational modifications during production that can alter mAb activity and function, extensive analytical characterization and process controls are required that substantially increase manufacturing complexity and costs.[55] mRNA sequences encoding mAbs can be delivered to patients to induce transient in situ expression,[56] leveraging intrinsic protein production machinery to synthesize functional mAbs, potentially for prolonged periods following a single treatment.[57] Respiratory tract infections are an attractive therapeutic target for mRNA-based mAb development in an effort to improve delivery efficiency and resident expression time. Delivery of an mRNA-based human mAb to the lungs effectively neutralized SARS-CoV-2 variants and protected transgenic mice.[58]

Alternative Antibody Delivery Methods

Most FDA-approved therapeutic mAbs are administered via intramuscular (IM) or intravenous (IV) injection.[59,60] Improving the ease of delivery can decrease the burden on related health care costs and resource use, in which scalability is key.[61]

Nanoparticle-Based Delivery

A fundamental limitation in using mAbs clinically is effective delivery to affected tissues, such as the central nervous system (CNS) and brain, owing to the blood-brain barrier.[62,63] Nanoparticles (NPs) represent a novel approach to overcoming this barrier, and there is evidence that administration of bNAb (PGT121)-conjugated NPs improved delivery to the CNS and decreased SHIV in infant rhesus macaques.[64] Additionally, the NP surface can be readily modified with proteins that target specific receptors to localize drug delivery.[65]

Aerosol Delivery

Aerosol delivery of mAbs directly to airways via inhalation or intranasal (IN) application offers an alternative to systemic delivery of mAbs for treating respiratory tract infections that is potentially more effective and convenient and less costly than IV administration owing to the dose-sparing effect of direct delivery to lung tissue.[66] Recent studies in small animals and nonhuman primates have suggested that aerosolizing antibodies may be more effective than systemic delivery in treating or preventing respiratory tract infections.[67–69] Aerosolized mAbs effectively prevented disease in rhesus macaques inoculated with the Delta variant of SARS-CoV-2.[66] A comparison of different routes of anti-influenza bNAbs in mice showed that local administration (ie, IN, aerosol) significantly decreases the amount of mAbs required for protection.[69]

SC Delivery

SC delivery of mAbs for oncology is effective, safe, well tolerated, and generally preferred by patients and health care providers and results in reduced drug delivery-related health care costs and resource use,[60,61,70] but it is relatively novel to infectious diseases. A population pharmacokinetics (PK) study compared the HIV bNAb VRC01 in pediatric and adult populations. At 20- to 40-mg/kg doses, infants demonstrated 2.79-times faster absorption rate and achieved faster suppressive plasma concentrations of HIV bNAb VRC01 compared to adults.[71] Additionally, IM and SC deliveries were shown to be equivalent in the VRC01 trial,[28] and SC administration was subsequently shown to be safe for newborns.[30] Respiratory viruses can also be therapeutically targeted with SC delivery, as has been reported in outpatients with Casirivimab and Imdevimab treatment of COVID-19.[61]

Oral Delivery

Patients prefer pills over injections,[71] leading to a tendency by health care professionals to avoid mAb therapies. Oral delivery provides a simple and noninvasive but challenging approach for mAbs owing to poor absorption and gastrointestinal degradation, limited drug loading, reduced systemic bioavailability, and delayed PK compared to parenteral dosing. To overcome these limitations, an oral pill was developed to deliver liquid formulations systemically, and, when delivered into the gastric submucosa of swine, it showed an excellent safety profile.[72] These promising results suggest that delivery of high doses of mAbs may be feasible, but oral delivery remains a challenge for newborns and very young children.

Delivery Through Breast Milk and Lacto-Therapeutics

Multiple studies have shown that SARS-CoV-2 spike-specific sIgA is induced in breast milk after COVID-19 infection or vaccination.[73] Improved infant stool neutralization of SARS-CoV-2 was observed following maternal vaccination, suggesting the potential utility of breast milk antibodies as COVID-19 therapeutics for infants.[74] In animal models, systemic administration of dimeric IgA (dIgA) that was passively transferred into the maternal milk and the stomach of suckling pups showed protection against rotavirus-induced diarrhea.[75] Therefore, use of breast milk antibodies could help harness early-life immunity against pathogens.

Use of Non-IgG Antibodies for Passive Immunization

IgA

Rapid IgA-mediated protection is essential against certain viral pathogens and emerging viruses with short therapeutic windows.[6] Considered fundamental for early mucosal defenses and protection against respiratory viral infections, IgA is primarily found as a monomer (ie, mIgA). dIgA and sIgA are 2 larger, more complex forms of IgA. When IgA was cloned from the B cells of 149 COVID-19-convalescent individuals, dIgA was 15-times more potent than mIgA against the same target.[76] Four neutralizing IgG mAbs showed increased avidity and more potent neutralization activity when engineered as dIgA and sIgA.[77] Both dIgA and sIgA versions neutralized the Omicron lineages BA.1, BA.2, and BA.4/5 up to 75-fold better than the IgG versions. In transgenic mice, IN-delivered dIgA reduced viral loads in the lungs and trachea, providing significant protection against Omicron BA.5.[78] These studies provide a rationale for considering the production and delivery of IgA.[79]

Immunoglobulin M

For flaviviruses, the multimeric structure of immunoglobulin M (IgM) may play a unique role in infection. An ultrapotent pentameric IgM specific for Zika virus protected mice from a lethal challenge, but, when expressed as monomeric IgG, it was less effective in controlling viremia.[80] Although IgM generally has a shorter half-life compared with IgG owing to its structural features, it can be long-lasting. Early and prolonged IgM neutralizing antibody responses have been observed in infections with West Nile and yellow fever viruses, as well as SARS-CoV-2.[81–84] Treatment with potent neutralizing IgM may also decrease the risk of congenital Zika virus transmission during pregnancy.

Polyspecific mAbs

Engineered polyspecific mAbs (PsMAbs) such as bi- and trispecific antibodies are genetically engineered proteins that simultaneously engage 2 or more different epitope types.[85] PsMAbs have several potential advantages for antiviral mAbs, such as blocking different pathways with unique or overlapping functions involved in pathogenesis,[86] interacting with 2 or more distinct antigens instead of 1, and reducing development and production costs compared to combinations of multiple single epitope antibodies.[87–89] Recently, the trispecific HIV antibody N6/αCD3-αCD28 was shown to reactivate and eliminate long-term ART-suppressed latently infected cells ex vivo.[90] A tetravalent bispecific antibody, A7A9 TVB, which neutralizes many SARS-CoV-2 variants, showed superior neutralization compared with a mixture of its parental mAbs.[91] The bispecific antibody CAP256.J3LS, consisting of the light chain of CAP256-VRC26.25 joined to the J3 nanobody, showed improved breadth, potency, half-life, and neutralizing properties compared with both antibody and nanobody parental components against over one-half of a 208-strain HIV panel.[92]

Current Challenges and the Future of Human mAb Therapy

The coordinated sharing of antibodies and related knowledge has significantly accelerated the discovery of antiviral antibody drugs. One notable outcome of these efforts is the Coronavirus Immunotherapeutic Consortium database, an open resource for researchers.[93] Although there are significant challenges to the widespread adoption of human mAbs for infectious disease therapy, the alternative of rapid and uncontrolled viral spread, as evidenced by the SARS-CoV-2 pandemic, underscores the critical need for proactive investment in outbreak preparedness. Given the uncertainty of future viral disease outbreaks, we must be prepared to protect our youngest and most vulnerable populations. mAbs represent a critical tool for pediatricians, offering an accessible, safe, and potent means to treat and prevent both endemic viral diseases and emerging viral threats in infants and children.

Despite the promise of mAbs for treating and preventing viral infections in pediatric populations, their widespread implementation is hindered by several challenges and limitations. Owing to physiological and immunological differences between adults and pediatric populations,[94] extensive pediatric-specific clinical trials are needed to establish safety, efficacy, and appropriate dosing regimens in pediatric populations; conducting these studies could be particularly challenging owing to ethical concerns and limited participant pools.[95,96] In addition, the rapid emergence of viral escape variants for SARS-CoV-2 and HIV renders monotherapy with single-target mAbs ineffective,[2,97] underscoring the importance of developing combination mAb therapies against viruses with higher rates of variants.[98] Additionally, the high cost of mAb development and large-scale production can limit accessibility,[99] a particular challenge in resource-limited settings where rapid responses to disease outbreaks are paramount.[100] In resource-limited settings, logistical issues such as the need for cold-chain storage and administration by health care professionals can further complicate drug delivery and distribution.[101] Additionally, repeated dosing of mAbs could result in ADA development, limiting long-term therapy's efficacy.[102] Addressing these challenges could be crucial in implementing mAb therapies for pediatric viral diseases, especially against pathogens for which vaccination options are limited or nonexistent.

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ABBREVIATIONS

AAV: adeno-associated virus
ADA: antidrug antibody
ART: antiretroviral therapy
bNAb: broadly neutralizing monoclonal antibody
CMV: cytomegalovirus
CNS: central nervous system
dIgA: dimeric immunoglobulin A
Env: envelope
EVD: Ebola virus disease
FcRn: neonatal Fc receptor
FDA: Food and Drug Administration
hACE2: human angiotensin-converting enzyme 2
HBV: heptatis B virus
HDV: heptatis D virus
HSV: herpes simplex virus
IgA: immunoglobulin A
IgG: immunoglobulin G
IgM: immunoglobulin M
IM: intramuscular
IN: intranasal
IV: intravenous
mAb: monoclonal antibody
mIgA: monomeric immunoglobulin A
mRNA: messenger RNA
NP: nanoparticle
PALM: Pamoja Tulinde Maisha
PK: pharmacokinetics
PsmAb: polyspecific monoclonal antibody
RSV: respiratory syncytial virus
SC: subcutaneous
SHIV: simian HIV
sIgA: secretory immunoglobulin A

REFERENCES

1. Crowe JE Jr. Human antibodies for viral infections. *Annu Rev Immunol.* 2022;40(1):349–386. PubMed doi: 10.1146/annurev-immunol-042718-041309
2. Crescioli S, Kaplon H, Chenoweth A, Wang L, Visweswaraiah J, Reichert JM. Antibodies to watch in 2024. *MAbs. 2024*;16(1): 2297450. PubMed doi: 10.1080/19420862.2023.2297450
3. Langel SN, Blasi M, Permar SR. Maternal immune protection against infectious diseases. *Cell Host Microbe.* 2022;30(5): 660–674. PubMed doi: 10.1016/j.chom.2022.04.007
4. Fouda GG, Martinez DR, Swamy GK, Permar SR. The impact of IgG transplacental transfer on early life immunity. *Immunohorizons.* 2018;2(1):14–25. PubMed doi: 10.4049/immunohorizons.1700057
5. Lorin V, Mouquet H. Efficient generation of human IgA monoclonal antibodies. *J Immunol Methods.* 2015;422:102–110. PubMed doi: 10.1016/j.jim.2015.04.010
6. Wallace AL, Schneider MI, Toomey JR, et al. IgA as a potential candidate for enteric monoclonal antibody therapeutics with improved gastrointestinal stability. *Vaccine.* 2020;38(47):7490–7497. PubMed doi: 10.1016/j.vaccine.2020.09.070
7. Marchant A, Sadarangani M, Garand M, et al. Maternal immunisation: collaborating with mother nature. *Lancet Infect Dis.* 2017;17 (7):e197–e208. PubMed doi: 10.1016/S1473-3099(17)30229-3
8. Saso A, Kampmann B. Maternal immunization: nature meets nurture. *Front Microbiol.* 2020;11:1499. PubMed doi: 10.3389/fmicb.2020.01499
9. Healy CM, Munoz FM, Rench MA, Halasa NB, Edwards KM, Baker CJ. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. *J Infect Dis.* 2004;190(2):335–340. PubMed doi: 10.1086/421033
10. Jacobson RM. Routine childhood vaccines given in the first 11 months of life. *Mayo Clin Proc.* 2020;95(2):395–405. PubMed doi: 10.1016/j.mayocp.2019.06.007
11. Jacobson RM. Routine childhood vaccines given from 1 through 18 years of age. *Mayo Clin Proc.* 2020;95(8):1780–1795. PubMed doi: 10.1016/j.mayocp.2020.06.004
12. Simões EAF, Bont L, Manzoni P, et al. Past, present and future approaches to the prevention and treatment of respiratory syncytial virus infection in children. *Infect Dis Ther.* 2018;7(1):87–120. PubMed doi: 10.1007/s40121-018-0188-z
13. Pantaleo G, Correia B, Fenwick C, Joo VS, Perez L. Antibodies to combat viral infections: development strategies and progress. *Nat Rev Drug Discov.* 2022;21(9):676–696. PubMed doi: 10.1038/s41573-022-00495-3
14. Taki E, Ghanavati R, Navidifar T, Dashtbin S, Heidary M, Moghadamnia M. Ebanga™: the most recent FDA-approved drug for treating Ebola. *Front Pharmacol.* 2023;14:1083429. PubMed doi: 10.3389/fphar.2023.1083429
15. Tshiani Mbaya O, Mukumbayi P, Mulangu S. Review: insights on current FDA-approved monoclonal antibodies against Ebola virus infection. *Front Immunol.* 2021;12:721328. PubMed doi: 10.3389/fimmu.2021.721328
16. Mulangu S, Dodd LE, Davey RT Jr, et al; PALM Writing Group; PALM Consortium Study Team. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med.* 2019;381(24): 2293–2303. PubMed doi: 10.1056/NEJMoa1910993
17. Saxena D, Kaul G, Dasgupta A, Chopra S. Atoltivimab/maftivimab/odesivimab (Inmazeb) combination to treat infection caused by Zaire ebolavirus. *Drugs Today (Barc).* 2021;57(8):483–490. PubMed doi: 10.1358/dot.2021.57.8.3280599
18. Deeks ED. Casirivimab/imdevimab: first approval. *Drugs.* 2021; 81(17):2047–2055. PubMed doi: 10.1007/s40265-021-01620-z
19. O'Brien MP, Forleo-Neto E, Sarkar N, et al; COVID-19 Phase 3 Prevention Trial Team. Effect of subcutaneous casirivimab and imdevimab antibody combination vs placebo on development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection: a randomized clinical trial. *JAMA.* 2022;327(5):432–441. PubMed doi: 10.1001/jama.2021.24939
20. Gupta A, Gonzalez-Rojas Y, Juarez E, et al; COMET-ICE Investigators. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med.* 2021;385(21):1941–1950. PubMed doi: 10.1056/NEJMoa2107934
21. Kaplon H, Crescioli S, Chenoweth A, Visweswaraiah J, Reichert JM. Antibodies to watch in 2023. *MAbs.* 2023;15(1):2153410. PubMed doi: 10.1080/19420862.2022.2153410
22. Holland TL, Ginde AA, Paredes R, et al; ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. *Lancet Respir Med.* 2022;10 (10):972–984. PubMed doi: 10.1016/S2213-2600(22)00215-6
23. Nguyen Y, Flahault A, Chavarot N, Melenotte C, Cheminant M, Deschamps P, et al. Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) for COVID-19 among 1112 severely immunocompromised patients. *Clin Microbiol Infect.* 2022;28(12): 1654 e1651–1654 e1654. PubMed doi: 10.1016/j.cmi.2022.07.015
24. Bock A. New guidance helps clinicians use pemivibart to protect immunocompromised patients from COVID-19. *JAMA.* 2024; 39269720(14):1127. PubMed doi: 10.1001/jama.2024.18589
25. Palivizumab , a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics.* 1998;102(3):531–537. PubMed doi: 10.1542/peds.102.3.531
26. Hammitt LL, Dagan R, Yuan Y, et al; MELODY Study Group. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N Engl J Med.* 2022;386(9):837–846. PubMed doi: 10.1056/NEJMoa2110275
27. Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023. Centers for Disease Control and Prevention. Updated August 25, 2023. Accessed March 17, 2025. https://www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm
28. Corey L, Gilbert PB, Juraska M, et al; HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams. Two randomized trials of neutralizing antibodies to prevent HIV-1 acquisition. *N Engl J Med.* 2021;384 (11):1003–1014. PubMed doi: 10.1056/NEJMoa2031738

29. Hsu DC, Mellors JW, Vasan S. Can broadly neutralizing HIV-1 antibodies help achieve an ART-free remission? *Front Immunol.* 2021; 12:710044. PubMed doi: 10.3389/fimmu.2021.710044

30. Cunningham CK, McFarland EJ, Morrison RL, et al; IMPAACT P1112 team. Safety, tolerability, and pharmacokinetics of the broadly neutralizing human immunodeficiency virus (HIV)-1 monoclonal antibody VRC01 in HIV-exposed newborn infants. *J Infect Dis.* 2020;222(4):628–636. PubMed doi: 10.1093/infdis/jiz532

31. Hessell AJ, Jaworski JP, Epson E, et al. Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques. *Nat Med.* 2016;22(4):362–368. PubMed doi: 10.1038/nm.4063

32. Shapiro MB, Cheever T, Malherbe DC, et al. Single-dose bNAb cocktail or abbreviated ART post-exposure regimens achieve tight SHIV control without adaptive immunity. *Nat Commun.* 2020;11(1):70. PubMed doi: 10.1038/s41467-019-13972-y

33. Bamford A, Foster C, Lyall H. Infant feeding: emerging concepts to prevent HIV transmission. *Curr Opin Infect Dis.* 2024;37(1):8–16. PubMed doi: 10.1097/QCO.0000000000000986

34. Sneller MC, Blazkova J, Justement JS, et al. Combination anti-HIV antibodies provide sustained virological suppression. *Nature.* 2022;606(7913):375–381. PubMed doi: 10.1038/s41586-022-04797-9

35. Shapiro RL, Ajibola G, Maswabi K, et al. Broadly neutralizing antibody treatment maintained HIV suppression in children with favorable reservoir characteristics in Botswana. *Sci Transl Med.* 2023;15(703):eadh0004. PubMed doi: 10.1126/scitranslmed.adh0004

36. Ishida JH, Burgess T, Derby MA, et al. Phase 1 randomized, double-blind, placebo-controlled study of RG7667, an anticytomegalovirus combination monoclonal antibody therapy, in healthy adults. *Antimicrob Agents Chemother.* 2015;59(8):4919–4929. PubMed doi: 10.1128/AAC.00523-15

37. Ishida JH, Patel A, Mehta AK, et al. Phase 2 randomized, double-blind, placebo-controlled trial of RG7667, a combination monoclonal antibody, for prevention of cytomegalovirus infection in high-risk kidney transplant recipients. *Antimicrob Agents Chemother.* 2017;61(2):e01794–16. PubMed doi: 10.1128/AAC.01794-16

38. Struble EB, Murata H, Komatsu T, Scott D. Immune prophylaxis and therapy for human cytomegalovirus infection. *Int J Mol Sci.* 2021; 22(16):8728. PubMed doi: 10.3390/ijms22168728

39. Grange ZL, Goldstein T, Johnson CK, et al; Expert Panel; PREDICT Consortium; University of Edinburgh Epigroup members those who wish to remain anonymous. Ranking the risk of animal-to-human spillover for newly discovered viruses. *Proc Natl Acad Sci U S A.* 2021;118(15):e2002324118. PubMed doi: 10.1073/pnas.2002324118

40. Cross RW, Heinrich ML, Fenton KA, et al. A human monoclonal antibody combination rescues nonhuman primates from advanced disease caused by the major lineages of Lassa virus. *Proc Natl Acad Sci U S A.* 2023;120(34):e2304876120. PubMed doi: 10.1073/pnas.2304876120

41. Hiatt A, Whaley KJ, Zeitlin L. Plant-derived monoclonal antibodies for prevention and treatment of infectious disease. *Microbiol Spectr.* 2014;2(1):AID-0004–AID-2012. PubMed doi: 10.1128/microbiolspec.AID-0004-2012

42. Budzianowski J. Tobacco against Ebola virus disease. *Przegl Lek.* 2015;72(10):567–571. PubMed

43. Rosenberg YJ, Jiang X, Cheever T, et al. Protection of newborn macaques by plant-derived HIV broadly neutralizing antibodies: a model for passive immunotherapy during breastfeeding. *J Virol.* 2021;95(18):e0026821. PubMed doi: 10.1128/JVI.00268-21

44. Grandits M, Grünwald-Gruber C, Gastine S, et al. Improving the efficacy of plant-made anti-HIV monoclonal antibodies for clinical use. *Front Plant Sci.* 2023;14:1126470. PubMed doi: 10.3389/fpls.2023.1126470

45. Anand SP, Ding S, Tolbert WD, et al. Enhanced ability of plant-derived PGT121 glycovariants to eliminate HIV-1-infected cells. *J Virol.* 2021;95(18):e0079621. PubMed doi: 10.1128/JVI.00796-21

46. Rosenberg YJ, Ordonez T, Khanwalkar US, et al. Evidence for the role of a second fc-binding receptor in placental IgG transfer in nonhuman primates. *MBio.* 2023;14(2):e0034123. PubMed doi: 10.1128/mbio.00341-23

47. Klimyuk V, Pogue G, Herz S, Butler J, Haydon H. Production of recombinant antigens and antibodies in Nicotiana benthamiana using 'magnifection' technology: GMP-compliant facilities for small- and large-scale manufacturing. *Curr Top Microbiol Immunol.* 2014;375:127–154. PubMed doi: 10.1007/82_2012_212

48. Naso MF, Tomkowicz B, Perry WL III, Strohl WR. Adeno-associated virus (AAV) as a vector for gene therapy. *BioDrugs.* 2017;31(4): 317–334. PubMed doi: 10.1007/s40259-017-0234-5

49. Rghei AD, Yates JGE, Lopes JA, et al. Antibody-based protection against respiratory syncytial virus in mice and their offspring through vectored immunoprophylaxis. *Gene Ther.* 2023. PubMed

50. Sun CP, Chiu CW, Wu PY, et al. Development of AAV-delivered broadly neutralizing anti-human ACE2 antibodies against SARS-CoV-2 variants. *Mol Ther.* 2023;31(11):3322–3336. PubMed doi: 10.1016/j.ymthe.2023.09.002

51. Johnson PR, Schnepp BC, Zhang J, et al. Vector-mediated gene transfer engenders long-lived neutralizing activity and protection against SIV infection in monkeys. *Nat Med.* 2009;15(8):901–906. PubMed doi: 10.1038/nm.1967

52. Phelps M, Balazs AB. Contribution to HIV prevention and treatment by antibody-mediated effector function and advances in broadly neutralizing antibody delivery by vectored immunoprophylaxis. *Front Immunol.* 2021;12:734304. PubMed doi: 10.3389/fimmu.2021.734304

53. Hahn PA, Martins MA. Adeno-associated virus-vectored delivery of HIV biologics: the promise of a "single-shot" functional cure for HIV infection. *J Virus Erad.* 2023;9(1):100316. PubMed doi: 10.1016/j.jve.2023.100316

54. Pagant S, Liberatore RA. In vivo electroporation of plasmid DNA: a promising strategy for rapid, inexpensive, and flexible delivery of anti-viral monoclonal antibodies. *Pharmaceutics.* 2021;13(11): 1882. PubMed doi: 10.3390/pharmaceutics13111882

55. Van Hoecke L, Roose K. How mRNA therapeutics are entering the monoclonal antibody field. *J Transl Med.* 2019;17(1):54. PubMed doi: 10.1186/s12967-019-1804-8

56. Pardi N, Muramatsu H, Weissman D, Karikó K. In vitro transcription of long RNA containing modified nucleosides. *Methods Mol Biol.* 2013;969:29–42. PubMed doi: 10.1007/978-1-62703-260-5_2

57. Weissman D, Pardi N, Muramatsu H, Karikó K. HPLC purification of in vitro transcribed long RNA. *Methods Mol Biol.* 2013;969:43–54. PubMed doi: 10.1007/978-1-62703-260-5_3

58. Tai W, Yang K, Liu Y, et al. A lung-selective delivery of mRNA encoding broadly neutralizing antibody against SARS-CoV-2 infection. *Nat Commun.* 2023;14(1):8042. PubMed doi: 10.1038/s41467-023-43798-8

59. Sánchez-Félix M, Burke M, Chen HH, Patterson C, Mittal S. Predicting bioavailability of monoclonal antibodies after subcutaneous administration: open innovation challenge. *Adv Drug Deliv Rev.* 2020;167:66–77. PubMed doi: 10.1016/j.addr.2020.05.009

60. Bittner B, Richter W, Schmidt J. Subcutaneous administration of biotherapeutics: an overview of current challenges and opportunities. *BioDrugs.* 2018;32(5):425–440. PubMed doi: 10.1007/s40259-018-0295-0

61. McCreary EK, Bariola JR, Wadas RJ, et al. Association of subcutaneous or intravenous administration of casirivimab and imdevimab monoclonal antibodies with clinical outcomes in adults with COVID-19. *JAMA Netw Open.* 2022;5(4):e226920. PubMed doi: 10.1001/jamanetworkopen.2022.6920

62. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. *Nat Med.* 2013;19(12):1584–1596. PubMed doi: 10.1038/nm.3407

63. Daneman R, Prat A. The blood-brain barrier. *Cold Spring Harb Perspect Biol.* 2015;7(1):a020412. PubMed doi: 10.1101/cshperspect.a020412

64. Wen J, Cheever T, Wang L, et al. Improved delivery of broadly neutralizing antibodies by nanocapsules suppresses SHIV infection in the CNS of infant rhesus macaques. *PLoS Pathog.* 2021;17(7):e1009738. PubMed doi: 10.1371/journal.ppat.1009738

65. Hersh DS, Wadajkar AS, Roberts N, et al. Evolving drug delivery strategies to overcome the blood brain barrier. *Curr Pharm Des.* 2016;22(9):1177–1193. PubMed doi: 10.2174/1381612822666151221150733

66. Streblow DN, Hirsch AJ, Stanton JJ, et al. Aerosol delivery of SARS-CoV-2 human monoclonal antibodies in macaques limits viral replication and lung pathology. *Nat Commun.* 2023;14(1):7062. PubMed doi: 10.1038/s41467-023-42440-x

67. Piepenbrink MS, Park JG, Oladunni FS, et al. Therapeutic activity of an inhaled potent SARS-CoV-2 neutralizing human monoclonal antibody in hamsters. *Cell Rep Med.* 2021;2(3):100218. PubMed doi: 10.1016/j.xcrm.2021.100218

68. Piepenbrink MS, Park JG, Deshpande A, et al. Potent universal beta-coronavirus therapeutic activity mediated by direct respiratory administration of a spike S2 domain-specific human neutralizing monoclonal antibody. *PLoS Pathog.* 2022;18(7):e1010691. PubMed doi: 10.1371/journal.ppat.1010691

69. Wolters RM, Ferguson JA, Nuñez IA, et al. Isolation of human antibodies against influenza B neuraminidase and mechanisms of protection at the airway interface. *Immunity.* 2024;57(6):1413–1427.e9. PubMed doi: 10.1016/j.immuni.2024.05.002

70. Pivot X, Gligorov J, Müller V, et al; PrefHer Study Group. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. *Ann Oncol.* 2014;25(10):1979–1987. PubMed doi: 10.1093/annonc/mdu364

71. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ.* 2011;12(3):219–230. PubMed doi: 10.1007/s10198-010-0224-8

72. Abramson A, Frederiksen MR, Vegge A, et al. Oral delivery of systemic monoclonal antibodies, peptides and small molecules using gastric auto-injectors. *Nat Biotechnol.* 2022;40(1):103–109. PubMed doi: 10.1038/s41587-021-01024-0

73. Shook LL, Atyeo CG, Yonker LM, et al. Durability of anti-spike antibodies in infants after maternal COVID-19 vaccination or natural infection. *JAMA.* 2022;327(11):1087–1089. PubMed doi: 10.1001/jama.2022.1206

74. Stafford LS, Valcarce V, Henry M, et al. Detection of SARS-CoV-2 IgA and IgG in human milk and breastfeeding infant stool 6 months after maternal COVID-19 vaccination. *J Perinatol.* 2023;43(6):775–781. PubMed doi: 10.1038/s41372-022-01581-5

75. Langel S, Steppe J, Chang J, et al. Protective transfer: maternal passive immunization with a rotavirus-neutralizing dimeric IgA protects against rotavirus disease in suckling neonates. *bioRxiv.* 2021:2021.2009.2021.461116.

76. Wang Z, Lorenzi JCC, Muecksch F, et al. Enhanced SARS-CoV-2 neutralization by dimeric IgA. *Sci Transl Med.* 2021;13(577):eabf1555. PubMed doi: 10.1126/scitranslmed.abf1555

77. Marcotte H, Cao Y, Zuo F, et al. Conversion of monoclonal IgG to dimeric and secretory IgA restores neutralizing ability and prevents infection of omicron lineages. *Proc Natl Acad Sci U S A.* 2024;121(3):e2315354120. PubMed doi: 10.1073/pnas.2315354120

78. Sun L, Kallolimath S, Palt R, et al. Increased in vitro neutralizing activity of SARS-CoV-2 IgA1 dimers compared to monomers and IgG. *Proc Natl Acad Sci U S A.* 2021;118(44):e2107148118. PubMed doi: 10.1073/pnas.2107148118

79. Virdi V, Juarez P, Boudolf V, Depicker A. Recombinant IgA production for mucosal passive immunization, advancing beyond the hurdles. *Cell Mol Life Sci.* 2016;73(3):535–545. PubMed doi: 10.1007/s00018-015-2074-0

80. Singh T, Hwang KK, Miller AS, et al. A Zika virus-specific IgM elicited in pregnancy exhibits ultrapotent neutralization. *Cell.* 2022;185(25):4826–4840.e17. PubMed doi: 10.1016/j.cell.2022.10.023

81. Murray KO, Garcia MN, Yan C, Gorchakov R. Persistence of detectable immunoglobulin M antibodies up to 8 years after infection with West Nile virus. *Am J Trop Med Hyg.* 2013;89(5):996–1000. PubMed doi: 10.4269/ajtmh.13-0232

82. Stone M, Bakkour S, Lanteri MC, et al; NHLBI Recipient Epidemiology Donor Evaluation Study REDS-III Program. Zika virus

RNA and IgM persistence in blood compartments and body fluids: a prospective observational study. *Lancet Infect Dis.* 2020;20(12): 1446–1456. PubMed doi: 10.1016/S1473-3099(19)30708-X

83. Wec AZ, Haslwanter D, Abdiche YN, et al. Longitudinal dynamics of the human B cell response to the yellow fever 17D vaccine. *Proc Natl Acad Sci U S A.* 2020;117(12):6675–6685. PubMed doi: 10.1073/pnas.1921388117

84. Gasser R, Cloutier M, Prévost J, et al. Major role of IgM in the neutralizing activity of convalescent plasma against SARS-CoV-2. *Cell Rep.* 2021;34(9):108790. PubMed doi: 10.1016/j.celrep.2021.108790

85. Fan G, Wang Z, Hao M, Li J. Bispecific antibodies and their applications. *J Hematol Oncol.* 2015;8(1):130. PubMed doi: 10.1186/s13045-015-0227-0

86. Zhang X, Yang Y, Fan D, Xiong D. The development of bispecific antibodies and their applications in tumor immune escape. *Exp Hematol Oncol.* 2017;6(1):12. PubMed doi: 10.1186/s40164-017-0072-7

87. Runcie K, Budman DR, John V, Seetharamu N. Bi-specific and tri-specific antibodies- the next big thing in solid tumor therapeutics. *Mol Med.* 2018;24(1):50. PubMed doi: 10.1186/s10020-018-0051-4

88. Sandeep, Shinde SH, Pande AH. Polyspecificity - an emerging trend in the development of clinical antibodies. *Mol Immunol.* 2023;155: 175–183. PubMed doi: 10.1016/j.molimm.2023.02.005

89. Nordstrom JL, Ferrari G, Margolis DM. Bispecific antibody-derived molecules to target persistent HIV infection. *J Virus Erad.* 2022;8 (3):100083. PubMed doi: 10.1016/j.jve.2022.100083

90. Promsote W, Xu L, Hataye J, et al. Trispecific antibody targeting HIV-1 and T cells activates and eliminates latently-infected cells in HIV/SHIV infections. *Nat Commun.* 2023;14(1):3719. PubMed doi: 10.1038/s41467-023-39265-z

91. Chiyyeadu A, Asgedom G, Bruhn M, et al. A tetravalent bispecific antibody outperforms the combination of its parental antibodies and neutralizes diverse SARS-CoV-2 variants. *Clin Immunol.* 2024; 260:109902. PubMed doi: 10.1016/j.clim.2024.109902

92. Zhang B, Gorman J, Kwon YD, et al. Bispecific antibody CAP256.J3LS targets V2-apex and CD4-binding sites with high breadth and potency. *MAbs.* 2023;15(1):2165390. PubMed doi: 10.1080/19420862.2023.2165390

93. Mahita J, Ha B, Gambiez A, Schendel SL, Li H, Hastie KM, et al. Coronavirus Immunotherapeutic Consortium Database. *Database (Oxford).* 2023;2023.

94. Kovalenko P, Kamal MA, Davis JD, et al. Base and covariate population pharmacokinetic analyses of dupilumab in adolescents and children ≥6 to <12 years of age using phase 3 data. *Clin Pharmacol Drug Dev.* 2021;10(11):1345–1357. PubMed doi: 10.1002/cpdd.986

95. Boat T, Fields MJ, eds. *Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.* National Academies Press; 2012.

96. Laventhal N, Tarini BA, Lantos J. Ethical issues in neonatal and pediatric clinical trials. *Pediatr Clin North Am.* 2012;59(5): 1205–1220. PubMed doi: 10.1016/j.pcl.2012.07.007

97. Callaway HM, Hastie KM, Schendel SL, et al. Bivalent intra-spike binding provides durability against emergent omicron lineages: results from a global consortium. *Cell Rep.* 2023;42(1):112014. PubMed doi: 10.1016/j.celrep.2023.112014

98. Berendam SJ, Styles TM, Morgan-Asiedu PK, et al. Systematic assessment of antiviral potency, breadth, and synergy of triple broadly neutralizing antibody combinations against simian-human immunodeficiency viruses. *J Virol.* 2021;95(3):e01667–20. PubMed doi: 10.1128/JVI.01667-20

99. Tang L, Persky AM, Hochhaus G, Meibohm B. Pharmacokinetic aspects of biotechnology products. *J Pharm Sci.* 2004;93(9): 2184–2204. PubMed doi: 10.1002/jps.20125

100. Vardavas C, Nikitara K, Zisis K, et al. Cost-effectiveness of emergency preparedness measures in response to infectious respiratory disease outbreaks: a systematic review and econometric analysis. *BMJ Open.* 2021;11(4):e045113. PubMed doi: 10.1136/bmjopen-2020-045113

101. Branch-Elliman W, Safdar N, Nelson R. Economic considerations in infectious diseases emergency response preparedness: it's all about the point of view. *Clin Infect Dis.* 2021;72(1):148–152. PubMed doi: 10.1093/cid/ciaa541

102. Gardner MR, Fetzer I, Kattenhorn LM, et al. Anti-drug antibody responses impair prophylaxis mediated by AAV-delivered HIV-1 broadly neutralizing antibodies. *Mol Ther.* 2019;27(3):650–660. PubMed doi: 10.1016/j.ymthe.2019.01.004

103. Dougan M, Nirula A, Azizad M, et al; BLAZE-1 Investigators. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med.* 2021;385(15):1382–1392. PubMed doi: 10.1056/NEJMoa2102685

104. Cohen YZ, Butler AL, Millard K, et al. Safety, pharmacokinetics, and immunogenicity of the combination of the broadly neutralizing anti-HIV-1 antibodies 3BNC117 and 10–1074 in healthy adults: a randomized, phase 1 study. *PLoS One.* 2019;14(8):e0219142. PubMed doi: 10.1371/journal.pone.0219142

105. Blank A, Hohmann N, Dettmer M, et al. First-in-human, randomized, double-blind, placebo-controlled, dose escalation trial of the anti-herpes simplex virus monoclonal antibody HDIT101 in healthy volunteers. *Clin Transl Sci.* 2022;15(10):2366–2377. PubMed doi: 10.1111/cts.13365

106. Degasperi E, Anolli MP, Lampertico P. Bulevirtide for patients with compensated chronic hepatitis delta: a review. *Liver Int.* 2023; 43(S1)(suppl 1):80–86. PubMed doi: 10.1111/liv.15389

107. August A, Attarwala HZ, Himansu S, et al. A phase 1 trial of lipid-encapsulated mRNA encoding a monoclonal antibody with neutralizing activity against Chikungunya virus. *Nat Med.* 2021;27(12): 2224–2233. PubMed doi: 10.1038/s41591-021-01573-6