# Promising approaches for the treatment and prevention of viral respiratory illnesses

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Viral respiratory tract infections are the most common human ailments, leading to enormous health and economic burden. Hundreds of viral species and subtypes have been associated with these conditions, with influenza viruses, respiratory syncytial virus, and rhinoviruses being the most frequent and with the highest burden. When considering prevention or treatment of viral respiratory tract infections, potential targets include the causative pathogens themselves but also the immune response, disease transmission, or even just the symptoms. Strategies targeting all these aspects are developing concurrently, and several novel and promising approaches are emerging. In this perspective we overview the entire range of options and highlight some of the most promising approaches, including new antiviral agents, symptomatic or immunomodulatory drugs, the re-emergence of natural remedies, and vaccines and public health policies toward prevention. Wide-scale prevention through immunization appears to be within reach for respiratory syncytial virus and promising for influenza virus, whereas additional effort is needed in regard to rhinovirus, as well as other respiratory tract viruses. (J Allergy Clin Immunol 2017;140:921-32.)

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The respiratory system is one of the main portals of entry for human pathogens. Although precise calculations are challenging because of methodology and inherent variability, the number of

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| Abbreviations used | |
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| COPD: | Chronic obstructive pulmonary disease |
| HA: | Hemagglutinin |
| ICAM-1: | Intercellular adhesion molecule 1 |
| IFV: | Influenza virus |
| NAI: | Neuraminidase inhibitor |
| PIV: | Parainfluenza Virus |
| RSV: | Respiratory syncytial virus |
| RTI: | Respiratory tract infection |
| SARS: | Severe acute respiratory syndrome |
| SPM: | Specialized proresolving lipid mediator |
| TLR: | Toll-like receptor |
| VLP: | Virus-like particle |
| vRTI: | Viral respiratory tract infection |

potentially infectious viruses we breathe every day can be in the range of many thousands.[1] Thus it is not surprising that viral respiratory tract infections (vRTI) are the most common human diseases, leading to enormous health and economic burden.[2] A wide variety of conditions fall within the spectrum of vRTIs. Many of these are by themselves major public health concerns: influenza, acute bronchiolitis, viral pneumonia, and common colds. Together with their downstream effects (ie, acute exacerbations of asthma and chronic obstructive pulmonary disease [COPD]), all result in vast amounts of morbidity, mortality, and health care costs, including primary care visits, hospitalizations, and deaths but also inappropriate use of antibiotics, loss of productivity, and effects on quality of life.[3-5] Respiratory tract viruses have been isolated and characterized during the last century, starting from influenza virus (IFV) in the 1930s and followed by respiratory syncytial virus (RSV), coronaviruses, adenoviruses, and rhinoviruses in the 1950 to 1960s; nevertheless, "new" viruses or subtypes, such as human metapneumovirus or rhinovirus C, are still being identified.[6,7] Even though several of these viruses are typically associated with a clinicopathologic entity (eg, IFV with influenza, RSV with bronchiolitis, and rhinovirus with the common cold), there is also extensive overlap, and it is often difficult to identify the etiologic agent based on clinical grounds alone.[8] Consequently, when considering prevention and treatment of vRTI, potential targets include specific pathogens, the immune response, disease transmission, or just symptoms.

Here we provide an overview of the options and highlight some of the most promising approaches in vRTI treatment, including symptomatic medication, immunomodulatory drugs, antiviral agents, and natural products, as well as in vRTI

prevention, ranging from vaccines to immunostimulators and public health policies. This is a vast field, and thus we emphasize advances that might be relevant in tackling the virus-induced aspects of allergic disease, such as asthma exacerbations.

## TREATMENT
### Symptom medications

Most mild viral respiratory illnesses are managed symptomatically with over-the-counter medications, such as nasal decongestants, antipyretics/analgesics, antitussives, or expectorants, on which no major improvements are foreseen. Although generally well tolerated for short-term relief, some agents can have adverse effects, especially in young children. Therefore the US Food and Drug Administration has issued a warning against the use of over-the-counter cough and cold products in children younger than 4 years of age.[9] Furthermore, the use of decongestants should be minimized, especially in children,[10] whereas codeine has been restricted in children by the European Medical Agency since 2015.[11] Selective COX inhibitors, such as celecoxib and mesalazine, have been widely used in clinics for their antipyretic, analgesic, and anti-inflammatory properties in patients with airway diseases,[12] whereas their combination with neuraminidase inhibitors (NAIs) has significantly improved the survival of IFV-infected mice.[13]

Recent studies have revealed a new genus of specialized proresolving lipid mediators (SPMs), including lipoxins, resolvins, protectins, and maresins, enhancing anti-inflammatory, antiviral, and proresolving mechanisms.[14] Medications interfering with prostanoid and lipoxygenase biosynthesis and signaling, thus affecting resolution and SPM switching, such as aspirin and nonsteroidal anti-inflammatory drugs, have been suggested as potential agents modulating antiviral immunity,[15,16] whereas several SPM resolution agonists are in clinical development programs.

Symptomatic relief can also be sought in severe cases. Noninvasive ventilation can reduce respiratory distress in patients with acute viral bronchiolitis.[17] Very recently, new devices delivering totally conditioned gas (37°C at 100% relative humidity) through a very high-flow nasal cannula (up to 60 L/min) have been indicated for bronchiolitis mainly as rescue therapy to reduce the need for admission to the intensive care unit.[18]

### Immune and antiviral pathway modulators

Although vRTIs are most often short-lived events, impaired antiviral clearance and/or activation of inflammatory pathways lead to important downstream complications, such as exacerbations of asthma or COPD.[19] The immune and antiviral mechanisms leading from infection to exacerbation have been scrutinized,[20] and medications targeting these pathways are being evaluated as promising candidates to reduce disease burden. Impaired interferon production has been observed in patients with various obstructive respiratory diseases, potentially contributing to enhanced susceptibility to and/or severity of virus-induced acute airway exacerbations.[21] Although inhaled IFN-β supplementation has not shown a clear effect in preventing virus-induced symptom worsening in patients with mild asthma, subanalysis in patients with severe asthma showed a protective effect.[22] Interestingly, in an experimental model exogenous administration of IFN-λ1 induced a strong and more prolonged antiviral state than IFN-β.[23] Moreover, experimental studies in an allergic asthma model showed that IFN-λ supplementation

enhanced $T_H1$ immunity by inducing IFN-γ and suppressing $T_H2$ and $T_H17$ responses through modulation of lung CD11c$^+$ dendritic cell function.[24,25] Novel antibody-based drugs with antirhinovirus and immunomodulatory effects act through IFN-β induction and suppression of $T_H2$ responses in experimental models.[26]

The prototype synthetic Toll-like receptor (TLR) 4 antagonist Eritoran (E5564) and anti-TLR4 IgG therapy have been shown to block IFV lethality in mice by suppressing lung pathology, clinical symptoms, and viral titers.[27,28] Other innate immune receptors, such as TLR2, also have potential for host-targeted therapeutic approaches.[21]

Interestingly, omalizumab, an anti-IgE mAb, prevents asthma exacerbations either by decreasing the duration and shedding of rhinovirus infection or by blocking the synergistic effect of rhinovirus infection on allergy.[29,30] Because high-affinity IgE receptor (FcεRI) cross-linking on plasmacytoid dendritic cells reduces IFN-α responses after viral infections, it is plausible that omalizumab enhances virus-induced IFN-α production in asthmatic patients, thus limiting virus spreading and infection severity.[31]

"Severe cytokine storm," an entity associated with markedly higher levels of proinflammatory cytokines, has been associated with severe influenza infections; immunomodulatory agents have been proposed as potential therapeutic strategies.[32] Peroxisome proliferator-activated receptor γ agonists (eg, rosiglitazone and pioglitazone) are critical regulators of inflammation and have been promising in improving the clinical outcome of severe influenza infections.[33] Their development slowed down from 2000 to 2005 because of possible cardiovascular side effects; however, in 2015, the US Food and Drug Administration lifted restrictions based on new safety data.[34] Moreover, sphingosine-1-phosphate receptor 1 agonists 1, which are located mainly on pulmonary endothelial cells, exhibit cytokine storm–blunting activity by suppressing both innate cellular and cytokine/chemokine responses, particularly when combined with antiviral agents.[35]

There is increasing interest in the use of macrolides to treat or prevent virus-induced asthma exacerbations, although microbial resistance remains a major hurdle, and therefore they are not currently indicated. Early *in vivo* evidence suggested that azithromycin has anti-inflammatory and antiviral effects through induction of interferon-stimulated gene mRNA expression and reduced viral replication and release in patients with asthma and chronic obstructive lung disease.[36,37] In a randomized clinical trial including wheezing preschool-aged children, early azithromycin administration significantly reduced the likelihood of a severe lower respiratory tract infection.[38] Novel macrolides (*Mycobacterium avium* complex 5) with anti-inflammatory, antibacterial, and, more importantly, interferon-augmenting activity in airway epithelium have been identified.[39] Finally, *in vitro* models have demonstrated that α$_1$-antitrypsin exerts anti-inflammatory effects in airway epithelial cells from rhinovirus-infected patients with COPD, potentially through inhibition on caspase-1 activity, suggesting α$_1$-antitrypsin as a potential anti-inflammatory agent.[40]

### Antivirals

vRTIs are usually characterized by an acute and self-limiting course, which means that the peak of viral replication usually precedes or parallels the appearance of clinical symptoms. As a result, the time window from verification and/or typing of the pathogen, allowing a specific therapeutic intervention, is
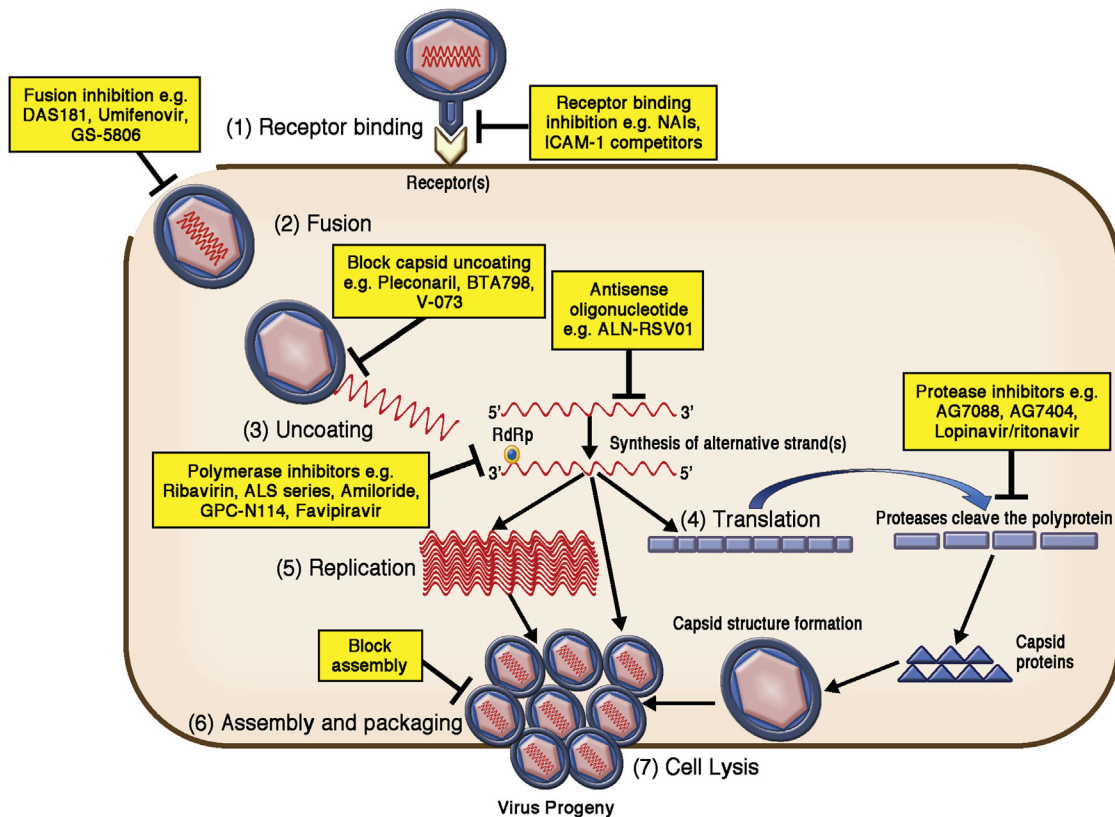
**FIG 1.** Viral infection cycle and antiviral medication targets. New antiviral agents have been designed to target most aspects of the viral lifecycle, including receptor binding, fusion, uncoating, translation, and replication. Examples of agents under development are listed alongside each function.

extremely narrow. Additional challenges need to be overcome, such as the structural variation of viral proteins, multiple genotypes, and high mutation rates. Accordingly, only a very limited number of specific antiviral drugs are currently licensed, and promising approaches mostly aim to control severe complications, reduce disease burden, or transmission. Antiviral strategies aim to block particular stages of the viral lytic cycle, including attachment and entry to the host cell, replication, transcription, and translation (Fig 1).[41]

In principle, preventing a viral pathogen from entering the host cell represents the ideal antiviral strategy because the virus is not allowed to "hack" the host: IFV NAIs have been successfully used to competitively bind the sialic acid–binding pocket of neuroaminidase and are good examples of this approach. Oseltamivir and zanamivir have been used as anti-flu therapies,[42] whereas laninamivir and peramivir show antiviral activity against wild-type but also against oseltamivir-resistant and NAI-resistant strains, respectively.[43,44] The nonenveloped rhinoviruses use viral capsid structures to bind their receptors (intercellular adhesion molecule 1 [ICAM-1], low-density lipoprotein receptor, and cadherin-related family member 3).[45] Even though more than 50% of rhinovirus strains use ICAM-1 for cell entry, an ICAM-1 competitor, tremacamra, did not make it into the clinic despite initially promising results,[46] and no anti–ICAM-1 drugs are currently available.

Another strategy is to prevent capsid uncoating and further assembly of new virions. This strategy has been successfully used against IFV and severe acute respiratory syndrome (SARS)–coronavirus, which use a class I fusion mechanism.[47] DAS181

(Fludase, NexBio, Inc, San Diego, Calif) is a fusion construct that cleaves the sialic acid receptors on host cells, and its antiviral spectrum includes IFV and parainfluenza viruses (PIVs).[48] Nonenveloped viruses, such as rhinovirus, release their genomes through a conformational shift of the capsid proteins accompanied by an expansion of the viral shell along with the opening of symmetry-related channels (pores) from which the genome is released (virus uncoating).[49,50] Various capsid-binding compounds against rhinoviruses have been tested (R and WIN series) without ultimate success.[51] Pleconaril, BTA798 (vapendavir), and pocapavir (V-073) are still under clinical evaluation.[52] Of note, a major drawback of capsid binders is the rapid emergence of resistance.[52] Several fusion inhibitors are being developed for the treatment of RSV and have been reviewed elsewhere.[3,53]

Because of their limited coding capacity, viruses rely on the production of polyproteins that need to be cleaved into functional subunits by viral proteases. The enterovirus polyprotein is cleaved by a family of cysteine proteases, which are highly conserved among different subtypes but lack homology with human proteases. Unfortunately, after failed attempts with ruprintrivir (AG7088) and AG7404, which showed antiviral activity *in vitro* but not *in vivo*, no similar agents are being pursued currently.[52] The use of HIV protease inhibitors, such as lopinavir and ritonavir, in patients with SARS has not been associated with any proved benefit, although retrospective studies reported that severe outcomes (acute respiratory distress syndrome or death) occurred less often in those receiving a combination of lopinavir/ritonavir and ribavirin with corticosteroids.[54]

Polymerase inhibitors (nucleoside/nucleotide analogs) act by leading to termination of the polynucleotide chain elongation. Ribavirin has been used for the treatment of severe RSV-related disease in high-risk infants and in combination with protease inhibitors in patients with SARS, but its use has been limited because of cost and unconfirmed efficacy toward severe outcomes. ALS-008176 is a promising orally bioavailable prodrug of the novel RSV replication inhibitor ALS-008112 (a cytidine nucleoside analogue), which inhibits RSV replication.[55] Other promising polymerase inhibitors include amiloride (competitive inhibitor of coxsackie virus B3 RNA polymerase) and GPC-N114 (multiple genera in Picornaviridae) but are still in the early stages.[52] Favipiravir (T-705) is an antiviral drug that selectively inhibits the RNA-dependent RNA polymerase of IFV, as well as several other viruses.[56]

Umifenovir has been shown to inhibit various human respiratory RNA viruses, including several strains of IFV-A and IFV-B, RSV, PIV3, and rhinovirus B14. It also demonstrates inhibitory activity against other viruses, enveloped or not, responsible for emerging or globally prevalent infectious diseases.[57]

Finally, a most promising but also challenging antiviral approach is through use of antisense oligonucleotides. Antisense oligonucleotides are single-stranded deoxyribonucleotide oligomers with a sequence complementary to a target mRNA transcript. Thus viral genomic RNA or viral mRNA can be targeted directly. Antisense technology and RNA interference have been experimentally explored in targeting measles virus, SARS-coronavirus, coxsackievirus, enteroviruses and rhinoviruses, PIV, human metapneumovirus, IFV, and RSV genomes.[58,59] The RNA inhibition–based therapeutic that is furthest advanced in clinical development at this time is against RSV.[58] ALN-RSV01 is an unmodified, naked, small interfering RNA designed to inhibit the replication of RSV by interrupting the synthesis of the viral N protein. The sequence of the target is well conserved throughout naturally occurring RSV A and B genotypes.[58]

In all, new antivirals are being explored continuously, particularly for life-threatening viruses, such as IFV (influenza) and RSV. Rhinoviruses, even though simple in terms of genome organization and protein coding, have proved extremely difficult to target, mostly because of their high diversity and immune-evading strategies but also to some extent to the underestimation of rhinovirus infection clinical consequences.

### Natural products

Within the past few years, scientific communities all over the world have shown renewed interest in the search for novel immune-stimulating or antiviral agents of plant origin for either treatment or prevention, often using ethnopharmacologic approaches.[60] Natural compounds are widely recognized as privileged structures trimmed by evolutionary processes to interact with macromolecular targets. Plants use a diverse set of biochemical pathways to generate several secondary metabolites representing ecosystem adaptations to help plants to survive various environmental stresses and protect them from infections and infestations.[61] The antiviral potential of plant extracts or compounds varies among viruses.[62] Natural compounds occupy an equally large and complex chemical space as synthetic compounds. In the case of antiviral agents, 80% of 46 entities registered in the last approximately 30 years (1981-2010) can

be classified as natural product botanicals, synthetic but natural product mimics, natural product pharmacophores, or a combination of the latter 2. Oseltamivir, a success story in IFV drug synthesis, has its roots in nature: the abundant plant constituents quinic acid and shikimic acid are used as its starting materials.[63]

A screening strategy was applied to investigate crude extracts from 260 plant species on their inhibiting potential toward NAIs of *Clostridium perfringens*.[64] Moreover, 14 bioactive compounds from *Cleistocalyx operculatus* buds were discovered by using an anti-IFV screening approach.[65] The Chinese Academy of Medical Sciences tested more than 10,000 plants. Among them, a pronounced neuroaminidase-inhibiting effect was observed for the herb extract of *Elsholtzia rugulos*. Some extracts from *Agrimonia pilosa*,[66] *Echinacea purpurea*,[67] and *Prunus mume*[68] or the multicomponent mixtures polyphenol fractions from *Punica granatum*[69] and secoiridoid glucosides from *Ligustrum lucidum*[70] have shown a significant reduction of virus-induced cytopathic effects and in general antiviral or anti-influenza activity.

A 10% to 20% risk reduction of common cold incidence with the use of *Echinacea* species supplements has been shown.[71] Moreover, a recent meta-analysis demonstrated benefit on long-term (2-4 months) prevention with *Echinacea* species on recurrent respiratory tract infections (RTIs).[72] Another promising compound is BNO 1016, a fixed combination of 5 herbal substances that significantly reduced symptoms and led to faster recovery in patients with acute viral rhinosinusitis.[73]

Reported antiviral effects from natural products, regardless of whether obtained from clinical trials or empiric knowledge, can only give clues for further research. However, it appears that we are entering a new golden age of natural product drug discovery.

## PREVENTION

Prevention of viral respiratory illness is attempted by either avoiding exposure or strengthening immune defenses, either nonspecifically with immunostimulators or specifically with vaccines. Often, but not always, interventions are targeted toward high-risk groups for a particular infection (eg, RSV in infants and the elderly and IFV in patients with asthma).

### Immunostimulators

A variety of compounds (of microbial, herbal, or synthetic origin) have been used and are still being developed as nonspecific immunostimulatory agents to enhance or modulate the immune response against respiratory pathogens in a preventive or sometimes also therapeutic context. The effectiveness of these agents is usually moderate, and therefore they are only used as secondary supportive measures. As such, however, their potential should not be underestimated.

Among several agents based on bacterial components (OM-85 BV, LW 50020, PMBL, D53, and RU 41740), OM-85 BV, a lyophilisate of water-soluble fractions of bacteria commonly detected in patients with RTIs, has been extensively studied, and a role in the prevention of both acute and recurrent RTIs has been shown.[74,75] Mechanistic studies have confirmed pleiotropic immunomodulating effects on both innate and adaptive immunity.[76,77]

Pidotimod, a synthetic dipeptide molecule, induces a variety of immunomodulatory effects[78,79] and has shown some efficacy in preventing RTIs, although this was not always confirmed.[80,81]

Probiotic supplementation has been shown to reduce the incidence, duration, and severity of upper respiratory tract infections through immune modulation[82] and in particular rhinovirus infection through altering nasal innate inflammatory responses.[83]

Vitamin D (25-hydroxyvitamin D) has a modulatory role in host defense, inflammation, immunity, and epithelial repair after respiratory tract infections.[84] A recent meta-analysis has confirmed that vitamin D supplementation reduces the overall risk of acute respiratory tract infections.[85] Data from *in vitro* rhinovirus-infected human primary bronchial epithelial cells showed that exogenous vitamin D can reduce rhinovirus replication through increasing interferon and cathelicidin gene expression.[86] A significant amount of research is still dedicated to the efficacy of vitamin D supplementation, although not without controversy. Hopefully, specific indications will be consolidated soon.

Despite widespread use and a multitude of studies, the role of vitamins C or zinc supplements is still inconclusive in relation to their action against the common cold.[87]

Interestingly, meditation and exercise might significantly contribute to the reduction of RTI burden,[88] suggesting that the immunostimulatory capacity of nonpharmacologic measures should also be considered.

## Public health measures

The high transmission rate and epidemic nature of respiratory tract viruses indicate that effective public health measures to reduce transmission can have a substantial role in the overall prevention of these infections. A plethora of studies and meta-analyses delineated the important contribution of health policies in reducing transmission of epidemic respiratory tract viruses. In an elegant randomized control trial, an automated Web-based intervention that maximized handwashing intention was associated with fewer episodes of influenza-like illness, shorter duration of symptoms, and fewer antibiotic prescriptions in the intervention group.[89] Although similar results regarding handwashing have been confirmed in a Cochrane meta-analysis,[90] hand hygiene interventions in educational settings were not as unequivocally effective.[91,92] Low adherence to hand hygiene recommendations was correlated with higher incidence of IFV infection among health care workers during the 2009 pandemic.[93] The use of face masks has been shown to be highly effective in the interruption of respiratory viral spread.[90] This has been demonstrated further in a cluster randomized trial in which a reduced odds ratio of influenza infection secondary attack was observed in the intervention group.[94] Face masks are now regularly worn in some communities, especially in Asia, but much less so in western societies. Taken together, it seems that public health measures might provide a valuable ally in decreasing the burden of respiratory tract infections in the community.

## Vaccines and mAbs

Both vaccines and mAbs (passive immunization) are relevant interventions. Vaccines for IFV, rhinovirus, and RSV were initially developed as long ago as the 1940s to 1960s, although with mixed success, mostly because of rapid virus evolution. Improved understanding of vaccine immunology and technologic developments place us now closer than ever to developing highly effective vaccines against the major respiratory tract viruses.

mAb therapies to viral infections, such as EBV (rituximab) or RSV (palivizumab), provide passive immunization and are licensed, whereas similar agents targeting influenza and other viruses are in preclinical development.[95] Neutralizing antibodies can bind and inactivate viruses, inhibit viral cell entry (blocking receptor binding or conformational changes), prevent the release of virions from the cell, or modulate immune effector functions.[96,97] Engineering and production strategies to produce antibody fragments, higher-affinity binding, and longer half-life are contributing to a lower overall cost for therapy,[95] although vaccines are still considered preferable in most cases. It is notable that effective neutralizing mAb epitopes can also inform the rational design of vaccines.[98]

Different types of vaccines to respiratory viruses exist, and these are shown in Fig 2. Traditionally, either live attenuated or inactivated viruses are used. More recently, subunit vaccines made of detergent-disrupted whole viruses or purified viral proteins are also common. Furthermore, promising approaches use microparticle/nanoparticle material and recombinant technologies to produce broadly immunogenic, often self-adjuvanting, reproducible, and safe vaccine responses.[99] These delivery systems include synthetic polymers, virosomes, virus-like particles (VLPs), liposomes, lipid nanoparticles, proteins, emulsions, and immune-stimulating complexes.[22]

Currently, naturally occurring particles are favored because of safety concerns,[100] even though synthetic polymers, such as poly lactic-co-glycolic acid, are in use,[101] and gold nanoparticles have shown promising results.[102] Self-assembling protein nanoparticles, such as ferritin cages and vaults, have also shown promising preclinical data.[103,104] Layer-by-layer peptide-fabricated vaccine containing alternately charged poly-L-glutamic acid and poly-L-lysine layers with RSV peptides added have been efficacious in animals.[105]

A virosomal adjuvanted vaccine composed of reconstituted IFV envelope, effectively removing the core proteins and RNA, has been available for years with excellent tolerability and efficacy.[106] Several VLP vaccines based on hepatitis B virus surface antigen have been approved for viral infections, such as human papilloma virus[107] and other microbes (eg, malaria[108]), although an IFV candidate has not progressed.[109] Nevertheless these and other VLPs offer promise because of their valency, similar immune presentation to pathogens, and antigenic preservation.[110]

Adjuvants form a vital part of many vaccines; however, only aluminum hydroxide and oil in water emulsions are currently approved. A number of novel adjuvants, such as microcrystalline tyrosine, Matrix M, pathogen-associated molecular patterns, and chitosan, are in development.[111-114]

DNA and RNA vaccines induce an immune response to the nucleic acid–encoded antigen.[115] Impressive results have been reported in animals for a single low-dose intradermal, nonreplicating DNA vaccine for RSV; however, whether this will translate effectively to human subjects is not yet known.[116] To enhance immunogenicity, RNA vaccines have been encapsulated in nanoparticles, achieving sterilizing immunity
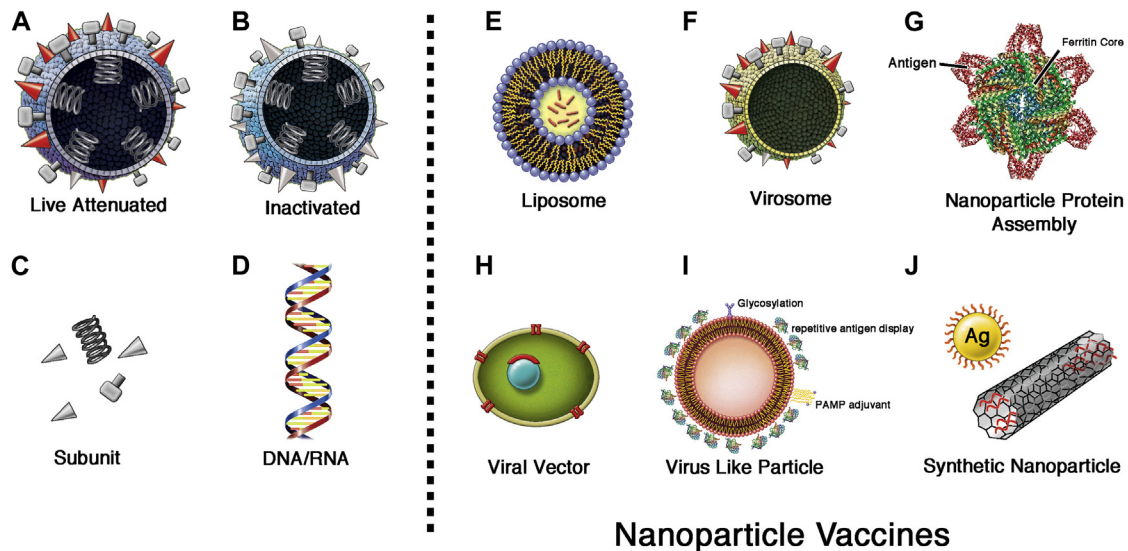
**FIG 2.** Vaccine types. **A,** Live attenuated vaccines are grown in culture to make them less virulent but can have the problem of reversion. **B,** Inactivated vaccines are treated with UV or formaldehyde to crosslink proteins and make them nonviable. **C,** Proteins can be purified, extracted, or dissolved by using detergents. **D,** Naked nucleic acids are also used as vaccines. **E,** Nanoparticle vaccines encompass natural and synthetic materials. Membranes can be used to make liposomes to contain and deliver an antigen to a target cell. **F,** Viruses can have nucleic acid and core protein removed to form virosomes. **G,** Viral proteins, such as HA stalks or antigens, can be engineered onto immunogenic core proteins (eg, ferritin or vaults). This example is HA on ferritin adapted from PBD codes 3BVE and 5C0S. **H,** Viruses, such as the vaccinia virus Ankara, with coat proteins and genetic material removed can be engineered to express other antigens, such as influenza M2 ion channel protein. **I,** VLPs can be engineered to express antigens and naturally glycosylated proteins and have adjuvants incorporated into the coat. *PAMP*, Pathogen-associated molecular pattern. **J,** Synthetic nanoparticles made from polymers (polystyrene or poly lactic-co-glycolic acid), gold, or carbon nanotubes can have peptides adsorbed, admixed, or encapsulated. *Ag*, Antigen.

for Zika virus in mice,[117] as well as being incorporated into virus-based self-replicating constructs known as replicons.[118,119]

Active IFV vaccination already forms the core of the global strategy against severe seasonal and pandemic influenza. Trivalent and more recent quadrivalent vaccines are largely efficacious in healthy adults provided an adequate match between circulating and vaccine strains.[120] Higher-dose (60 μg) and MF59-adjuvanted vaccines are available for elderly patients.[121,122] Similarly, pandemic vaccines can offer greater cross-clade protection because of the presence of improved (AS03 or MF59) adjuvants.[123]

The current frontier of IFV vaccine development is "universal" vaccines (Table I).[124-146] Ideally, these would protect not only from circulating and pandemic strains but also from novel epitopes that might evolve in the future. Many such vaccines are currently in preclinical and early clinical stages.

Heterosubtypic cross-reactive antibodies to IFV-A against the hemagglutinin (HA) stalk[147] have been isolated from immune subjects,[148] leading to mAbs now in phase 2.[98,124] Similar multilineage HA-stalk antibodies to IFV-B have also been reported.[149] Other conserved proteins have also been targeted, and an anti-M2e antibody is in development.[150] Therefore passive immunization or postinfection treatment might soon become another tool to combat IFV.[125,126,151]

HA-stalk and chimeric head/stalk-based vaccines have also shown encouraging preclinical results.[103,152-154] A further vaccine strategy based on conserved epitopes in proteins, such as M1, NP, and PB1, involves induction of $CD4^+$ and $CD8^+$ T-cell immunity,[155] leading to development of a promising MVA viral vector vaccine. Other vaccines use multiepitope peptides to induce IFV-specific T-cell responses, reducing viral shedding in human subjects.[127,133] Self-replicating RNA nanoparticles also encoding multiple proteins and hepatitis B virus–based VLPs expressing M2e and HA epitopes also appear promising.[156]

There are currently no licensed vaccines and only 1 mAb (palivizumab) approved for the prevention of RSV infection. However, there are numerous candidates in clinical trials, as recently reviewed.[3]

Suptavumab, an anti-F mAb,[157] has reached phase III trials in preterm infants. MEDI8897 offers 9-fold greater potency than palivizumab and has extended half-life in primates, suggesting a once per season dosing.[128]

Candidate vaccines are based on live attenuated strains, subunit, vector, and nanoparticle technologies with a range of adjuvants. Chimeric and combination vaccines using expression vectors in VLPs show much promise.[158] Recent preclinical results exhibit effective neutralization of RSV.[159-163] The most advanced of these is the Novavax F-protein VLP nanoparticle vaccine with aluminum hydroxide adjuvant, which is in phase III for maternal vaccination.[129,130] Transplacental transmission of neutralizing antibodies has been demonstrated in preclinical studies, although this has not conferred significant protection from RSV.[164]

Recombinant DNA vaccines are also promising because of their apparent ability to induce a balanced $T_H1/T_H2$ response, with a broad IgG/IgA profile mimicking live RSV challenge.[165] Intranasal and oral vaccine formulations are now in the early stages of clinical studies.[166]

**TABLE I.** IFV and RSV vaccines and mAbs currently in clinical trials

| | Phase | Type | Registration no. | Study sponsor | References | Comments |
|---|---|---|---|---|---|---|
| **Influenza** | | | | | | |
| **Standard vaccines** | | | | | | |
| Topical imiquimod in immunocompromised patients | Phase 2, pilot | ID and IM vaccination (Intanza/Mutagrip) | NCT02960815 | University of Lausanne Hospitals | | TLR7 adjuvant |
| H7N9 with AS03 adjuvant | Phase 1 | | NCT02957656 | NIAID | | |
| H7N9 with MF59 | Phase 1 | | NCT02251288 | NIAID | | |
| H5N8 with AS03 or M59 | Phase 1 | Inactivated vaccine | NCT03014310 | NIAID | | |
| IVACFLU-A/H5N1 | Phase 2/3 | Inactivated vaccine | NCT02612909 | Institute of Vaccines and Medical Biologicals, Vietnam | | |
| GC3110B | Phase 3 | Multidose quadrivalent | NCT02915809 | Green Cross Corporation | | |
| V118_18 | Phase 3 | Quadrivalent MF59 adjuvanted | EudraCT: 2015-000728-27 | Sequiris | | |
| **Heterotypic vaccines** | | | | | | |
| FLU-v004 | Phase 2b | Broad-spectrum synthetic epitope mixture: M1, NP, and M2 | NCT02962908 EudraCT: 2016-002134-74 | PepTcell | 131-133 | H1N1 challenge model |
| MVA-NP+M1 | Phase 2a | MVA viral vector vaccine | EudraCT: 2009-010334-21 NCT00942071 (Phase I study) | University of Oxford/ Wellcome Trust | 134,135 | Completed 2010, reported 2017 |
| M-001 | Phase 2b | Recombinant multimeric protein – 9 conserved epitopes from HA stem, M1, NP | EudraCT: 2015-001979-46 | BiondVax Pharmaceuticals | 127,136-138 | |
| Multimeric M-001 followed by H7N9 with M59 | Phase 2 | | NCT03058692 | NIAID | | |
| **Passive immunization** | | | | | | |
| MEDI8852 | Phase 2a | | NCT03028909 | MedImmune | | Monoclonal IgG$_1$κ against type A influenza—targets conserved HA stalk group 1 and 2 |
| VIS410 | Phase 2a | | NCT03040141 | Visterra | 126 | Anti-HA monocolonal for type A influenza group 1 and 2 |
| CR6261 | Phase 2 | | NCT02371668 | NIAID | 98 | Anti-HA monocolonal for type A influenza; targets helical region in the stem; group 1 only |
| MHAA4549A | Phase 2 | | NCT02623322 NCT02293863 EudraCT: 2016-000425-40 | Genentech | 124 | Monoclonal IgG$_1$ against type A influenza —targets conserved HA stalk group 1 and 2 |
| CTP27 | Phase 2 | | NCT02071914 EudraCT: 2013-004544-32 KCT0002211 | Celltrion | | Mixed antibodies to group 1 and 2 |
| TCN-032 | Phase 2a (completed 2012) | | NCT01719874 | Theraclone Sciences | 125 | M2e monoclonal type A influenza |
| **RSV** | | | | | | |
| **Vaccines** | | | | | | |
| RSV vaccine GSK3389245A | Phase 2 | RSV viral proteins in chimpanzee-derived adenovector | NCT02927873 EudraCT: 2016-000117-76 | GlaxoSmithKline | | Phase 2 started recruiting in January 2017 IM in infants 12-17 mo |

*(Continued)*

**TABLE I**. *(Continued)*

| | Phase | Type | Registration no. | Study sponsor | References | Comments |
|---|---|---|---|---|---|---|
| GSK3003891A | Phase 2 | Viral fusion protein | NCT02956837 EudraCT: 2015-005742-58 | | | Vaccination of pregnant women started recruitment in January 2017 |
| RSV cps2 vaccine | Phase 1 | Live attenuated vaccine | NCT01968083 | NIAID | | |
| RSV Vaccines (multiple formulations) | Phase 1 | Recombinant live attenuated vaccine | NCT02237209 NCT02601612 | NIAID | | Nasal delivery to infants; expected results this year |
| DPX-RSV(A) | Phase 1 | RSV SH antigen with DepoVax adjuvant | NCT02472548 | Dalhousie University with ImmunoVaccine Technologies | | Liposome in oil delivery |
| MEDI7510 | Phase 2b | RSV sF antigen with GLA adjuvant | NCT02508194 | MedImmune | | Study terminated early |
| MEDI-534 | Phase 2a | RSV/PIV3 live attenuated vaccine | NCT00686075 | MedImmune | 139,140 | |
| RSV-F Particle Vaccine | Phase 3 | RSV F protein nanoparticle vaccine with aluminum hydroxide adjuvant | NCT02624947 | Novavax | 129,130,141 | Maternal vaccination strategy |
| RSV001 | Phase 1 | | NCT01805921 | ReiThera | | |
| VXA-RSV-f | Phase 1 | Adenoviral vector–based RSV F Protein Vaccine | NCT02830932 | Vaxart | | Oral formulation |
| MVA-BN RSV | Phase 2b | Recombinant vaccine expressing 5 epitopes from F & G proteins | NCT02873286 | Bavarian Nordic | | |
| SynGem | Phase 1 | F protein VLP– *Lactococcus* | NCT02958540 | Mucosis | | |
| Passive immunization | | | | | | |
| MEDI8897 | Phase 2b | | NCT02878330 | MedImmune | 128 | RSV monoclonal |
| MEDI-524 (Motavizumab) | Phase 3 | | NCT00121108 | MedImmune | 142,143 | RSV monoclonal, positive results |
| ALX-0171 | Phase 2b | Trivalent RSV F-protein binder | NCT02979431 | Ablynx | 144 | Inhaled anti-RSV nanobody |
| REGN-2222 (Suptavumab) | Phase 3 | | NCT02325791 | Regeneron Pharmaceuticals | | Human anti-RSV F protein mAb |
| RSV-IVIG RI-001 & RI-002 | Phase 3, primary end point met | | NCT01814800 | ADMA biologics | 145,146 | Pooled donor plasma with high neutralizing RSV immunoglobulin; primary immunodeficiency disease |

*GLA*, Glucopyranosyl lipid adjuvant; *ID*, intradermal; *IM*, intramuscular; *NIAID*, National Institute of Allergy and Infectious Diseases.

Initial vaccination attempts[167] and more recent preclinical experiments show that inactivated rhinovirus vaccines are type specific and not cross-neutralizing.[8] However, although in animals[168] rhinovirus antibody responses might be weakly cross-neutralizing, data from human subjects suggest that responses are mainly misdirected to internal epitopes.[169] Understanding the full extent of rhinovirus diversity would probably be required to develop a panspecies vaccine.

## CONCLUSION

Multiple strategies are being developed to reduce the burden of viral respiratory illnesses. It is likely that many of these strategies will find a relevant indication: antiviral strategies will most probably make sense in severe life-threatening situations or when a window of opportunity is clearly present, such as in specific virus seasons and susceptible populations. Ideally, prevention at a wide scale through immunization will be able to reduce the overall burden of respiratory infections with a huge effect. This appears to be within reach for RSV and IFV, whereas additional effort is needed toward rhinovirus. In the meantime, symptomatic and immunostimulatory measures provide relief, and they hold promise in relation to postviral reactive airway disease. Public health measures should be expanded because they can be critical in reducing the effect and contain potential epidemics.

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