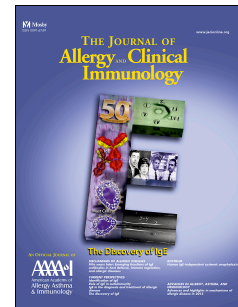


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Nikolaos G. Papadopoulos, MD, PhD, Spyridon Megremis, PhD, Nikolaos A. Kitsioulis, Olympia Vangelatou, Peter West, PhD, Paraskevi Xepapadaki, MD, PhD



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Promising approaches for treatment and prevention of viral respiratory illnesses

Nikolaos G. Papadopoulos, MD, PhD ^{1, 2}, Spyridon Megremis ¹, PhD, Nikolaos A. Kitsioulis ², Olympia Vangelatou ³, Peter West, PhD ¹, Paraskevi Xepapadaki, MD, PhD ².

¹ Division of Infection, Immunity & Respiratory Medicine, The University of Manchester, Manchester, UK

² Allergy Department, 2nd Pediatric Clinic, National & Kapodistrian University of Athens, Athens, Greece

³ Department of Nutritional Physiology & Feeding, Agricultural University of Athens, Athens, Greece

Key words:

Influenza, bronchiolitis, common cold, respiratory syncytial virus, rhinovirus, vaccine, monoclonal, antiviral, natural products, public health

List of Abbreviations:

A1AT Alpha-1 Antitrypsin
ARDS Acute Respiratory Distress Syndrome
ASOs Antisense Oligonucleotides
CD Cluster of Differentiation
CDHR3 Cadherin Related family member 3
COPD Chronic Obstructive Pulmonary Disease
COX Cyclooxygenase
DNA Deoxyribonucleic acid
EBV Epstein-Barr Virus
FDA Food and Drug Administration
HBV Hepatitis B Virus
HIV Human Immunodeficiency Virus
ICAM-1 Intercellular Adhesion Molecule 1
IFN Interferon
IFV Influenza virus
Ig Immunoglobulin

39 LDLR Low Density Lipoprotein Receptor
 40 Mac Mycobacterium avium complex
 41 mAb monoclonal antibody
 42 MPV Metapneumovirus
 43 mRNA messenger RNA
 44 NAIs Neuraminidase Inhibitors
 45 OTC Over-the-counter
 46 PAMPs Pathogen-Associated Molecular Patterns
 47 PIV Parainfluenza Virus
 48 PLGA Poly Lactic-co-Glycolic Acid
 49 PPARs Peroxisome Proliferator-Activated Receptors
 50 RNA Ribonucleic acid
 51 RSV Respiratory syncytial virus
 52 RV Rhinovirus
 53 Th T helper
 54 TLR Toll Like Receptor
 55 SARS Severe Acute Respiratory Syndrome
 56 SARS-CoV Severe Acute Respiratory Syndrome Coronavirus
 57 SIP Sphingosine-1-Phosphate
 58 (si)RNA small interfering RNA
 59 VLP Virus-like Particles
 60 vRTI viral Respiratory Tract Infections

62 Abstract

63 Viral respiratory infections are the most common human ailments, leading to enormous
 64 health and economic burden. Hundreds of virus species and subtypes have been associated
 65 with these conditions, with influenza viruses (IFV), respiratory syncytial virus (RSV) and the
 66 rhinoviruses (RV) being the most frequent and with the highest burden. When considering
 67 prevention or treatment of viral respiratory infections, potential targets include the
 68 causative pathogens themselves but also the immune response, disease transmission or
 69 even just the symptoms. Strategies targeting all these aspects are concurrently developing
 70 and several novel and promising approaches are emerging. In this perspective, we overview
 71 the entire range of options and highlight some of the most promising approaches, including
 72 new antivirals, symptomatic or immunomodulatory drugs, the re-emergence of natural
 73 remedies, as well as vaccines and public health policies towards prevention. Wide scale
 74 prevention through immunisation appears to be within reach for RSV and promising for IFV,
 75 while additional effort is needed in regard to RV, as well as other respiratory viruses.

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1. Introduction

The respiratory system is one of the main portals of entry for human pathogens. Although precise calculations are challenging due to methodology and inherent variability, the number of potentially infectious viruses we breathe every day can be at the range of many thousands¹. It is thus not surprising that viral respiratory tract infections (vRTI) are the most common human diseases, leading to enormous health and economic burden². A wide variety of conditions fall within the spectrum of vRTI. Many of these are by themselves major public health concerns: influenza, acute bronchiolitis, viral pneumonia, common colds. Together with their downstream effects, i.e. acute exacerbations of asthma and COPD, all result in vast amounts of morbidity, mortality and health costs, including primary care visits, hospitalizations, deaths, but also inappropriate use of antibiotics, loss of productivity and effects on quality of life³⁻⁵. Respiratory viruses have been isolated and characterised during the last century, starting from influenza (IFV) in the 1930s, followed by respiratory syncytial virus (RSV), coronaviruses, adenoviruses and rhinoviruses (RVs) in the 1950-60s; nevertheless, 'new' viruses or subtypes, such as human metapneumovirus (MPV) or RV-C, are still being identified^{6,7}. Even though several of these viruses are typically associated with a clinicopathological entity (e.g. IFV with influenza, RSV with bronchiolitis, RV with the common cold) there is also extensive overlap and it's often difficult to identify the aetiological agent based on clinical grounds alone⁸. Consequently, when considering prevention and treatment of vRTI, potential targets include specific pathogens, the immune response, disease transmission or just the symptoms. Herein, we overview the options and highlight some of the most promising approaches on vRTI treatment, including symptomatic medication, immunomodulatory drugs, antivirals and natural products, as well as on vRTI prevention, ranging from vaccines to immunostimulators and public health policies. This is a vast field; we thus emphasize advances that may be relevant in tackling the virus-induced aspects of allergic disease, such as asthma exacerbations.

2. Treatment

2.1 Symptomatic medication

Most mild viral respiratory illnesses are managed symptomatically with over-the-counter (OTC) 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 may have adverse effects especially in young children. Therefore, the FDA has issued a warning against the use of OTC cough and cold products in children younger than 4 years of age⁹. Furthermore, the use of decongestants should be minimized, especially in children¹⁰, while codeine has been restricted in children by the European Medical Agency since 2015¹¹. Selective cyclooxygenase (COX) inhibitors, such as celecoxib and mesalazine, have been widely used in clinics for their antipyretic, analgesic, and anti-inflammatory properties in airway diseases¹², while their combination with neuraminidase inhibitors has significantly improved the survival of IFV infected mice¹³. Recent studies have revealed a new genus of specialized pro-resolving lipid mediators (SPM) including lipoxins, resolvins, protectins and maresins, enhancing anti-inflammatory, anti-viral and pro-resolving mechanisms¹⁴. Medications interfering with prostanoid and lipoxygenase biosynthesis and signaling, thus affecting resolution and SPM switching, such as aspirin and NSAIDs have been suggested as potential agents modulating antiviral immunity^{15,16}, while several SPM resolution agonists are in clinical development programs. Symptomatic relief can also be sought in severe cases. Non-invasive ventilation may reduce respiratory distress in acute viral bronchiolitis¹⁷. Very recently, new devices delivering totally conditioned gas (37 °C, 100% relative humidity) through 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 unit¹⁸.

2.2 Immune and antiviral pathway modulators

While vRTI are most often short-lived events, impaired antiviral clearance and/or activation of inflammatory pathways leads to important downstream complications such as exacerbations of asthma or COPD¹⁹. The immune and antiviral mechanisms leading from infection to exacerbation have been scrutinized²⁰ and medications targeting these pathways are being evaluated as promising candidates to reduce disease burden. Impaired interferon (IFN) production has been observed in various obstructive respiratory diseases, potentially contributing to enhanced susceptibility and/or severity of viral induced acute airway exacerbations²¹. Although inhaled IFN- β supplementation has failed to show a clear effect in preventing virus-induced symptom worsening in mild asthmatics, sub-analysis in severe asthmatics showed a protective effect²². Interestingly, in an experimental model, exogenous administration of IFN- λ 1 has induced a strong and more prolonged antiviral state than IFN- β ²³. Moreover, experimental studies in an allergic asthma model showed that IFN-

lamba (λ) supplementation enhanced Th1 immunity, by inducing IFN- γ and suppressing Th2 and Th17 responses through modulation of lung CD11c(+) dendritic cell (DC) function²⁴.

²⁵Novel antibody-based drugs with anti-RV and immunomodulatory effects, act through IFN- β induction and suppression of Th2 responses in experimental models²⁶.

The prototype synthetic TLR4 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 approaches²¹.

Interestingly, omalizumab, an anti-IgE monoclonal antibody, prevents asthma exacerbations either by decreasing the duration and shedding of RV infection or by blocking the synergistic effect of RV infection on allergy^{29,30}. As high affinity IgE receptors' (Fc ϵ RI) cross-linking on plasmacytoid DCs reduces IFN- α responses following viral infections, it is plausible that omalizumab enhances virus-induced IFN- α production in asthmatic patients, thus limiting virus spreading and infection severity³¹.

"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 strategies³².

Peroxisome proliferator-activated receptor (PPAR)-gamma agonists (e.g., rosiglitazone and pioglitazone) are critical regulators of inflammation, and have been promising in improving the clinical outcome of severe influenza infections³³, however their development has slowed down from 200-2005 due to possible cardiovascular side-effects; however in 2015 the FDA lifted restrictions based on new safety data³⁴. Moreover, sphingosine-1-phosphate receptor 1 agonists (S1P)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 antivirals³⁵.

There is increasing interest in the use of macrolides to treat or prevent virus-induced asthma exacerbations, although microbial resistance remains a major hurdle, therefore they are not currently indicated. Early in-vivo evidence suggested that azithromycin has anti-inflammatory and anti-viral effects through induction of interferon stimulated gene mRNA expression and reduced virus 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 infection³⁸. Novel macrolides (Mac5) with anti-inflammatory, antibacterial and, more importantly, IFN augmenting activity in airway epithelium have been identified³⁹. Finally, in vitro models have demonstrated that alpha-1 antitrypsin (A1AT) exerts anti-inflammatory effects in RV-infected COPD airway epithelial cells, potentially through inhibition on caspase-1 activity, suggesting A1AT as potential anti-inflammatory agent⁴⁰.

2.3 Antivirals

vRTIs are usually characterized by an acute, self-limiting course which means that the peak of virus 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 extremely narrow. Additional challenges need to be overcome, such as the structural variation of virus proteins, multiple genotypes and high mutation rates. Accordingly, only a very limited number of specific antiviral drugs are currently licensed, while promising approaches mostly aim to control severe complications, reduce disease burden or transmission. Antiviral strategies aim to block particular stages of the virus lytic cycle, including attachment and entry to the host cell, replication, transcription and translation (Figure 1)⁴¹.

In principle, preventing a viral pathogen from entering the host cell represents the ideal antiviral strategy since the virus is not allowed to 'hack' the host; IFV neuraminidase (NA) inhibitors (NAIs) have been successfully used to competitively bind the sialic acid-binding pocket of NA and are good examples of this approach; Oseltamivir and zanamivir have been used as anti-flu therapies⁴², whereas laninamivir and peramivir show antiviral activity against wild type but also against oseltamivir-resistant and NAI-resistant strains, respectively^{43,44}. The non-enveloped RVs use viral capsid structures to bind their receptors (ICAM-1, LDLR, CDHR3)⁴⁵. Even though more than 50% of RV strains use ICAM-1 for cell entry, an ICAM-1 competitor, tremacamra, did not make it into the clinic despite initially promising results⁴⁶ 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 coronavirus (SARS-CoV) which use a class I fusion mechanism⁴⁷. DAS181 (Fludase) is a fusion construct that cleaves the sialic acid receptors on host cells and its antiviral spectrum includes IFV and parainfluenza viruses (PIV)⁴⁸. Non-enveloped viruses, such as RV, release their genomes

through a conformational shift of the capsid protein(s) 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 RVs have been tested (R and WIN series) without ultimate success⁵¹. Pleconaril, BTA798 (varendavir) and pocapavir (V-073) are still under clinical evaluation⁵². Of note, a major drawback of capsid binders is the rapid emergence of resistance⁵². Several fusion inhibitors are being developed for the treatment of RSV and have been reviewed elsewhere^{3,53}.

Due to their limited coding capacity, viruses rely on the production of polyproteins which 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 rupintrivir (AG7088) and AG7404, which showed antiviral activity in vitro but not in vivo, no similar agents are currently pursued⁵². The use of HIV protease inhibitors such as lopinavir and ritonavir in SARS patients have not been associated with any proven benefit, although retrospective studies reported that severe outcomes (ARDS or death) occurred less often in those receiving a combination of lopinavir/ritonavir and ribavirin with corticosteroids⁵⁴.

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 disease in high-risk infants and in combination with protease inhibitors in SARS patients, but its use has been limited due to cost and unconfirmed efficacy towards 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 replication⁵⁵. 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 early stages⁵². Favipiravir (T-705) is an antiviral drug that selectively inhibits the RNA-dependent RNA polymerase of IFV, as well as several other viruses⁵⁶.

Umifenovir has been shown to inhibit various human respiratory RNA viruses including several strains of IFV-A and B, RSV, PIV3 and RV-B14. It also demonstrates inhibitory activity against other viruses, enveloped or not, responsible for emerging or globally prevalent infectious diseases⁵⁷.

Finally, a most promising but also challenging antiviral approach is through antisense oligonucleotides (ASOs). ASOs are single-stranded deoxyribonucleotide oligomers with a sequence complementary to a target mRNA transcript. Thus, viral genomic RNA, or viral mRNA can be directly targeted. Antisense technology and RNA interference have been experimentally explored in targeting measles virus, SARS-CoV, coxsackievirus, enteroviruses and RV, 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 RSV⁵⁸. ALN-RSV01 is an unmodified naked small interfering (si)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 genotypes⁵⁸. In all, new antivirals are continuously explored, particularly for life-threatening viruses such as IFN and RSV. RVs, even though simple in terms of genome organization and protein coding have proven extremely difficult to target, mostly due to its high diversity, immune evading strategies, but also to some extent to the underestimation of RV infection clinical consequences.

2.4 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, for either treatment or prevention, from plant origin, often using ethnopharmacological approaches⁶⁰. 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 ecosystemic adaptations, to help plants to survive various environmental stresses and protect them from infections and infestations⁶¹. The antiviral potential of plant extracts or compounds varies among viruses⁶². 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 ~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 two. 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 materials⁶³. A screening strategy was applied to investigate crude extracts from 260 plant species on their inhibiting potential towards NAI of *Clostridium perfringens*⁶⁴. Moreover 14 bioactive

compounds from *Cleistocalix operculatus* buds, were discovered by using an anti-IFV screening approach⁶⁵. The Chinese Academy of Medical Sciences tested more than 10 000 plants. Among them, a pronounced NA 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 multi-component 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 anti-viral or anti-influenza activity.

A 10%-20% risk reduction of common cold incidence with the use of *Echinacea* supplements has been shown⁷¹. Moreover, a recent meta-analysis demonstrated benefit upon long-term (2-4 months) prevention with *Echinacea* on recurrent RTIs⁷². Another promising compound is BNO 1016, a fixed combination of 5 herbal substances, which significantly reduced symptoms and led to faster recovery in acute viral rhinosinusitis⁷³.

Reported antiviral effects from natural products, regardless if obtained from clinical trials or empirical knowledge, can only give clues for further research. It appears however that we are entering a new 'Golden Age' of natural products drug discovery.

3. Prevention

Prevention of viral respiratory illness is attempted by either avoiding exposure or by strengthening immune defences, either non-specifically with immunostimulators or specifically with vaccines. Often, but not always, interventions are targeted towards high-risk groups for a particular infection (e.g. RSV in infants and elderly, IFN in patients with asthma etc).

3.1 Immunostimulators

A variety of compounds (of microbial, herbal or synthetic origin) have been used and are still being developed as non-specific immunostimulatory agents to enhance or modulate the immune response against respiratory pathogens, in a preventive or sometimes also in a 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, RU 41740), OM-85 BV, a lyophilisate of water-soluble fractions of bacteria commonly detected in 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 the 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 infections, through immune modulation⁸² and in particular RV infection through altering nasal innate inflammatory responses⁸³.

Vitamin D (25-hydroxyvitamin D) has a modulatory role in host defence, inflammation, immunity, and epithelial repair following respiratory infections⁸⁴. A recent meta-analysis has confirmed that Vitamin D supplementation reduces the overall risk of acute respiratory infections⁸⁵. Data from *in vitro* RV infected human primary bronchial epithelial cells showed that exogenous vitamin D can reduce RV replication via increasing IFN and cathelicidin gene expression⁸⁶. A significant amount of research is still dedicated to the efficacy of Vitamin D supplementation, 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 cold⁸⁷.

Interestingly, meditation and exercise may significantly contribute in the reduction of RTI burden⁸⁸, suggesting that the immunostimulatory capacity of non-pharmacological measures should also be considered.

3.2 Public Health measures

The high transmission rate and epidemic nature of respiratory viruses indicate that effective public health measures to reduce transmission may 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 viruses. In an elegant randomized control trial, an automated web-based intervention that maximised handwashing intention was associated with fewer episodes of influenza-like illness, shorter duration of symptoms and fewer antibiotic prescriptions in the intervention group⁸⁹. Although similar results regarding handwashing have been confirmed in a Cochrane meta-analysis⁹⁰, 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 further demonstrated 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 may provide a valuable ally in lowering the burden of respiratory infections in the community.

3.3 Vaccines and monoclonal antibodies

Both vaccines and monoclonal antibodies (passive immunisation) are relevant interventions. Vaccines for IFV, RV and RSV were initially developed as long ago as the 1940-1960s but with mixed success, mostly due to rapid virus evolution. Improved understanding of vaccine immunology and technological developments place us now closer than ever to developing highly effective vaccines against the major respiratory viruses.

Monoclonal antibody (mAb) therapies to viral infections like EBV (Rituximab) or RSV (Palivizumab) provide passive immunisation and are licensed, while similar agents targeting influenza and other viruses are in preclinical development ⁹⁵. Neutralising 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 neutralising mAb epitopes can also inform the rational design of vaccines ⁹⁸.

Different vaccine types to respiratory viruses exist and these are shown in Figure 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 utilise micro/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 (VLP), liposomes, lipid nanoparticles, proteins, emulsions and immune stimulating complexes²².

Currently, naturally occurring particles are favoured due to safety concerns¹⁰⁰, even though synthetic polymers such as PLGA are in use¹⁰¹ and gold nanoparticles have shown promising results¹⁰². Self-assembling protein nanoparticles, such as ferritin cages and vaults, have also shown promising pre-clinical 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 animals¹⁰⁵.

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 efficacy¹⁰⁶. Several VLP vaccines based on HBV surface antigen have been approved for viral infections such as human papilloma virus¹⁰⁷ and other microbes (e.g. malaria¹⁰⁸), although an IFV candidate has not progressed¹⁰⁹. Nevertheless these and other VLPs offer promise due to their valency, similar immune presentation to pathogens and antigenic preservation¹¹⁰.

Adjuvants form a vital part of many vaccines, however, only alum and oil in water emulsions are currently approved. A number of novel adjuvants like microcrystalline tyrosine, Matrix M™, PAMPs and chitosan are in pre-clinical development¹¹¹⁻¹¹⁴.

DNA and RNA vaccines induce an immune response to the nucleic acid encoded antigen¹¹⁵. Impressive results have been reported in animals for a single low dose intradermal, non-replicating DNA vaccine for RSV, however whether this will translate effectively to humans is not yet known¹¹⁶. To enhance immunogenicity, RNA vaccines have been encapsulated in nanoparticles, achieving sterilising immunity for Zika virus in mice¹¹⁷ 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 vaccines and more recent quadrivalent vaccines are largely efficacious in healthy adults, provided an adequate match between circulating and vaccine strains¹²⁰. Higher dose (60 µg) and MF59 adjuvanted vaccines are available for elderly patients^{121,122}. Similarly, pandemic vaccines may offer greater cross-clade protection, due to the presence of improved (AS03 or MF59) adjuvants¹²³.

The current frontier of IFV vaccine development is 'universal' vaccines (Table). Ideally these would protect not only from circulating and pandemic strains, but also from novel epitopes

that may evolve in the future. Many such vaccines are currently in pre-clinical and early clinical stages.

Hetero-subtypic cross reactive antibodies to IFV-A against the HA stalk¹²⁴, have been isolated from immune individuals¹²⁵, leading to mAbs now in phase 2^{98,126}. Similar multi-lineage HA-stalk antibodies to IFV-B have also been reported¹²⁷. Other conserved proteins have also been targeted and an anti-M2e antibody is in development¹²⁸. Passive immunisation or post infection treatment may therefore soon become another tool to combat IFV^{129,130}, reviewed in¹³¹.

HA stalk and chimeric head/stalk based vaccines have also shown encouraging pre-clinical results^{103,132-134}. A further vaccine strategy based on conserved epitopes in proteins such as M1, NP and PB1 involves the induction of CD4+ and CD8+ T-cell immunity¹³⁵, leading to the development of a promising MVA viral vector vaccine. Other vaccines use multi-epitope peptides to induce IFV specific T-cell responses reducing viral shedding in humans^{136,137}. Self-replicating RNA nanoparticles also encoding multiple proteins, and HBV based VLPs expressing M2e and HA epitopes also appear promising¹³⁸.

There are currently no licensed vaccines and only one Mab (palivizumab) approved for the prevention of RSV infection. However, there are numerous candidates in clinical trials, recently reviewed³.

Suptavumab, an anti-F mAb¹³⁹ has reached phase III trials in pre-term infants. MEDI8897, offers 9-fold greater potency than palivizumab and has extended half-life in primates, suggesting a once per season dosing¹⁴⁰.

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 promise¹⁴¹. Recent preclinical results exhibit effective neutralisation of RSV¹⁴²⁻¹⁴⁶. The most advanced of these is the Novavax F-protein VLP nanoparticle vaccine with alum adjuvant which is in phase III for maternal vaccination^{147,148}. Transplacental transmission of neutralising antibodies has been demonstrated in preclinical studies although this has not conferred significant protection from RSV¹⁴⁹.

Recombinant DNA vaccines are also promising due to their apparent ability to induce a balanced Th1/Th2 response, with a broad IgG/IgA profile mimicking live RSV challenge¹⁵⁰.

Intranasal and oral vaccine formulations are now in the early stages of clinical studies¹⁵¹.

Initial vaccination attempts¹⁵² and more recent pre-clinical experiments show that inactivated RV vaccines are type specific and not cross neutralising⁸. However, whilst in animals¹⁵³ RV antibody responses may be weakly cross neutralising, data from humans suggest that responses are mainly misdirected to internal epitopes¹⁵⁴. Understanding the full extent of RV diversity would probably be required to develop a pan-species vaccine.

4. 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: i.e. antiviral strategies will most probably make sense in severe, life-threatening situations, or when a window of opportunity is clearly present, e.g. in specific virus seasons and susceptible populations. Ideally, prevention at a wide scale through immunisation will be able to reduce the overall burden of respiratory infections with huge impact. This appears to be within reach for RSV and IFV, while additional effort is needed towards RV. In the meantime, symptomatic and immunostimulatory measures provide relief, while they hold promise in relation to post-viral reactive airway disease. Public health measures should be expanded as they can be critical in reducing the impact and contain potential epidemics.

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Legends to the Figures

Figure 1: Virus infection cycle and antiviral medication targets

New antiviral agents are been designed to target most aspects of the virus life cycle, including receptor binding, fusion, uncoating, translation and replication. Examples of agents under development are listed alongside each function

Figure 2: Vaccine Types

Live attenuated vaccines are grown in culture to make them less virulent but can have problem of reversion (A). Inactivated vaccines are treated with UV or formaldehyde to crosslink proteins and make them non-viable (B). Proteins can be purified or extracted or dissolved using detergents (C). Naked nucleic acids are also used as vaccines (D). Nanoparticle vaccines encompass natural and synthetic materials. Membranes can be used to make liposomes to contain and deliver an antigen to a target cell (E). Viruses can have nucleic acid and core protein removed to form virosomes (F). Viral proteins such as hemagglutinin stalk or antigens can be engineered onto immunogenic core proteins (e.g. ferritin or valuts). This example is HA on ferritin adapted from PBD codes 3BVE and 5C0S. Viruses such as vaccinia virus Ankara with coat proteins and genetic material removed can be engineered to express other antigens such are influenza M2 ion channel protein (H). Virus-like particles can be engineered to express antigens, naturally glycosylated proteins and have adjuvants incorporated into the coat (I). Synthetic nanoparticles made from polymers (polystyrene or PGLA), gold, or carbon nanotubes can have peptides adsorbed, admixed or encapsulated (J).

Table: IFV and RSV vaccines and monoclonal antibodies currently in clinical trials.

	Phase	Type	Registration #	Study Sponsor	Refs	Comments
Influenza						
<i>Standard Vaccines</i>						
Topical Imiquimod in immunocompromised patients	Phase 2 Pilot	ID & IM vaccination (Intanza/Mutagrip)	NCT02960815	University of Lausanne Hospitals		TLR7 adjuvant
H7N9 with AS03 adjuvant	Phase 1		NCT02957656	National Institute of Allergy and Infectious Diseases (NIAID)		
H7N9 with MF59	Phase 1		NCT02251288	National Institute of Allergy and Infectious Diseases (NIAID)		
H5N8 with AS03 or M59	Phase 1	Inactivated vaccine	NCT03014310	National Institute of Allergy and Infectious Diseases (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		
<i>Heterotypic Vaccines</i>						
FLU-v004	Phase2b	Broad Spectrum synthetic epitope mixture. M1, NP, M2	NCT02962908 EudraCT: 2016-002134-74	PepTcell Limited	[1–3]	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	[4, 5]	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 Ltd	[6–9]
Multimeric M-001 followed by H7N9 with M59	Phase 2		NCT03058692	National Institute of Allergy and Infectious Diseases (NIAID)	
<i>Passive Immunization</i>					
MEDI8852	Phase 2a		NCT03028909	MedImmune	Monoclonal IgG1 kappa against type A influenza – targets conserved HA stalk group 1&2
VIS410	Phase 2a		NCT03040141	Visterra	[10] Anti-HA monoclonal for type A influenza group 1&2
CR6261	Phase 2		NCT02371668	National Institute of Allergy and Infectious Diseases (NIAID)	[11] Anti-HA monoclonal for type A influenza Targets helical region in the stem. Group 1 only
MHAA4549A	Phase 2		NCT02623322 NCT02293863 EudraCT:2016-000425-40	Genentech	[12] Monoclonal IgG1 against type A influenza – targets conserved HA stalk group 1&2
CTP27	Phase 2		NCT02071914 EudraCT: 2013-004544-32 KCT0002211	Celltrion	Mixed antibodies to group 1 and group 2.

TCN-032	Phase 2a (completed 2012)		NCT01719874	Theraclone	[13]	M2e monoclonal type A influenza.
RSV						
Vaccines						
RSV vaccine GSK3389245A	Phase 2	RSV Viral proteins in Chimpanzee- derived Adenovector	NCT02927873 EudraCT: 2016- 000117-76	GSK		Phase 2 started recruiting in Jan 2017 IM in infants 12-17 months
GSK3003891A	Phase 2	Viral fusion protein	NCT02956837 EudraCT: 2015- 005742-58			Vaccination of Pregnant women started recruitment in Jan 2017
RSV cps2 vaccine	Phase 1	Live attenuated vaccine	NCT01968083	National Institute of Allergy and Infectious Diseases (NIAID)		
RSV Vaccines (multiple formulations)	Phase 1	Recombinant live attenuated vaccine	NCT02237209 NCT02601612	National Institute of Allergy and Infectious Diseases (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, Inc		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	[14, 15]	
RSV-F Particle Vaccine	Phase 3	RSV F protein nanoparticle vaccine with Alum	NCT02624947	Novavax	[16–18]	Maternal vaccination strategy

RSV001	Phase 1	adjuvant	NCT01805921	ReiThera Srl		
VXA-RSV-f	Phase 1	Adenoviral-Vector Based Respiratory Syncytial Virus (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		
<i>Passive Immunization</i>						
MEDI8897	Phase 2b		NCT02878330	MedImmune	[19]	RSV monoclonal
MEDI-524 (Motavizumab)	Phase 3		NCT00121108.	MedImmune	[20, 21]	RSV monoclonal, positive results
ALX-0171	Phase 2b	Trivalent RSV F-protein binder	NCT02979431	Ablynx	[22]	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 endpoint met		NCT01814800	ADMA biologics	[23, 24]	Pooled donor plasma with high neutralising RSV Ig. Primary immunodeficiency disease.

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Figure 1

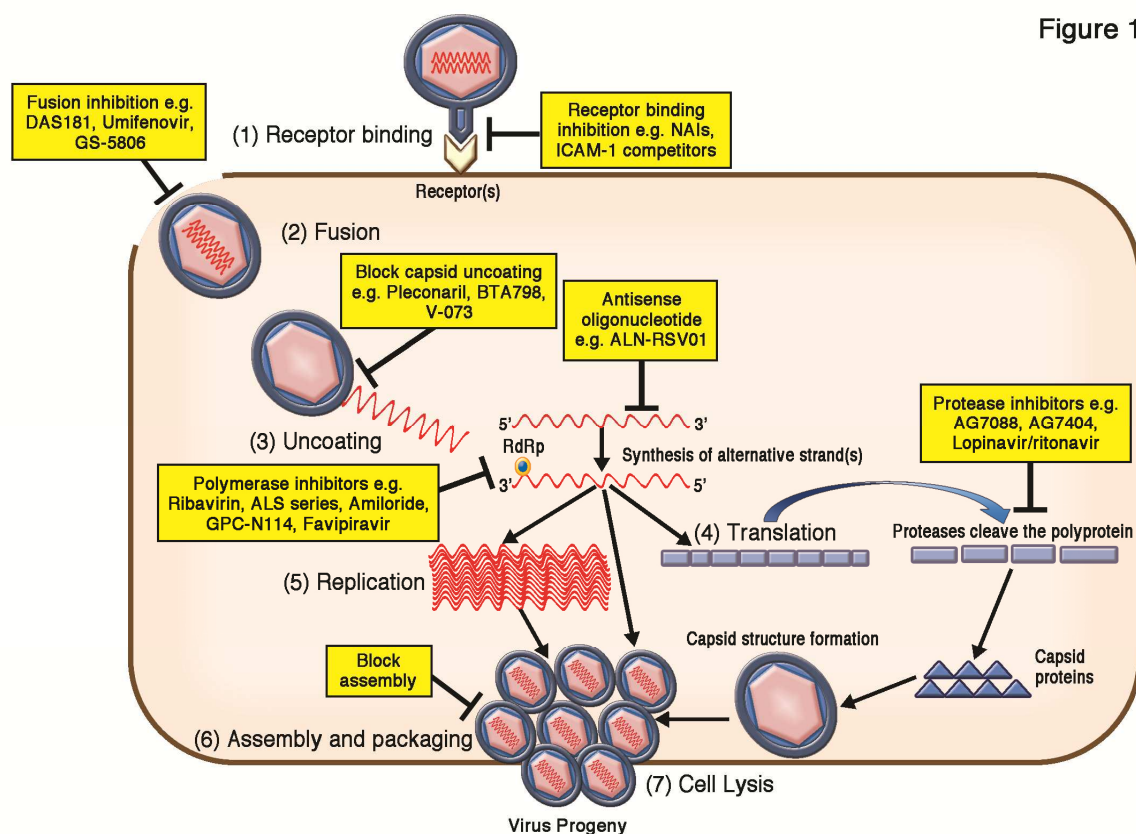
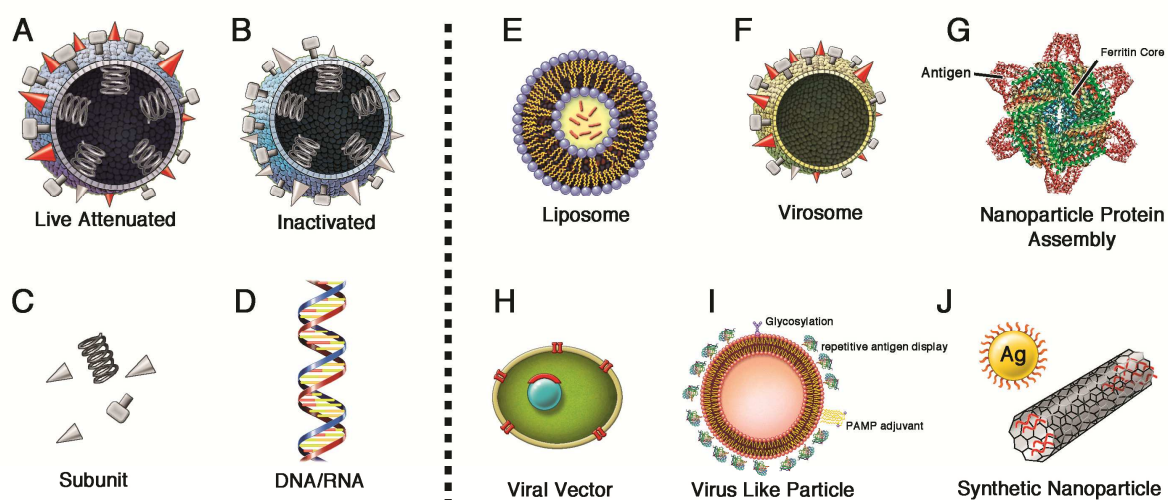


Figure 2



Nanoparticle Vaccines