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Management of acute upper respiratory tract infection: the role of early intervention

De Yun Wang [1], Ronald Eccles[2], John Bell[3], Antonio Hao Chua[4], Sundeep Salvi[5], Natalie Schellack[6], Paulette Marks[7], and Yong Chiat Wong[8]

[1] Department of Otolaryngology, Yong Loo Lin School of Medicine National University of Singapore, Singapore [2] School of Biosciences, Cardiff University, United Kingdom [3] Graduate School of Health, University of Technology Sydney, Australia [4] Department of Otorhinolaryngology-Head and Neck Surgery, St. Luke's Medical Center- Global City, Philippines [5] Department of Clinical Research, Pulmocare Research and Education (PURE) Foundation, India [6] Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, South Africa [7] Procter & Gamble South African Trading (Pty) Ltd, South Africa [8] Procter & Gamble International Operations SA Singapore Branch, Singapore

INTRODUCTION Upper respiratory tract infection (URTI) is an illness caused by an acute infection by viruses or bacteria of the nose, sinuses, pharynx, and larynx. Most URTIs are short, mild, and self-limiting, but some can lead to serious complications, resulting in heavy social and economic burden on individuals and society.

AREAS COVERED This article presents the management guidelines and consensus established through the Delphi method during an expert roundtable conducted in November 2020 and results of a targeted literature review.

EXPERT OPINION There is currently no available cure for acute URTI and management strategies aim towards symptom alleviation and prevention of URTI virus transmission. The effectiveness of these strategies is highly increased with early intervention, administered prior to the peaking of viral shedding. This reduces the chances of developing a full-blown acute URTI, decreases symptom severity, and reduces viral transmission. Mucoadhesive gel nasal sprays have shown promising results for early intervention of acute URTI. They act by creating a barrier that can trap virus particles, thereby preventing invasion of the mucosa by the virus. Additionally, they deliver broad spectrum activity that is effective against a wide variety of pathogens that cause acute URTI. Acute URTI warrants greater attention and proactive management in reducing its burden.

KEYWORDS
acute URTI, mucoadhesive gel nasal spray, hydroxypropyl methylcellulose, HPMC, acute URTI early intervention, acute URTI management, acute URTI treatment, acute URTI risk group, acute upper respiratory tract infection

CONTACT Correspondence: Yong Chiat WONG, Procter & Gamble International Operations SA Singapore Branch, Singapore, Email: wong.y.3@pg.com

1.0 Introduction

Acute upper respiratory tract infections (URTIs) involve the nose, sinuses, pharynx and larynx. Most URTIs are short, mild and self-limiting but some can lead to serious complications such as pneumonia, sinusitis, otitis media and exacerbation of asthma and chronic obstructive pulmonary disease (COPD) (1).

URTIs are among the most important human health problems because of their high incidence and consequent economic costs. It is one of the most common diagnoses in the primary care setting across the world (2, 3), with 17.2 billion cases occurring worldwide in a year (4). Adults tend to have 2-4 episodes of

acute URTI in a year, while pre-school children have an average of 6-10 episodes within the same period (5-8).

URTI also places a heavy economic burden on countries. The estimated annual direct and indirect medical costs for acute URTI exceeds US$40 billion in the US, and £60 million (US$82 million) in the UK (9). Additionally, every year more than US$2 billion is spent on over-the-counter (OTC) medications for URTI worldwide(10). Furthermore, the burden of acute URTI goes beyond economic and clinical aspects. Significant impact is also felt on an individual's quality of life, including their social life, sleep, and school or work performance, illustrating the significant burden of the disease to society (11).

1.1 Aetiology

The majority of URTIs are caused by viruses, while a smaller number of cases are attributed to bacterial infections (1). There are over 200 types of respiratory virus that cause URTIs (6). Among the most common causes of viral URTIs are rhinoviruses (RV; more than 100 antigenic types), influenza viruses (IV; 3 antigenic types), coronaviruses (COV; 5 antigenic types), respiratory syncytial virus (RSV; 2 antigenic types), human parainfluenza viruses (HPIV; 5 antigenic types), and adenoviruses (AV; 47 antigenic types). Bacterial infections may cause ~15% of sudden onset pharyngitis presentations, most commonly caused by *S. pyogenes*, a Group A streptococcus (1).

Several groups of people are at a high risk of contracting a URTI, spreading URTI viruses or developing serious complications, such as those with pre-existing respiratory conditions, smokers, children, older individuals, and those in frequent contacts with infected individuals(1, 12).

2.0 Management of URTI

There is currently no available cure for acute URTI, therefore, guidelines focus on treatments that are aimed at alleviating symptoms. A summary of management guidelines by various authorities is presented in **Table 1**.(13-15)

Table 1. Guideline recommendations on treatment of acute URTI (13-15) (Table view)

Organization	Treatment strategy
World Health Organization (WHO)(13) *(recommendations for young children)*	• Antibiotics should not be used for URTI • Simple, inexpensive cough syrups without alcohol may soothe a sore throat and provide some relief from cough • Oral hydration is safe, beneficial and recommended for a child with a cough or cold • Saline nose drops, administered by a moistened wick, are safe and may be effective to clear a blocked nose • Paracetamol may be used for reduction of high fever and pain relief • Home remedies such as menthol and camphor may be used in topical preparations to be rubbed on the chest

Organization	Treatment strategy
American College of Chest Physicians (ACCP)(14)	• Antibiotics should not be used for the treatment of URTI symptoms in children or adults • First-generation antihistamine/decongestant preparation (brompheniramine and sustained-release pseudoephedrine) for the treatment of acute cough, throat clearing, and postnasal drip • Topical anticholinergic therapy is effective in decreasing rhinorrhea and sneezing • Home remedies, including buckwheat honey and geranium extracts, nasal saline irrigation, vapor rub or zinc sulphate may decrease URTI symptoms in children
UK physician recommendation(15)	• Antibiotics should not be used in uncomplicated URTIs • Combination of a first-generation antihistamine such as chlorphenamine maleate and a nonsteroidal anti-inflammatory drug may reduce rhinorrhea, sneezing, and the amount of nasal secretions • Saline gargle can relieve a sore throat

Immunization has been shown to be a promising wide-scale preventive strategy for containment of IV. However, additional efforts are required for it to be effective in the prevention of RV, as well as many other viral URTI (16). Extensive research and development efforts are underway to find strategies to reduce the burden of viral respiratory diseases through immunization. For the time being, interventions only provide relief for symptoms of URTI.

However, there is a higher likelihood of halting viral replication if medical intervention is administered in the early stages of an infection, prior to the peaking of viral shedding thus minimising transmission (17). Therefore, it is important to intervene as early as possible to disrupt the viral replication cycle.

3.0 What is early intervention?

3.1 URTI viral life cycle

Critical towards administering effective early intervention in acute URTI is the understanding of the viral life cycle. The viral life cycle describes multiple steps involved in the propagation of virus that occurs inside a host cell. This life cycle can be divided into three stages, including viral entry, genome replication, and exit (18). Following the genome replication stage, new viral particles are released, leading to onset of symptoms and viral transmission. **Table 2** describes this process in the URTI viruses (18).

Table 2. Generic overview of the URTI viruses life cycle (18) (Table view)

Stage	Activity	Description
1	Entry	• The nose is the main site of respiratory viral infection(19). • The virus particle arrives at the nasal/nasopharyngeal epithelium and binds to a receptor of epithelial cells • The particle enters the cell via endocytosis/fusion to reach the cytoplasm

Stage	Activity	Description
2	Genome Replication	• In some URTI virus types, the virus releases its genome through a process called “uncoating”. Different uncoating mechanisms are used that may be pH/ temperature dependent or receptor mediated • The viral proteins and RNA are accumulated and assembled to form a progeny viral particle
3	Exit	• Viral shedding occurs via host cell lysis or non-lytic exocytosis • Virus releases to invade more cells

The duration of a virus’ life cycle varies across different URTI viruses. In RV, which is the most common cause of acute URTIs, the length of its life cycle is 8-12 hours, with viral shedding peaking at 48 hours after infection (20).

3.2 URTI symptoms

Upon infection by a virus, a period of incubation takes place before the appearance of URTI symptoms. Incubation times vary among the URTI viruses, for example, 1-5 days for RVs, 1-4 days for IV and HPIV, and 1 week for RSV. Immune response to the infection may be the main factor in generating the symptoms, rather than damage to the airway itself (2). A complex mix of proinflammatory cytokines and mediators generates URTI symptoms, such as bradykinin is believed to play a major role in generating local symptoms of URTI, including sore throat and nasal congestion while cytokines are thought to be responsible for the systemic symptoms, such as fever (2).

Symptoms of URTIs are variable across individuals and are partly influenced by the nature of the infecting virus, while greatly modulated by the age, physiological state, and immunological experience of the host(2). Generally, acute URTI symptoms can be classified as early and late symptoms (2, 21) (**Figure 1**). The duration of symptoms varies from 7-10 days, with a peak occurring on the second or third day. Early symptoms include sniffling, sneezing, throat irritations with occasional chills, headache, and malaise develop and resolve 24-48 hours after infection. Late symptoms are nasal discharge/ obstruction, throat pain from inflamed tonsils/adenoids and cough that develop over several days and last 1 week or more after infection.

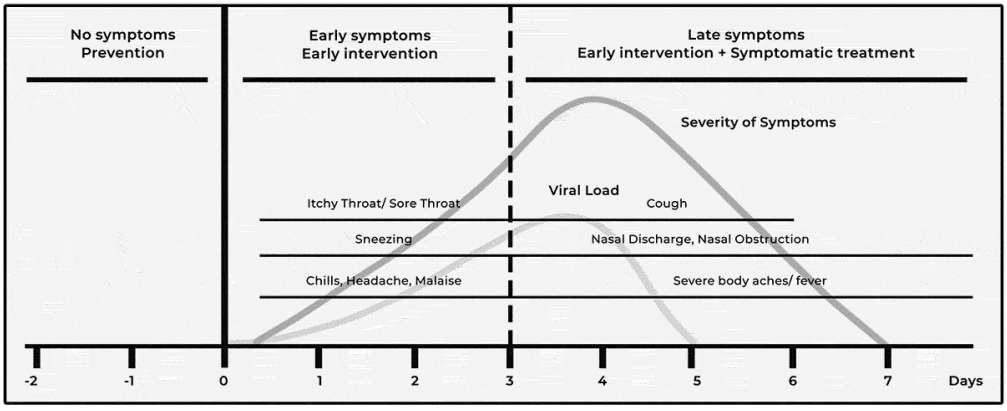

Figure 1. Schematic illustration of early and late symptoms of URTI

4.0 When to intervene?

URTI intervention can be guided by three timepoints that are important for prevention of progression or development of acute URTI.

i. ***As early as possible: during symptom onset.*** Intervening as early as possible, immediately upon the appearance of first symptoms reduces the chance of developing a full blown acute URTI(22-25). It may be easier to slow down or halt viral replication at the early stages of infection.

ii. ***After symptoms progress:*** While intervention at this stage may not be as effective in preventing the development of a full blown URTI or the progression of symptoms, nevertheless, it remains critical even when symptoms are prominent to minimise viral transmission.

iii. ***In the absence of symptoms.*** Those frequently exposed to infected individuals should intervene even in the absence of symptoms when they feel they are at risk of catching an URTI. Intervening at this stage can create a hostile environment for viruses to bind and replicate.

4.1 Benefits of early intervention

The lack of an effective cure or prevention strategy for acute URTIs makes it critical for intervention to be administered as early as possible to disrupt the viral replication cycle. Timely and appropriate early intervention in acute URTI will bring about important benefits, as follows:

i. ***Reduced chances of developing a full blown acute URTI.*** Early intervention is crucial towards the slowing down and potential halting of viral replication. This may potentially allow the immune system to catch up and eliminate the viruses.

ii. ***Decreased severity of acute URTI symptoms.*** Even if a full blown acute URTI is unavoidable, early intervention can result in a shorter or less severe disease manifestation owing to the reduced viral load in the infected individual (26-27).

iii. ***Reduced viral transmission.*** Early intervention can reduce the breadth of viral transmission by preventing virus particles from reaching their host cells and creating a hostile environment for replication (28).

4.2 High risk groups for acute URTI

URTI is a multi-symptom illness with symptom profiles that vary across individuals in terms of severity, duration and types. However, the risk of acquiring the condition is disproportionate and some people are at a higher risk of having a URTI, spreading URTI viruses, or developing more serious URTI complications.

i. Individuals with pre-existing respiratory conditions or smokers

- Inflammation and obstruction from allergic rhinitis or asthma can predispose individuals to URTI·[12]
- Incidence: URTI is a key cause of asthma exacerbations, particularly for children (29) 80-85% of asthma exacerbations among school age children are associated with URTI (29,30).
- Severity: URTI is associated with over 50% of COPD exacerbations (30). The presence of URTI leads to more severe exacerbations and longer recovery times; URTI occurring during an exacerbation can lead to hospitalization (31).

ii. Children

- Children who frequent activities in group settings, such as school or daycare are more prone to exposure to URTI viruses (12).

- Incidence: Children can have 2-4 more URTI episodes than adults per year (2).
- Severity: While URTI symptoms only persist in 20% of adult at day 10, 73% of children still experience symptoms (32).

iii. Elderly

- Upper and lower respiratory tract infections are the leading causes of death and disability due to infection in the elderly.
- Incidence: Compared to the general population, hospitalization rates for URTI-related pneumonia are 12 times higher for those over age 75 years (33).
- Severity: Pneumonia combined with influenza rank seventh as a cause of death in the US and are

the fifth leading cause of death in individuals older than age 65 (33).

As URTI can easily spread from an infected individual to people around them by contact and airborne transmission (34), family members of an infected person, healthcare professionals, and adults having frequent contact with children can also be at high risk of developing acute URTI.

5.0 How to provide early intervention?

Early intervention should be directed to the first site of infection, the nasal cavity. As most early intervention agents have been designed to target specific stages of the viral life cycle, they provide minimal symptom relief and therefore should be used in combination with other treatments to alleviate discomfort caused by URTI symptoms(16).

5.1 Which early intervention?

The ideal early intervention for acute URTI should have the following characteristics (20):

i. Designed to be administered very early in infection to tackle rapid viral replication
ii. Suitable for broad application across the general population
iii. Delivers broad spectrum activity that is effective against a wide variety of viral pathogens that cause acute URTI
iv. Associated with a low risk of resistance development against the intervention

Research into promising anti-viral agents sourced from different origins and targeting different aspects of URTI pathophysiology has been gaining traction in the past decades (20). Among these, antiviral neuraminidase inhibitors and mucoadhesive gel nasal sprays, have been gaining more attention in recent years.

5.2 Antiviral neuraminidase inhibitors for influenza prophylaxis

Neuraminidase inhibitors prevent influenza virus reproduction by blocking the virus release from the host cell (35). Despite being limited by confounding variables, early intervention of influenza with oral or inhaled neuraminidase inhibitors within 48 hours of symptom onset may provide net benefit by reducing duration of symptoms, severity of complications and mortality of influenza (36). Whilst small, non-specific effects in reducing influenza symptom durations were observed in adults and healthy children, no effects were found in children with asthma (35).

5.3 Mucoadhesive gel nasal sprays with non-specific viral actions

Penetration of a virus into the epithelial barrier to result in an infection must be preceded by adherence of the virus to the surface of the mucosal epithelial cells. This process can be interrupted with the use of nasal sprays containing mucoadhesive polymers like iota carrageenan and hydroxypropyl methylcellulose (HPMC) that adhere to the nasopharyngeal mucosa (37-41) to create a barrier that can trap virus particles and thereby prevent invasion of the mucosa by the virus(42, 43). The viral particles are then removed via irrigation and mucociliary clearance towards the nasopharynx and onwards into the stomach, where the virus is destroyed (44). HPMC is useful for the prevention and management of nasal symptoms in allergic rhinitis (45), this helps to demonstrate the non-specific barrier effect of mucoadhesive polymers.

In addition, these mucoadhesive polymers, are widely used in nasal spray drug delivery formulations because they act as gels to increase the retention time in the nasal cavity, thus improving drug uptake (46).

The support for use of mucoadhesive gel as intranasal matrixes against respiratory infections in a non-specific effect was demonstrated by recent studies. The in vitro results showing reduction in viral load were shown to be corroborated by in vivo studies also showing a significant reduction of viral load of different respiratory viruses (28). Importantly, this viral load reduction is clinically demonstrated to manifest shorter and less severe disease (26).

This non-specific viral action is demonstrated across different mucoadhesive gel nasal sprays with similar physico-chemical formulations. Published clinical studies that have investigated iota carrageenan or HPMC mucoadhesive gel nasal sprays on URTI symptoms, recruited natural cold sufferers at the first signs of a cold (22) or who had been experiencing general URTI symptoms for 24-48 hours (2, 23-25). These mucoadhesive gel nasal sprays were shown to reduce duration of URTI symptoms for up to 2.1 to 2.4 days and symptom severity for up to 10 to 17%, validating the notion that mucoadhesive gel nasal sprays that have non-specific actions against respiratory viruses are most likely to be effective in the early stages of a URTI, i.e., under 48 hours, before virus levels have reached their peak. Early intervention using such spray also demonstrated to significantly reduce cold symptoms during the first 4 days when symptoms were most severe, together with a reduction in virus load (27). However, the duration of a virus' life cycle varies across different URTI viruses and the symptoms can be modulated by age (2). In a study conducted in children, mucoadhesive gel nasal spray treatment did not significantly reduce early cold symptoms during days 2 to 7 but however, found to significantly reduce the time to cold resolution at the end of 21 days with reduced viral load (25). All these studies concluded that cold symptoms severity and/ or duration were reduced.

In addition, lower acidity may also cause nasal irrigation and support normal nasal fluid secretion. Published clinical studies showed that HPMC in low pH buffer nasal spray increases mucociliary flow in healthy subjects and subjects with impaired mucociliary flow and reduces nasal resistance (47, 48), suggesting that the application of HPMC in an acidic buffer formula is effective in reducing cold duration and severity when used at the first signs of a cold (22). Overall, the clinical studies results show mucoadhesive gel nasal sprays to be safe, well-tolerated and minimally invasive.

As an early intervention, users are encouraged to use the agent at the first signs of a cold symptoms, within the first 24-48 hours. This is in line with clinical studies, which show that RV infection normally lasts around 7 days with cold symptoms peaking between the second and third days of infection (28). The acute phase of rhinitis (inflammation of the mucous membrane of the nose) usually corresponds with peak virus excretion (28).

6.0 Conclusion

Acute URTI warrants greater attention and proactive management in reducing its burden owing to its high incidence and significant economic and social burden. Timely and appropriate interventions can reduce the impact of acute URTI on individuals and society. A multi-stakeholder engagement approach involving healthcare professionals and patients is required for acceptance towards early intervention of acute URTI

with the objectives to identify high-risk groups for acute URTI and increase communication of the value of early intervention to patients. Mucoadhesive gel nasal sprays are generally safe, well-tolerated and minimally invasive. Healthcare professionals should be encouraged to guide patients on the appropriate use of early intervention, including timing, duration and method of administration.

7.0 Expert Opinion

Although most URTIs are of short duration with mild symptoms, they can lead to serious complications such as pneumonia, rhinosinusitis, otitis media, and exacerbation among high-risk patients with asthma or COPD. In addition to the patient's health, other life aspects are impacted like social interaction, sleep and work performance representing an important burden to society.

Following the diagnosis of URTI infection, both healthcare providers and patients adopt the conventional approach of using over the counter medicines for symptomatic treatment of multiple symptoms like nasal congestion, cough and headache. In addition, according to a World Health Organisation report (49), multi-symptom relief products have potential advantages over single-ingredient medicinal products including better patient adherence, lower cost, simplified logistics of procurement and distribution, and convenience for prescribers and patients.

As most URTIs have neither cure nor effective immunization available, early intervention offers an effective treatment strategy against disease progression. In addition, early intervention may be relevant to prevent infection severity in high-risk patients and disease progression during the pandemic of an acute URTI. However, early intervention in URTI is not widely adopted by either healthcare providers or patients. A multi-stakeholder engagement approach involving both parties is required for acceptance with the objectives to identify high-risk groups for acute URTI and increase communication of the value of early intervention to patients. An effective early intervention reduces viral replication by preventing virus particles from reaching the host cells thus lowering the probability of progression to a full blown acute URTI. Evidence also suggests this approach leads to shorter duration of and/or less severe acute URTI symptoms.

Emerging evidence support for use of non-specific mucoadhesive polymers like carrageenan and hydroxypropyl methylcellulose as intranasal matrixes against respiratory infections. This lack of viral specificity has been clinically demonstrated across different mucoadhesive gel nasal sprays with similar physico-chemical formulations with reduced duration and severity of URTI symptoms being observed. This data helps validate the notion that mucoadhesive gel nasal sprays that have non-specific actions against respiratory viruses are most likely to be effective in the early stages of a URTI. Mucoadhesive gel nasal sprays can be used when URTI symptoms initially manifest, on the virtue that they will minimize further virus replication and decrease overall impact of the infection. In addition, acute application can be recommended for people who suspect they have been being exposed to sources of infection. Given the incubation period of the rhinovirus, the most common cause of URTI, is about 1-5 days then continuous application for 4 days in the absence of URTI symptoms or daily use until symptoms subside is the recommended usage regimen.

Given their rapid onset and non-specific viral activities, it is reasonable to consider mucoadhesive gel nasal sprays in the prophylactic context as a preventative measure against acute URTIs. Current clinical studies demonstrate mucoadhesive gel nasal sprays are generally well tolerated and minimally invasive for acute applications up to two weeks. Further longitudinal studies evaluating mucosal tolerability, desensitization effects and viral load dynamics are required to increase the level of evidence for universal prophylactic use against acute URTIs.

In summary, non-specific mucoadhesive polymers delivered in nasal spray format offer a viable early intervention for treating acute viral URTI. Further research is required to determine their role as prophylactic agents against the same infections. Incorporated into relevant clinical guidelines, combined with adequate

education and awareness among healthcare professionals the use of these polymers may offer a promising and simplified alternative to vaccines.

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References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Thomas M, Bomar PA. Upper Respiratory Tract Infection. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.
2. Eccles R. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis. 2005;5(11):718-25. 10.1016/S1473-3099(05)70270-X. 16253889. *This paper provides the an overview of the disease of interest.
3. MOH. Primary Care Survey 2010. 2010.
4. Jin X, Ren J, Li R, Gao Y, Zhang H, Li J, Zhang J, Wang X, Wang G. Global burden of upper respiratory infections in 204 countries and territories, from 1990 to 2019. EClinicalMedicine 37 (2021) 100986. 10.1016/j.eclinm.2021.100986 34386754; Central PMCID: PMC8343248
5. Heikkinen T, Järvinen A. The common cold. Lancet. 2003;361(9351):51-9. Epub 2003/01/09. 10.1016/s0140-6736(03)12162-9. 12517470; Central PMCID: PMC7112468.
6. Grief SN. Upper Respiratory Infections. Primary Care: Clinics in Office Practice. 2013; 40(3): 757-770 ISBN 9780323188685.
7. Turner RB. The common cold. Goldman's Cecil Medicine. 2012: 2089-2091. 10.1016/B978-1-4377-1604-7.00369-9. Central PMCID: PMC7173442.
8. Winther B, Gwaltney JM, Mygind N, Hendley JO. Viral Induced Rhinitis. American Journal of Rhinology. 1998;12(1):17-20. 10.2500/105065898782102954
9. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015;386(9995):743-800. 10.1016/S0140-6736(15)60692-4.
10. West JV. Acute upper airway infections: Childhood respiratory infections. British Medical Bulletin. 2002;61(1):215-30. 10.1093/bmb/61.1.215.
11. Linder JA, Singer DE. Health-related quality of life of adults with upper respiratory tract infections. J Gen Intern Med. 2003;18(10):802-7. 10.1046/j.1525-1497.2003.21246.x. 14521642.
12. Meneghetti A. Upper Respiratory Tract Infection: Medscape; 2020. Available from: https://emedicine.medscape.com/article/302460-overview.
13. Cough and Cold Remedies for the Treatment of Acute Respiratory Infections in Young Children 2001. World Health Organization. https://apps.who.int/iris/handle/10665/66856.
14. Pratter MR. Cough and the common cold: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):72S-4S. 10.1378/chest.129.1_suppl.72S. 16428695.
15. Virgincar N, Spencer R. Current management options for upper respiratory tract infection. Prescriber. 2006;17(1):16-23. Epub 2009/02/11. 10.1002/psb.326. PMC7168120.
16. Papadopoulos NG, Megremis S, Kitsioulis NA, Vangelatou O, West P, Xepapadaki P. Promising approaches for the treatment and prevention of viral respiratory illnesses. J Allergy Clin Immunol. 2017;140(4):921-32. Epub 2017/07/21. 10.1016/j.jaci.2017.07.001. 28739285.
17. Arruda E, Cintra OA, Hayden FG. Respiratory Tract Viral Infections. Tropical Infectious Diseases. 2006:637-59. Epub 2009/05/15. 10.1016/B978-0-443-06668-9.50064-8. PMC7152450.
18. Ryu W-S. Virus Life Cycle. Molecular Virology of Human Pathogenic Viruses. 2017:31-45. Epub 2016/05/06. 10.1016/B978-0-12-800838-6.00003-5. PMC7158286.*This paper discusses the pathophysiology of the disease of interest.
19. Andersen I. The fate and effects of inhaled materials. The nose: Upper airway physiology and the atmospheric environment. 1982:423-55.
20. Rollinger JM, Schmidtke M. The human rhinovirus: human-pathological impact, mechanisms of antirhinoviral agents, and strategies for their discovery. Med Res Rev. 2011;31(1):42-92. 10.1002/med.20176. 19714577.

21. Witek TJ, Ramsey DL, Carr AN, Riker DK. The natural history of community-acquired common colds symptoms assessed over 4-years. Rhinology. 2015; 53(1):81-8. 10.4193/Rhino14.149. 25756083. *This paper gives an overview of the symptoms progression of the disease.
22. Hull D, Rennie P, Noronha A, Poore C, Harrington N, Fearnley V, et al. Effects of creating a non-specific, virus-hostile environment in the nasopharynx on symptoms and duration of common cold. Acta Otorhinolaryngol Ital. 2007;27(2):73-7. 17608134. **This study demonstrated the effectiveness of HPMC in low pH buffer for early intevention against cold.
23. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. Qjm. 2003;96(1):35-43. Epub 2003/01/02. 10.1093/qjmed/hcg004. 12509647.
24. Ludwig M, Enzenhofer E, Schneider S, Rauch M, Bodenteich A, Neumann K, et al. Efficacy of a carrageenan nasal spray in patients with common cold: a randomized controlled trial. Respir Res. 2013;14(1):124. Epub 2013/11/14. 10.1186/1465-9921-14-124. 24219370; Central PMCID: PMCPMC3840586. **This study demonstrated the effectiveness of carrageenan for early intevention against cold.
25. Fazekas T, Eickhoff P, Pruckner N, Vollnhofer G, Fischmeister G, Diakos C, et al. Lessons learned from a double-blind randomised placebo-controlled study with a iota-carrageenan nasal spray as medical device in children with acute symptoms of common cold. BMC Complement Altern Med. 2012;12:147-. 10.1186/1472-6882-12-147. 22950667.
26. Eccles R, Meier C, Jawad M, Weinmüllner R, Grassauer A, Prieschl-Grassauer E. Efficacy and safety of an antiviral Iota-Carrageenan nasal spray: a randomized, double-blind, placebo-controlled exploratory study in volunteers with early symptoms of the common cold. Respir Res. 2010;11(1):108. Epub 2010/08/11. 10.1186/1465-9921-11-108. 20696083; Central PMCID: PMCPMC2923116.
27. Eccles R, Winther B, Johnston SL, Robinson P, Trampisch M, Koelsch S. Efficacy and safety of iota-crrageenan nasal spray versus placebo in early treatment of the common cold in adults: the ICICC trial. Respir Res. 2015; 16: 121. 10.1186/s12931-015-0281-8. 26438038; Central PMCID: PMC4595062.
28. Rennie P, Bowtell P, Hull D, Charbonneau D, Lambkin-Williams R, Oxford J. Low pH gel intranasal sprays inactivate influenza viruses in vitro and protect ferrets against influenza infection. Respir Res. 2007;8(1):38. Epub 2007/05/19. 10.1186/1465-9921-8-38. 17509128; Central PMCID: PMCPMC1885256.
29. Guilbert TW, Denlinger LC. Role of infection in the development and exacerbation of asthma. Expert Rev Respir Med. 2010;4(1):71-83. Epub 2010/03/23. 10.1586/ers.09.60. 20305826; Central PMCID: PMCPMC2840256.
30. Rakes GP, Arruda E, Ingram JM, Hoover GE, Zambrano JC, Hayden FG, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. Am J Respir Crit Care Med. 1999;159(3):785-90. Epub 1999/03/02. 10.1164/ajrccm.159.3.9801052. 10051251.
31. Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2004;1(2):115-20. Epub 2005/08/23. 10.1513/pats.2306030. 16113423.
32. Cotton M, Innes S, Jaspan H, Madide A, Rabie H. Management of upper respiratory tract infections in children. South African family practice: official journal of the South African Academy of Family Practice/Primary Care. 2008;50:6-12. 10.1080/20786204.2008.10873685.
33. Meyer KC. Lung infections and aging. Ageing Res Rev. 2004;3(1):55-67. Epub 2004/05/28. 10.1016/j.arr.2003.07.002. 15163102; Central PMCID: PMCPMC7129100.
34. Kutter JS, Spronken MI, Fraaij PL, Fouchier RAM, Herfst S. Transmission routes of respiratory viruses among humans. Current Opinion in Virology. 2018;28:142-51. https://doi.org/10.1016/j.coviro.2018.01.001.
35. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2014;2014(4):Cd008965. Epub 2014/04/11. 10.1002/14651858.CD008965.pub4. 24718923.
36. Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Annals of Internal Medicine. 2012;157(7). 10.7326/0003-4819-156-7-201204030-00411. 22371849. Central PMCID: PMC6679687
37. Moraga-Espinoza D, Warnken Z, Moore A, Williams RO, 3rd, Smyth HDC. A modified USP induction port to characterize nasal spray plume geometry and predict turbinate deposition under flow. Int J Pharm. 2018;548(1):305-13. Epub 2018/07/01. 10.1016/j.ijpharm.2018.06.058. 29960037.
38. Shin Y, Kokate R, Desai V, Bhushan A, Kaushal G. D-cycloserine nasal formulation development for anxiety disorders by using polymeric gels. Drug Discov Ther. 2018;12(3):142-53. Epub 2018/07/13. 10.5582/ddt.2018.01017. 29998995.
39. Pandey P, Cabot PJ, Wallwork B, Panizza BJ, Parekh HS. Formulation, functional evaluation and ex vivo performance of thermoresponsive soluble gels - A platform for therapeutic delivery to mucosal sinus tissue. Eur J Pharm Sci. 2017;96:499-507. Epub 2016/10/28. 10.1016/j.ejps.2016.10.017. 27771516.
40. Braga PC, Alfieri M, Dal Sasso M, Culici M. Visual evaluation of binding to mucosal cells of a medical device against the common cold. Drug Dev Ind Pharm. 2008;34(5):459-64. Epub 2008/05/14. 10.1080/03639040701657909. 18473226.
41. Cook SL, Bull SP, Methven L, Parker JK, Khutoryanskiy VV. Mucoadhesion: A food perspective. Food Hydrocolloids. 2017;72:281-96. https://doi.org/10.1016/j.foodhyd.2017.05.043.
42. Leibbrandt A, Meier C, König-Schuster M, Weinmüllner R, Kalthoff D, Pflugfelder B, et al. Iota-carrageenan is a potent inhibitor of influenza A virus infection. PLoS One. 2010;5(12):e14320. Epub 2010/12/24. 10.1371/journal.pone.0014320. 21179403

43. Grassauer A, Weinmuellner R, Meier C, Pretsch A, Prieschl-Grassauer E, Unger H. Iota-Carrageenan is a potent inhibitor of rhinovirus infection. Virol J. 2008;5:107. Epub 2008/09/27. 10.1186/1743-422x-5-107. 18817582; Central PMCID: PMCPMC2562995.

44. Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Adv Drug Deliv Rev. 2005;57(11):1640-65. Epub 2005/09/27. 10.1016/j.addr.2005.07.009. 16182408.

45. Popov TA, Åberg N, Emberlin J, Josling P, Ilyina NI, Nikitin NP, et al. Methyl-cellulose powder for prevention and management of nasal symptoms. Expert Rev Respir Med. 2017;11(11):885-92. Epub 2017/09/02. 10.1080/17476348.2017.1375408. 28862062.

46. Gänger S, Schindowski K. Tailoring Formulations for Intranasal Nose-to-Brain Delivery: A Review on Architecture, Physico-Chemical Characteristics and Mucociliary Clearance of the Nasal Olfactory Mucosa. Pharmaceutics. 2018;10(3). Epub 2018/08/08. 10.3390/pharmaceutics10030116. 30081536; Central PMCID: PMCPMC6161189.

47. Giranda VL, Heinz BA, Oliveira MA, Minor I, Kim KH, Kolatkar PR, et al. Acid-induced structural changes in human rhinovirus 14: possible role in uncoating. Proc Natl Acad Sci U S A. 1992;89(21):10213-7. Epub 1992/11/01. 10.1073/pnas.89.21.10213. 1332036; Central PMCID: PMCPMC50308.

48. Passàli D, Giannuzzi AL, Salerni L, Passàli FM, De Benedetto L, De Benedetto M. [Efficacy and distribution pattern of the medical device Prima Difesa on rhinosinusal area]. Clin Ter. 2006;157(1):15-8. Epub 2006/05/04. 16669547.

49. World Health Organization. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Annex 5, Guideline for registration of fixed-dose combination medicinal products. WHO Technical Report Series, No. 929, 2005. https://www.gmp-compliance.org/files/guidemgr/WHO_TRS_929_annex5.pdf