Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Postviral Complications
Bacterial Pneumonia

Jason E. Prasso, MDa, Jane C. Deng, MD, MSb,*

BACKGROUND

Introduction
As the so-called Spanish flu raged around the world during 1918 to 1919, the burden of morbidity and mortality resulted not only from influenza infection but also from subsequent bacterial pneumonia, accounting for more than 90% of the estimated 50 million deaths caused by the pandemic.1–4 During the 1957 and 1968 influenza pandemics, secondary bacterial infection was associated with 50% to 70% of severe infections, with the decrease attributed to the advent of antibiotics.5–7 Coinfection was noted in approximately 30% of those infected during the H1N1 pandemic in 2009, particularly in fatal cases.8–11 Despite substantial advances in medicine and the availability of potent antibacterial and antiviral agents, influenza and pneumonia remain among the leading causes of death in the United States and worldwide.12,13 The complex mechanisms underlying the pathogenesis of postviral bacterial pneumonia are incompletely understood, but involve a variety of host and microbial factors that allow secondary opportunistic bacterial infections to arise in virally infected individuals. This article reviews the current understanding of how virally infected hosts are more susceptible to bacterial pneumonia as well as the management of this important complication of viral infections.

Common Causal Organisms

Viral-bacterial coinfections are a commonly encountered clinical problem. Although the precise rates of secondary bacterial infections are difficult to quantify because of a lack of comprehensive reporting systems and the impracticality of obtaining microbiologic testing in all patients with respiratory infections, bacterial pneumonia...
is estimated to complicate from 0.5% to 6% of influenza infections, with higher rates among hospitalized patients in intensive care units and fatal cases. Influenza is one of many viral pathogens that have been associated with bacterial coinfections. Human parainfluenza virus, adenovirus, human metapneumovirus, measles, respiratory syncytial virus (RSV), human rhinovirus, and coronavirus are also commonly associated with secondary bacterial pneumonia. Of these viruses, influenza is arguably most important given its continuously evolving virulence factors and the sheer number of individuals infected on an annual basis. Given its public health importance, as well as the fact that influenza is the most extensively studied, bacterial pneumonia following influenza infections is the primary focus of this article.

Irrespective of the offending viral organism, causal agents of secondary bacterial pneumonia largely reflect colonizing nasopharyngeal flora. This finding has fueled the theory that viral infection causes impaired mucosal and ciliary clearance of these normally nonpathogenic bacteria, which enables particular bacteria to flourish and causes invasive infections. Epidemiologically, *Streptococcus pneumoniae* and *Staphylococcus aureus* (both methicillin-sensitive *S. aureus* and methicillin-resistant *S. aureus* [MRSA]) are most common, with *Streptococcus pyogenes* and *Hemophilus influenzae* less frequently isolated. However, infections in humans are often polymicrobial, involving combinations of multiple viruses and/or bacteria. Common viral-bacterial coinfections are summarized in Table 1.

### Clinical Presentation

The incidence of bacterial pneumonia mirrors the seasonal nature of viral infections, with increases during peak viral seasons. Data from the 2009 H1N1 epidemic show that coinfection usually occurs within the first 6 days of influenza infection, although it can develop up to 14 days after other viral infections. This delay likely represents the time needed for viral replication and the immunomodulatory effects of infection to occur. Patients with secondary pneumonia tend to have a more severe, protracted course, with increased mortality compared with those without antecedent viral infection. Although patients with comorbid conditions or at the extremes of age are at increased risk of complicated influenza infections, even previously

---

### Table 1

| Virus                         | Known Bacterial Coinfections    | Associated Secondary Infections |
|-------------------------------|---------------------------------|---------------------------------|
| Influenza                     | *S. pneumoniae*                 | Pneumonia                       |
|                               | *S. aureus*                     |                                 |
|                               | *S. pyogenes*                   |                                 |
|                               | *H. influenzae*                 |                                 |
|                               | *Moraxella catarrhalis*         |                                 |
|                               | *Neisseria meningitidis*        |                                 |
| Respiratory syncytial virus   | *S. pneumoniae*                 | Pneumonia                       |
| Adenovirus                    |                                 | Bronchitis/bronchiolitis        |
|                               |                                 |                                 |
| Coronavirus                   | *H. influenzae*                 | Pneumonia                       |
|                               | *M. catarrhalis*                |                                 |
| Human rhinovirus              | *S. pneumoniae*                 | Pneumonia                       |
|                               | *H. influenzae*                 |                                 |
|                               | *S. aureus*                     |                                 |
|                               | *M. catarrhalis*                |                                 |
| Parainfluenza virus           | *S. pneumoniae*                 | Pneumonia                       |
|                               | *M. catarrhalis*                |                                 |
| Human metapneumovirus         | *S. pneumoniae*                 | Pneumonia                       |
| Measles virus                 | *S. pneumoniae*                 |                                 |
|                               | *S. aureus*                     | Otitis media                    |
|                               | *H. influenzae*                 | Pneumonia                       |
|                               |                                 | Tracheobronchitis               |
healthy patients can develop severe respiratory failure and death from bacterial pneumonias following influenza, underscoring the clinical significance of this problem.

Secondary bacterial pneumonia is one of several known infectious complications of respiratory viruses. Viral infections have also been associated with acute otitis media and bacterial sinusitis in children. In addition, meningococcal meningitis has been reported as a complication of influenza infections.

**PATHOGENESIS**

Several excellent reviews have been published of the current mechanistic understanding of how viral infections increase susceptibility to secondary bacterial pneumonias. Thus, this article provides only a brief overview, with a primary focus on virally mediated effects on pulmonary host defense and subsequent impairment of bacterial clearance (Table 2). However, the authors acknowledge that microbiologic and epidemiologic factors can contribute to the pathogenesis of viral-bacterial coinfections.

**Colonization**

Colonization of the nasopharynx is generally the first step in the development of pneumonia and other bacterial infections of the upper respiratory tract, including sinusitis and otitis media. S pneumoniae, S aureus, H influenzae, S pyogenes, and Moraxella catarrhalis are normal inhabitants of the upper respiratory tract in healthy human hosts, with the lower respiratory tract generally considered to have low abundance of bacteria. Although these bacteria normally exist in an equilibrium governed by host, intermicrobial, and environmental factors, under the appropriate circumstances, they can proliferate and become invasive. Studies have shown an inverse relationship between nasal carriage of S pneumoniae and S aureus. Other groups have

| Immune Function | Viral-mediated Effect |
|-----------------|----------------------|
| Nasopharyngeal colonization | • Altered host microbiota, possibly in favor of more pathogenic organisms |
| Direct mucosal/epithelial damage | • Breakdown of mucin by viral and bacterial neuraminidase  
• Destruction of epithelium and exposure of basement membrane  
• Impairment of ciliary function |
| Enhanced bacterial adherence | • Cleavage of sialic acid → exposure of receptors for bacteria on mucosal surface |
| Alveolar macrophage response | • Decreased number of AMs after viral infection  
• Downregulation of MARCO (macrophage receptor with collagenous structure) receptor resulting in impaired phagocytosis of bacteria  
• Reduced chemokine expression and immune cell recruitment  
• Desensitization of Toll-like receptors → long-term immune defects |
| Neutrophil response | • Possible reduced recruitment to the lung  
• Decreased phagocytic function  
• Reduced production of reactive oxygen species  
• Impaired NETs function |
| Altered cytokine milieu | • Increased type I interferons → reduced macrophage and neutrophil recruitment to the lung  
• Increased type II interferons → impaired macrophage phagocytic function, possible viral skewing of neutrophils  
• Attenuated T_17 cell function and decreased IL-17 secretion → increased susceptibility to S pneumoniae, decreased production of antimicrobial peptides |

*Abbreviations: AMS, alveolar macrophages; IL, interleukin; NETs, neutrophil extracellular traps; T_17, T-helper.*
revealed antagonistic as well as synergistic relationships between members of the normal respiratory community (e.g., corynebacteria and S. aureus, Corynebacterium accolens and S. pneumoniae, H. influenzae and S. pneumoniae).59–62

In addition, viruses can alter bacterial composition. Our laboratory recently examined changes in the nasal microbiome following intranasal administration of live attenuated influenza vaccine. Although individual hosts had disparate microbiome profiles at baseline, after vaccination, the relative abundance of staphylococcal and Bacteroides species was significantly increased. This finding suggests that viral stimuli can alter the host microbiota, potentially by creating a suitable environment in which an otherwise nonpathogenic organism can grow and become invasive.68–70

**Mucosal Barrier Function and Bacterial Adherence**

Disruption of the mucosal barrier is an important potentiating mechanism for secondary bacterial infection. Mucin present in the respiratory tract can be partially degraded by viral and bacterial neuraminidase.65,66 Viral neuraminidase is tropic for the sialic acid present on respiratory epithelial cells, cleavage of which may uncover receptors for bacterial ligand, thereby promoting bacterial adhesion and infection. Furthermore, the increased availability of sialic acid in the airway has been shown to promote growth and proliferation of pneumococcus, which uses this moiety as a nutrient source.67 In murine models, higher levels of viral neuraminidase are associated with increased severity of secondary bacterial infection, whereas treatment with oseltamivir decreases bacterial adherence to epithelial cells.68–70

Influenza and paramyxoviruses such as RSV can also augment bacterial adhesion by augmenting expression of receptors for bacteria on the epithelial cell surface. One example is platelet-activating factor receptor (PAFR), which binds to the phosphorylcholine present in some bacterial cell walls and facilitates bacterial invasion.71 In a mouse model of pneumococcus pneumonia, PAFR was shown to increase total lung bacterial load, bacteremia, and mortality.72 However, blocking this receptor did not show any benefit in an influenza coinfection model, suggesting that this mechanism is not a sufficient factor for enhancing susceptibility to secondary bacterial pneumonias.73 Other receptors involved in adhesion, such as CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) and ICAM-1 (intracellular adhesion molecule 1), are overly expressed on pulmonary epithelial cells after viral infection as well.74,75

Epithelial cell death and breakdown of tight junctions resulting from viral infection can cause increased translocation of bacteria such as H. influenzae.76,77 In addition, certain bacterial species have a known binding affinity for the basement membrane and extracellular matrix proteins,78–81 suggesting that breakdown of the epithelium might lead to increased translocation, although this has never been proved to be a critical mechanism during infections with less cytotoxic strains of influenza in vivo. In addition, viral respiratory infections are known to negatively affect respiratory ciliary function, thereby impairing the host’s ability to mechanically clear aspirated pathogens from the lung.82,83

**Macrophage and Neutrophil Function**

 Resident alveolar macrophages (AMs) play an integral role in host defense against viral and bacterial pathogens alike. As the main resident innate immune cells to encounter pathogens in the resting lung, they engage in phagocytosis and killing, antigen presentation, recruitment of other cell types, and paracrine and endocrine signaling. Viral respiratory infections are known to impair macrophage phagocytic function as well as monocyte chemotaxis to the lung early after influenza infection, and this has been proposed as a potential cause for secondary bacterial infection.59,84–89

In mouse models of sequential influenza-bacterial infection, AMs are known to be decreased in number with increased susceptibility and mortality to secondary bacterial challenge. Influenza infection has also been shown to downregulate expression of the class A scavenger receptor MARCO on AMs, which phagocytose unopsonized bacteria in the lung.84 Augmenting AM numbers and function by exogenous granulocyte-macrophage colony-stimulating factor in animals infected with influenza improves pneumococcus clearance following secondary bacterial challenge, increases reactive oxygen species, and decreases incidence of secondary pneumonia.90–92

Viral infections affect the ability of AMs to attract other cell types to the lung. Neutrophils are robustly recruited following the elaboration of chemokines by AMs and epithelial cells in the setting of invasive bacterial infection. Our laboratory has shown that macrophage expression of neutrophil chemoattractants CXCL1 (C-X-C motif chemokine ligand 1) (KC) and CXCL2 (C-X-C motif chemokine ligand 2) (MIP2) is reduced after influenza infection, with consequent diminished recruitment of neutrophils to the lung.93 Desensitization of
Toll-like receptors (TLRs) on alveolar macrophages may partially explain the decrease in neutrophil recruitment and impaired bacterial clearance. Mice infected with influenza or RSV showed decreased activation of nuclear factor kappa-B (NF-KB) and expression of KC and MIP2, resulting in decreased neutrophil recruitment to the lung after stimulation with bacterial ligands. In addition, influenza infection results in an early, prolonged decrease in PMN (polymorphonuclear cell) phagocytic function and depressed reactive oxygen species production. Thus, during viral infection, multiple aspects of pulmonary innate immunity are compromised, leading to impaired antibacterial host defense.

**Viral Effects on the Cytokine Milieu**

Viral infection elicits a robust cytokine response via activation of TLRs and retinoic acid inducible gene (RIG-I) in immune cells and downstream upregulation of NF-KB. This response results in production of type I and II interferons (IFN) as part of the host antiviral response, and these in turn alter other cytokine-mediated effects.

**Type I interferons**

Predominantly comprised of multiple IFN-alpha proteins and 1 IFN-beta protein, these antiviral mediators can be secreted by multiple different immune cells and help to limit viral replication. Induction of type I IFNs is known to increase the risk of secondary bacterial infection, despite type I IFNs also contributing to host antibacterial response. Mice deficient in the type I IFN receptor are protected against subsequent bacterial challenge after influenza infection, likely because type I IFNs inhibit KC and MIP2 production and neutrophil recruitment to the lung. Monocyte and macrophage recruitment to the upper respiratory tract is suppressed by type I IFNs via blockade of Nod2-mediated expression of CCl2 (C-C motif chemokine ligand 2; a macrophage chemoattractant), with resultant increase in carriage of *S. pneumoniae*. These studies highlight the heterogeneous effects of IFNs in the immune response to pathogens.

**Type II interferon (interferon-gamma)**

Viral respiratory infection also stimulates IFN-gamma production, primarily by natural killer cells but also by CD4+ T-helper (Th) cells and CD8+ cytotoxic T cells and neutrophils. In the context of secondary bacterial pneumonia following influenza, IFN-gamma has been shown to impair phagocytosis in alveolar macrophages, partially by downregulation of the scavenger receptor MARCO. Inhibition of interleukin (IL)-10 results in increased neutrophil recruitment to the lung and improved clearance of *S. pneumoniae*, and can salvage animals from death after sequential influenza-bacterial infection. However, in normal hosts, exogenous administration of IL-12 results in increased levels of IFN-gamma in the lung, robust neutrophil recruitment, and improved innate pulmonary defense against *S. pneumoniae*. In addition, in mouse models of *S. pneumoniae* and *S aureus* pneumonia, IL-12–independent IFN-gamma production by neutrophils in the lung was shown to be essential to bacterial clearance, possibly because of IFN-gamma–regulated production of neutrophil extracellular traps (NETs). These paradoxical findings in naive hosts versus hosts infected with influenza suggest that neutrophils recruited in the setting of viral respiratory infection are unable to mount antibacterial functions that would normally be activated by interferon-gamma, which may reflect distinct neutrophil phenotypes in the setting of viral versus bacterial infections. Unpublished data from our laboratory show striking transcriptional differences in neutrophils that are recruited to the lung in the setting of influenza and sequential influenza–*S pneumoniae* infection, compared with those recruited in the setting of *S pneumoniae* infection alone.

**T-helper 17 cells and interleukin-17**

Influenza infection is known to attenuate Th17 cell–mediated immunity. Type I IFNs decrease production of IL-1β and IL-23, which are necessary for polarization of Th17 cells. During influenza–*S aureus* coinfection, there are resultant decreases in IL-17, IL-22, and monocyte chemoattractant protein-1 that correlate with reduced clearance of bacteria. They also likely inhibit IL-17 secretion by gamma-delta T cells, resulting in increased susceptibility to secondary *S pneumoniae* infection. In addition, influenza infection in mice was shown to suppress production of antimicrobial peptides in response to subsequent *S aureus* infection via a Th17–mediated mechanism, leaving animals more susceptible to pneumonia. Exogenous administration of the antimicrobial peptide lipocalin 2 restored bacterial clearance in these animals.
whereas point-of-care influenza antigen tests are insufficiently sensitive. PCR-based panels for common respiratory viral pathogens are more sensitive and can be useful, but are expensive for routine use and are not able to distinguish between colonization versus true viral infection. Furthermore, in low-volume laboratories, results may not be available for days. On radiologic imaging, lobar consolidation with or without pleural effusion is presumed to be bacterial; however, multifocal infiltrates can represent either multilobar bacterial pneumonia or acute respiratory distress syndrome from severe viral infection alone. RSV and adenovirus have some hallmark features on computed tomography scan of the chest; however, imaging studies are generally unhelpful. Increased C-reactive protein level in the blood correlates with presence of pneumonia but poorly distinguishes viral from bacterial causes. Procalcitonin (PCT), another serum biomarker, is better able to differentiate the two. In one study of coinfection, low PCT level was associated with 94% negative predictive value for bacterial infection, although in patients with shock, or in malaria endemic areas, it may be less reliable. Thus, given the absence of rapid and reliable diagnostic tests, clinicians must always consider the possibility of secondary bacterial infection in patients presenting with severe respiratory infections during influenza season and manage them accordingly.

**Vaccination**

Infections caused by influenza, measles, *H influenzae*, *S pneumoniae*, and some strains of adenovirus are all considered vaccine-preventable illnesses. Although influenza vaccination is universally recommended, vaccination against invasive pneumococcal infection is reserved for high-risk groups, including children, the elderly, and patients with immunosuppressive or chronic lung conditions. Although robust evidence from randomized placebo-controlled trials is lacking, data from animal models of influenza-bacterial coinfection and observational studies in patients have indicated that influenza vaccine can reduce the morbidity and mortality associated with bacterial pneumonia. Thus, on balance, vaccination against influenza currently represents the most effective public health strategy for reducing the incidence of secondary bacterial pneumonia. However, pneumococcal vaccination did not have the same effect in a large study of elderly patients, potentially because of replacement of covered serotypes with those not included in the vaccine. This finding mirrors data from animal models of dual infection. In contrast, vaccination against the M protein of *S pyogenes* seems to be protective against superinfection. It is unknown whether vaccination against other pathogens affects the incidence or severity of secondary bacterial pneumonia.

**Antibiotic Therapy**

Antibiotic treatment of secondary bacterial pneumonia should mirror local guidelines for that of community-acquired pneumonia (ie, based on local patterns of antibiotic resistance), with the caveat that these patients are at increased risk of *S aureus* infection, including MRSA. In patients with cavitation noted on imaging, severe respiratory infection requiring admission to the intensive care unit, or risk factors for hospital-acquired pathogens, treatment with either vancomycin or linezolid should be started empirically. As an aside, in a mouse model of influenza-MRSA infection, treatment with linezolid showed unique immunomodulatory effects on toxic production and lung inflammation with equivalent bacterial clearance; however, whether or not this translates to improved clinical outcomes in humans still needs to be studied.

**Antiviral Agents**

There are 2 classes of antiviral drugs with activity against influenza: the adamantines (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir). At present, use of the adamantines has become uncommon because of high levels of drug resistance and side effects. As previously mentioned, viral infection is often indistinguishable from lower respiratory tract infection. As such, during seasons of heightened influenza prevalence, empiric antiviral therapy is warranted pending the results of microbiologic testing. In ambulatory patients who have had symptoms for fewer than 48 hours, treatment with oseltamivir or zanamivir has been shown to reduce the duration of symptoms. In hospitalized patients, they may have benefit irrespective of when symptoms began.

Given their mechanism of action, neuraminidase inhibitors should theoretically prevent or reduce the severity of secondary bacterial pneumonia. This effect has been described in animal models of disease. In the pediatric population, oseltamivir use has been associated with a 44% reduction in subsequent diagnosis of otitis media. Although individual trials in adult patients were not powered to detect any effect of oseltamivir on lower respiratory tract infection, a meta-analysis showed decreased incidence. Inhaled ribavirin is approved for treatment of severe RSV
bronchiolitis; however, the treatment is cumbersome and the drug teratogenic, which presents a problem for hospital personnel because it is aerosolized for administration. As such, it is rarely used and its effects on secondary bacterial infection are unknown.

**Immunomodulatory Agents**

Given the role of inflammation in viral-bacterial co-infection and the pathogenesis of secondary pneumonia, there is significant interest in the utility of immunomodulatory drugs in this setting. Corticosteroids have been studied, and although data from mouse models show some protection against secondary pneumonia, they resulted in delayed viral clearance.150 In patients with severe influenza infection, the results of such studies show either no benefit or possible harm to patients caused by worsened infectious complications.151–155 As such, their use is not recommended. Other agents under active investigation include statins (coenzyme A reductase inhibitors), peroxisome proliferator–activated receptor agonists, cyclooxygenase inhibitors, macrolide antibiotics, and antibody-based therapies such as intravenous immunoglobulin and experimental monoclonal antibodies, all of which are in the preclinical stages of testing.146

**SUMMARY**

Secondary bacterial pneumonia after viral respiratory infection remains a significant source of morbidity and mortality. Susceptibility is mediated by a variety of viral and bacterial factors, as well as complex interactions with the immune system of the infected host. To date, prevention and treatment strategies are limited to influenza vaccination and antibiotics/antivirals respectively. Novel approaches to identifying the individuals infected with influenza who are at increased risk for secondary bacterial pneumonias are urgently needed, given the ongoing threat of another influenza pandemic. Given the threat of further pandemics and the heightened prevalence of these viruses in general, more research into the immunologic mechanisms of this disease is warranted with the hope of discovering new potential therapies.

**REFERENCES**

1. Chien YW, Klugman KP, Morens DM. Bacterial pathogens and death during the 1918 influenza pandemic. N Engl J Med 2009;361(26):2582–3.
2. Morens DM, Fauci AS. The 1918 influenza pandemic: insights for the 21st century. J Infect Dis 2007;195(7):1018–28.
3. Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. Emerg Infect Dis 2006;12(1):15–22.
4. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 2008;198(7):962–70.
5. Bisno AL, Griffin JP, Van Epps KA, et al. Pneumonia and Hong Kong influenza: a prospective study of the 1968-1969 epidemic. Am J Med Sci 1971;261(5):251–63.
6. Oswald NC, Shooter RA, Curwen MP. Pneumonia complicating Asian influenza. Br Med J 1958;2(5108):1305–11.
7. Louria DB, Blumenfeld HL, Ellis JT, et al. Studies on influenza and Rhinovirus 1934. J Clin Invest 1959;38(1 Pt 2):213–65.
8. Martin-Looches I, Sanchez-Corral A, Diaz E, et al. Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A(H1N1) virus. Chest 2011;139(3):555–62.
9. Gill JR, Sheng ZM, Ely SF, et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Arch Pathol Lab Med 2010;134(2):235–43.
10. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol 2010;177(1):166–75.
11. Cilloniz C, Ewig S, Menendez R, et al. Bacterial coinfection with H1N1 infection in patients admitted with community acquired pneumonia. J Infect 2012;65(3):223–30.
12. Heron M. Deaths: leading causes for 2013. Natl Vital Stat Rep 2016;65(2):1–95.
13. The top 10 causes of death. 2014; fact sheet. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed June 16, 2016.
14. Metersky ML, Masterton RG, Lode H, et al. Epidemiology, microbiology, and treatment considerations for bacterial pneumonia complicating influenza. Int J Infect Dis 2012;16(5):e321–31.
15. Ballinger MN, Standiford TJ. Postinfluenza bacterial pneumonia: host defenses gone awry. J Interferon Cytokine Res 2010;30(9):643–52.
16. Simusika P, Bateman AC, Theo A, et al. Identification of viral and bacterial pathogens from hospitalized children with severe acute respiratory illness in Lusaka, Zambia, 2011-2012: a cross-sectional study. BMC Infect Dis 2015;15:52.
17. Sangil A, Calbo E, Robles A, et al. Aetiology of community-acquired pneumonia among adults in an H1N1 pandemic year: the role of respiratory viruses. Eur J Clin Microbiol Infect Dis 2012;31(10):2765–72.
18. Falsay AR, Becker KL, Swinburne AJ, et al. Bacterial complications of respiratory tract viral illness: a comprehensive evaluation. J Infect Dis 2013; 208(3):432–41.

19. Glezen P, Denny FW. Epidemiology of acute lower respiratory disease in children. N Engl J Med 1973;288(10):498–505.

20. Louie JK, Roy-Burman A, Guardia-Labar L, et al. Rhinovirus associated with severe lower respiratory tract infections in children. Pediatr Infect Dis J 2009;28(4):337–9.

21. Echenique IA, Chan PA, Chapin KC, et al. Clinical characteristics and outcomes in hospitalized patients with respiratory viral co-infection during the 2009 H1N1 influenza pandemic. PLoS One 2013; 8(4):e60845.

22. Jennings LC, Anderson TP, Beynon KA, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax 2008;63(1):42–8.

23. Podewils LJ, Liedtke LA, McDonald LC, et al. A national survey of severe influenza-associated complications among children and adults, 2003-2004. Clin Infect Dis 2005;40(11):1693–6.

24. Centers for Disease Control and Prevention (CDC). Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - United States, May-August 2009. MMWR Morb Mortal Wkly Rep 2009;58(38):1071–4.

25. Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics 2011;128(6):e1450-8.

26. Murray RJ, Robinson JO, White JN, et al. Community-acquired pneumonia due to pandemic A(H1N1)2009 influenzavirus and methicillin resistant Staphylococcus aureus co-infection. PLoS One 2010;5(1):e8705.

27. Luchsinger V, Ruiz M, Zunino E, et al. Community-acquired pneumonia in Chile: the clinical relevance in the detection of viruses and atypical bacteria. Thorax 2013;68(11):1000–6.

28. Murphy TF, Henderson FW, Clyde WA Jr, et al. Pneumonia: an eleven-year study in a pediatric practice. Am J Epidemiol 1981;113(1):12–21.

29. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on the clinical presentation and outcome of invasive pneumococcal disease. Eur J Clin Microbiol Infect Dis 2015;34(1):177–86.

30. Investigators AI, Webb SA, Pettila V, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009;361(20):1925–34.

31. Tyrrell DA. The pulmonary complications of influenza as seen in Sheffield in 1949. Q J Med 1952; 21(83):291–306.

32. Chertow DS, Memoli MJ. Bacterial co-infection in influenza: a grand rounds review. JAMA 2013; 309(3):273–82.

33. Rice TW, Robinzon L, Uyeki TM, et al. Critical illness from 2009 pandemic influenza a virus and bacterial coinfection in the United States. Crit Care Med 2012;40(5):1487–98.

34. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 2008; 14(5):558–64.

35. Lee KH, Gordon A, Foxman B. The role of respiratory viruses in the etiology of bacterial pneumonia: an ecological perspective. Evol Med Public Health 2016;2016(1):95–109.

36. Belongia EA, Irving SA, Waring SC, et al. Clinical characteristics and 30-day outcomes for influenza A 2009 (H1N1), 2008-2009 (H1N1), and 2007-2008 (H3N2) infections. JAMA 2010;304(10):1091–8.

37. Deng JC. Viral-bacterial interactions-therapeutic implications. Influenza Other Respir Viruses 2013; 7(Suppl 3):24–35.

38. Harms PW, Schmidt LA, Smith LB, et al. Autopsy findings in eight patients with fatal H1N1 influenza. Am J Clin Pathol 2010;134(1):27–35.

39. Weinberger DM, Simonsen L, Jordan R, et al. Impact of the 2009 influenza pandemic on pneumococcal pneumonia hospitalizations in the United States. J Infect Dis 2012;205(3):458–65.

40. Damasio GA, Pereira LA, Moreira SD, et al. Does virus-bacteria coinfection increase the clinical severity of acute respiratory infection? J Med Virol 2015;87(9):1456–61.

41. Viasus D, Pano-Pardo JR, Pachon J, et al. Pneumonia complicating pandemic (H1N1) 2009: risk factors, clinical features, and outcomes. Medicine (Baltimore) 2011;90(5):328–36.

42. Mina MJ, Klugman KP. The role of influenza in the severity and transmission of respiratory bacterial disease. Lancet Respir Med 2014;2(9):750–63.

43. Brealey JC, Sty PD, Young PR, et al. Viral bacterial co-infection of the respiratory tract during early childhood. FEMS Microbiol Lett 2015. [Epub ahead of print].

44. Marom T, Alvarez-Fernandez PE, Jennings K, et al. Acute bacterial sinusitis complicating viral upper respiratory tract infection in young children. Pediatr Infect Dis J 2014;33(8):803–8.

45. Cohen AL, McMorrow M, Walaza S, et al. Potential impact of co-infections and co-morbidities prevalent in Africa on influenza severity and frequency: a systematic review. PLoS One 2015; 10(6):e0128580.

46. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol 2014;12(4):252–62.
47. Smith AM, McCullers JA. Secondary bacterial infections in influenza virus infection pathogenesis. Curr Top Microbiol Immunol 2014;385:327–56.

48. Rynda-Apple A, Robinson KM, Alcorn JF. Influenza and bacterial superinfection: illuminating the immunologic mechanisms of disease. Infect Immun 2015;83(10):3764–70.

49. Didierlaurent A, Goulding J, Hussell T. The impact of successive infections on the lung microenvironment. Immunology 2007;122(4):457–65.

50. Bogaert D, De Groot R, Hermans PW. Strep-tococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis 2004;4(3):144–54.

51. Bosch AA, Biesbroek G, Trzcinski K, et al. Viral and bacterial interactions in the upper respiratory tract. PloS Pathog 2013;9(1):e1003057.

52. Morris A, Beck JM, Schloss PD, et al. Comparison of the respiratory microbiome in healthy non-smokers and smokers. Am J Respir Crit Care Med 2013;187(10):1067–75.

53. Charlson ES, Bittinger K, Haas AR, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. Am J Respir Crit Care Med 2011;184(8):957–63.

54. Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? Nat Rev Microbiol 2009;7(12):887–94.

55. Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? Nat Rev Microbiol 2009;7(12):887–94.

57. Reiss-Mandel A, Regev-Yochay G. The administration of Staphylococcus aureus and Streptococcus pneumoniae in healthy human nasal cavities by artificial implantation of Corynebacterium sp. J Hosp Infect 2000;44(2):127–33.

58. Reis-Mandel A, Regev-Yochay G. Epidemiological markers for interactions among Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus in upper respiratory tract carriage. J Infect Dis 2016;213(10):1596–605.

59. Garcia-Rodriguez JA, Fresnadillo Martinez MJ. Dynamics of nasopharyngeal colonization by potential respiratory pathogens. J Antimicrob Chemother 2002;50(Suppl S2):59–73.

60. Reiss-Mandel A, Regev-Yochay G. Staphylococcus aureus and Streptococcus pneumoniae interaction and response to pneumococcal vaccination: myth or reality? Hum Vaccin Immunother 2016;12(2):351–7.

61. Yan M, Pamp SJ, Fukuyama J, et al. Nasal microenvironments and interspecific interactions influence nasal microbiota complexity and S. aureus carriage. Not Found In Database 2013;14(6):631–40.

62. Bomar L, Brugger SD, Yost BH, et al. Corynebacterium accolens releases antipneumococcal free fatty acids from human nostril and skin surface triacylglycerols. MBio 2016;7(1):e01725-15.

63. Tarabichi Y, Li K, Hu S, et al. The administration of intranasal live attenuated influenza vaccine induces changes in the nasal microbiota and nasal epithelium gene expression profiles. Microbiome 2015;3:74.

64. Mina MJ, McCullers JA, Klugman KP. Live attenuated influenza vaccine enhances colonization of Streptococcus pneumoniae and Staphylococcus aureus in mice. MBio 2014;5(1):e01040–13.

65. Wheeler AH, Nungester WJ. Effect of mucin on influenza virus infection in hamsters. Science 1942;96(2482):92–3.

66. Williams OW, Sharafkhaneh A, Kim V, et al. Airway mucus: from production to secretion. Am J Respir Cell Mol Biol 2006;34(5):527–36.

67. Siegel SJ, Roche AM, Weiser JN. Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. Cell Host Microbe 2014;16(1):55–67.

68. Peitola VT, McCullers JA. Respiratory viruses predisposing to bacterial infections: role of neuraminidase. Pediatr Infect Dis J 2004;23(Suppl 1):S87–97.

69. Peitola VT, Murti KG, McCullers JA. Influenza virus neuraminidase contributes to secondary bacterial pneumonia. J Infect Dis 2005;192(2):249–57.

70. McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and Streptococcus pneumoniae. J Infect Dis 2003;187(6):1000–9.

71. Cundell DR, Gerard NP, Gerard C, et al. Streptococcus pneumoniae anchor to activated human cells by the receptor for platelet-activating factor. Nature 1995;377(6548):435–8.

72. Rijneveld AW, Weijer S, Florquin S, et al. Improved host defense against pneumococcal pneumonia in platelet-activating factor receptor-deficient mice. J Infect Dis 2004;189(4):711–6.

73. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 2002;186(3):341–50.

74. Avadhanula V, Rodriguez CA, Devincenzo JP, et al. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. J Virol 2006;80(4):1629–36.
75. Swords WE, Buscher BA, Ver Steeg li K, et al. Non-typeable *Haemophilus influenzae* adhere to and invade human bronchial epithelial cells via an interaction of lipooligosaccharide with the PAF receptor. Mol Microbiol 2000;37(1):13–27.

76. Comstock AT, Ganesan S, Chattoraj A, et al. Rhinovirus-induced barrier dysfunction in polarized airway epithelial cells is mediated by NADPH oxidase 1. J Virol 2011;85(13):6795–808.

77. Sajjan U, Wang Q, Zhao Y, et al. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. Am J Respir Crit Care Med 2008;178(12):1271–81.

78. Tan TT, Nordstrom T, Forsgren A, et al. The respiratory syncytial virus. Am Rev Respir Dis 1986;134(5):1040–4.

79. Heilmann C. Adhesion mechanisms of staphylococci. Adv Exp Med Biol 2011;715:105–23.

80. van der Flier M, Chhun N, Wizemann TM, et al. Adherence of *Streptococcus pneumoniae* to immobilized fibronectin. Infect Immun 1995;63(11):4317–22.

81. Plotkowski MC, Puchelle E, Beck G, et al. Adherence of type I *Streptococcus pneumoniae* to tracheal epithelium of mice infected with influenza A/PR8 virus. Am Rev Respir Dis 1986;134(5):1040–4.

82. Carson JL, Collier AM, Hu SS. Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. N Engl J Med 1985;312(8):463–8.

83. Pittet LA, Hall-Stoodley L, Rutkowski MR, et al. Influenza virus infection decreases tracheal mucociliary velocity and clearance of *Streptococcus pneumoniae*. Am J Respir Cell Mol Biol 2010;42(4):450–60.

84. Nickerson CL, Jakab GJ. Pulmonary antibacterial defenses during mild and severe influenza virus infection. Infect Immun 1990;58(9):2809–14.

85. Astry CL, Jakab GJ. Influenza virus-induced immune complexes suppress alveolar macrophage phagocytosis. J Virol 1984;50(2):287–92.

86. Franke-Ullmann G, Portner C, Walter P, et al. Alteration of pulmonary macrophage function by respiratory syncytial virus infection in vitro. J Immunol 1996;154(1):268–80.

87. Jakab GJ. Immune impairment of alveolar macrophage phagocytosis during influenza virus pneumonia. Am Rev Respir Dis 1982;126(5):778–82.

88. Kleinerman ES, Daniels CA, Polisson RP, et al. Effect of virus infection on the inflammatory response. Depression of macrophage accumulation in influenza-infected mice. Am J Pathol 1976;85(2):373–82.

89. Nicholls JM. The battle between influenza and the innate immune response in the human respiratory tract. Infect Chemother 2013;45(1):11–21.

90. Huang FF, Barnes PF, Feng Y, et al. GM-CSF in the lungs protects against lethal influenza infection. Am J Respir Crit Care Med 2011;184(2):259–68.

91. Ghoneim HE, Thomas PG, McCullers JA. Depletion of alveolar macrophages during influenza infection facilitates bacterial superinfections. J Immunol 2013;191(3):1250–9.

92. Subramaniam R, Barnes PF, Fletcher K, et al. Protecting against post-influenza bacterial pneumonia by increasing phagocyte recruitment and ROS production. J Infect Dis 2014;209(11):1827–36.

93. Shahangian A, Chow EK, Tian X, et al. Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. J Clin Invest 2009;119(7):1910–20.

94. Didierlaurent A, Goulding J, Patel S, et al. Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. J Exp Med 2008;205(2):323–9.

95. Abramson JS, Mills EL, Giebink GS, et al. Depression of monocyte and polymorphonuclear leukocyte oxidative metabolism and bactericidal capacity by influenza A virus. Infect Immun 1982;35(1):350–5.

96. Damjanovic D, Lai R, Jeyanathan M, et al. Marked improvement of severe lung immunopathology by influenza-associated pneumococcal superinfection requires the control of both bacterial replication and host immune responses. Am J Pathol 2013;183(3):688–80.

97. Stark JM, Stark MA, Colasurdo GN, et al. Decreased bacterial clearance from the lungs of mice following primary respiratory syncytial virus infection. J Med Virol 2006;78(6):829–38.

98. Abramson JS, Giebink GS, Mills EL, et al. Polymorphonuclear leukocyte dysfunction during influenza virus infection in chinchillas. J Infect Dis 1981;143(6):836–45.

99. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nat Rev Immunol 2014;14(1):36–49.

100. Nakamura S, Davis KM, Weiser JN. Synergistic stimulation of type I interferons during influenza virus coinfection promotes *Streptococcus pneumoniae* colonization in mice. J Clin Invest 2011;121(9):3657–65.

101. Kudva A, Scheller EV, Robinson KM, et al. Influenza A inhibits Th17-mediated host defense against bacterial pneumonia in mice. J Immunol 2011;186(3):1666–74.

102. Tian X, Xu F, Lung WY, et al. Poly I: C enhances susceptibility to secondary pulmonary infections by gram-positive bacteria. PLoS One 2012;7(9):e41879.

103. Boxx GM, Cheng G. The roles of type I interferon in bacterial infection. Not Found In Database 2016;19(6):760–9.
104. Schliehe C, Flynn EK, Vilagos B, et al. The methyltransferase Setdb2 mediates virus-induced susceptibility to bacterial superinfection. Nat Immunol 2015;16(1):67–74.

105. van der Sluijs KF, van Elden LJ, Nijhuis M, et al. IL-10 is an important mediator of the enhanced susceptibility to pneumococcal pneumonia after influenza infection. J Immunol 2004;172(12):7603–9.

106. Penaloza HF, Nieto PA, Munoz-Durango N, et al. Mechanisms of interferon-gamma production by neutrophils and its function during Streptococcus pneumoniae pneumonia. Immunology 2015;146(1):100–12.

107. Gomez JC, Yamada M, Martin JR, et al. Interferon-gamma production by neutrophils during bacterial pneumonia in mice. Am J Respir Cell Mol Biol 2015;52(3):349–64.

108. Yamada M, Gomez JC, Chugh PE, et al. Interferon-gamma production by neutrophils during bacterial pneumonia. Am J Respir Crit Care Med 2011;183(10):1391–401.

109. Zhang Z, Clarke TB, Weiser JN. Cellular effectors mediating Th17-dependent clearance of pneumococcal colonization in mice. J Clin Invest 2009;119(7):899–909.

110. Li W, Moltedo B, Moran TM. Type I interferon induction during influenza virus infection increases susceptibility to secondary Streptococcus pneumoniae infection by negative regulation of gamma-delta T cells. J Virol 2012;86(22):12304–12.

111. Robinson KM, McHugh KJ, Mandalapu S, et al. Influenza A virus exacerbates Staphylococcus aureus pneumonia in mice by attenuating antimicrobial peptide production. J Infect Dis 2014;209(6):865–75.

112. Miller WT Jr, Mickus TJ, Barbosa E Jr, et al. CT of viral lower respiratory tract infections in adults: comparison among viral organisms and between viral and bacterial infections. AJR Am J Roentgenol 2011;197(5):1088–95.

113. Flanders SA, Stein J, Shochat G, et al. Performance of a bedside C-reactive protein test in the diagnosis of community-acquired pneumonia in adults with acute cough. Am J Med 2004;116(8):529–35.

114. Meili M, Kutz A, Briel M, et al. Infection biomarkers in primary care patients with acute respiratory tract infections-comparison of procalcitonin and C-reactive protein. BMC Pulm Med 2016;16:43.

115. Muller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 2007;7:10.

116. Branche AR, Walsh EE, Vargas R, et al. Serum procalcitonin measurement and viral testing to guide antibiotic use for respiratory infections in hospitalized adults: a randomized controlled trial. J Infect Dis 2015;212(11):1692–700.

117. Li H, Luo YF, Blackwell TS, et al. Meta-analysis and systematic review of procalcitonin-guided therapy in respiratory tract infections. Antimicrob Agents Chemother 2011;55(12):5900–6.

118. Liu D, Su LX, Guan W, et al. Prognostic value of procalcitonin in pneumonia: a systematic review and meta-analysis. Respirology 2016;21(2):280–8.

119. Timbrook T, Maxam M, Bosso J. Antibiotic discontinuation rates associated with positive respiratory viral panel and low procalcitonin results in proven or suspected respiratory infections. Infect Dis Ther 2015;4(3):297–306.

120. Schuetz P, Chiappa V, Briel M, et al. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med 2011;171(15):1322–31.

121. Rodriguez AH, Aviles-Jurado FX, Diaz E, et al. Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: a CHAID decision-tree analysis. J Infect 2016;72(2):143–51.

122. Diez-Padrisa N, Bassat Q, Machevo S, et al. Procalcitonin and C-reactive protein for invasive bacterial pneumonia diagnosis among children in Mozambique, a malaria-endemic area. PLoS One 2010;5(10):e13226.

123. Sanchez JL, Cooper MJ, Myers CA, et al. Respiratory infections in the U.S. military: recent experience and control. Clin Microbiol Rev 2015;28(3):743–800.

124. Jefferson T, Di Pietrantonj C, Rivetti A, et al. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2014;3:CD001269.

125. Caldwell R, Roberts CS, An Z, et al. The health and economic impact of vaccination with 7-valent pneumococcal vaccine (PCV7) during an annual influenza epidemic and influenza pandemic in China. BMC Infect Dis 2015;15:284.

126. Tessmer A, Welte T, Schmidt-Ott R, et al. Influenza vaccination is associated with reduced severity of community-acquired pneumonia. Eur Respir J 2011;38(1):147–53.

127. Wang CS, Wang ST, Lai CT, et al. Impact of influenza vaccination on major cause-specific mortality. Vaccine 2007;25(7):1196–203.

128. Oster G, Weycker D, Edelberg J, et al. Benefits and risks of live attenuated influenza vaccine in young children. Am J Manag Care 2010;16(9):e235–44.

129. Nichol KL, Nordin JD, Nelson DB, et al. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med 2007;357(14):1373–81.

130. Spaude KA, Abrutyn E, Kirchner C, et al. Influenza vaccination and risk of mortality among adults
hospitaled with community-acquired pneumonia. Arch Intern Med 2007;167(1):53–9.

131. Voordouw BC, van der Linden PD, Simonian S, et al. Influenza vaccination in community-dwelling elderly: impact on mortality and influenza-associated morbidity. Arch Intern Med 2003;163(9):1089–94.

132. Voordouw BC, Sturkenboom MC, Dieleman JP, et al. Annual influenza vaccination in community-dwelling elderly individuals and the risk of lower respiratory tract infections or pneumonia. Arch Intern Med 2006;166(18):1980–5.

133. Voordouw BC, Sturkenboom MC, Dieleman JP, et al. Mortality benefits of influenza vaccination in elderly people. Lancet Infect Dis 2008;8(8):461–2 [author reply: 463–5].

134. Huber VC, Peltola V, Iverson AR, et al. Contribution of vaccine-induced immunity toward either the HA or the NA component of influenza viruses limits secondary bacterial complications. J Virol 2010;84(8):4105–8.

135. Li C, Gubbins PO, Chen GJ. Prior pneumococcal and influenza vaccinations and in-hospital outcomes for community-acquired pneumonia in elderly veterans. J Hosp Med 2015;10(5):287–93.

136. Christopoulou I, Roose K, Ibanez LI, et al. Influenza vaccines to control influenza-associated bacterial infection: where do we stand? Expert Rev Vaccines 2015;14(1):55–67.

137. Mina MJ, Klugman KP, McCullers JA. Live attenuated influenza vaccine, but not pneumococcal conjugate vaccine, protects against increased density and duration of pneumococcal carriage after influenza infection in pneumococcal colonized mice. J Infect Dis 2013;208(8):1281–5.

138. Klonoski JM, Hurtig HR, Juber BA, et al. Vaccination against the M protein of Streptococcus pyogenes prevents death after influenza virus: S. pyogenes super-infection. Vaccine 2014;32(40):5241–9.

139. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community-acquired pneumonia in adults: update 2009. Thorax 2009;64(Suppl 3):iii1–55.

140. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl 2):S27–72.

141. Bhan U, Podsidi AB, Kovach MA, et al. Linezolid has unique immunomodulatory effects in post-influenza community acquired MRSA pneumonia. PLoS One 2015;10(1):e0114574.

142. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantine resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005;366(9492):1175–81.

143. Bright RA, Shay DK, Shu B, et al. Adamantine resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. JAMA 2006;295(8):891–4.

144. Rahman M, Bright RA, Kieke BA, et al. Adamantine-resistant influenza infection during the 2004-05 season. Emerg Infect Dis 2008;14(1):173–6.

145. Viasus D, Pano-Pardo JR, Pachon J, et al. Timing of oseltamivir administration and outcomes in hospitalized adults with pandemic 2009 influenza A(H1N1) virus infection. Chest 2011;140(4):1025–32.

146. McCullers JA. Preventing and treating secondary bacterial infections with antiviral agents. Antivir Ther 2011;16(2):123–35.

147. McCullers JA. Effect of antiviral treatment on the outcome of secondary bacterial pneumonia after influenza. J Infect Dis 2004;190(3):519–26.

148. Whittle RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001;20(2):127–33.

149. Dobson J, Whittle RJ, Pocock S, et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015;385(9979):1729–37.

150. Ghoneim HE, McCullers JA. Adjuvant corticosteroid therapy improves lung immunopathology and survival during severe secondary pneumococcal pneumonia in mice. J Infect Dis 2014;209(9):1459–68.

151. Ramos I, Fernandez-Sesma A. Modulating the innate immune response to influenza a virus: potential therapeutic use of anti-inflammatory drugs. Front Immunol 2015;6:361.

152. Quispe-Laime AM, Bracco JD, Barberio PA, et al. H1N1 influenza A virus-associated acute lung injury: response to combination oseltamivir and prolonged corticosteroid treatment. Intensive Care Med 2010;36(1):33–41.

153. Kudo K, Takasaki J, Manabe T, et al. Systemic corticosteroids and early administration of antiviral agents for pneumonia with acute wheezing due to influenza A(H1N1)pdm09 in Japan. PLoS One 2012;7(2):e32280.

154. Kim SH, Hong SB, Yun SC, et al. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 2011;183(9):1207–14.

155. Zhang Y, Sun W, Svendsen ER, et al. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. Crit Care 2015;19:46.