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Using Precision Medicine for the Diagnosis and Treatment of Viral Pneumonia

Richard R. Watkins

ABSTRACT

The COVID-19 pandemic has drawn considerable attention to viral pneumonia from clinicians, public health authorities, and the general public. With dozens of viruses able to cause pneumonia in humans, differentiating viral from bacterial pneumonia can be very challenging in clinical practice using traditional diagnostic methods. Precision medicine is a medical model in which decisions, practices, interventions, and therapies are adapted to the individual patient on the basis of their predicted response or risk of disease. Precision medicine approaches hold promise as a way to improve outcomes for patients with viral pneumonia. This review describes the latest advances in the use of precision medicine for diagnosing and treating viral pneumonia in adults and discusses areas where further research is warranted.

Keywords: Viral pneumonia; Precision medicine; Diagnosis; Therapy; COVID-19

Key Summary Points

Viral pneumonia is difficult to differentiate from bacterial pneumonia in clinical practice.

One of the silver linings of the COVID-19 pandemic has been the gain of important insights into the pathophysiology of viral pneumonia.

Precision medicine has the potential to help diagnose viral pneumonia, optimize therapies, and lead to improved outcomes.

Symptoms of viral pneumonia are nonspecific, so it is not possible to determine a viral etiology without laboratory testing.

Novel biomarkers for viral pneumonia are being developed using meta-genomics.

Immunologic therapies directed against viral pathogens hold promise, although further understanding of the pathogenesis of viral pneumonia is needed to optimize their use.

R. R. Watkins (✉)
Department of Medicine, Northeast Ohio Medical University, Rootstown, OH, USA
e-mail: rwatkins@neomed.edu

INTRODUCTION

Viral pneumonia has historically been a significant cause of morbidity and mortality for humankind. Indeed, the 1918 influenza pandemic caused over 50 million deaths worldwide and its pathobiology is still incompletely understood [1]. Viral pneumonia is increasingly recognized as a cause of hospital-acquired pneumonia, with comparable mortality to bacterial pneumonia [2]. Distinguishing bacterial from viral pneumonia on clinical grounds is very challenging and a microbiological diagnosis is achieved only in approximately half of all cases [3, 4]. The COVID-19 pandemic has caused millions of cases of viral pneumonia, one result of which has been a more nuanced understanding of the underlying pathophysiology and immune response [5]. The development of messenger ribonucleic acid (mRNA) vaccines for COVID-19 has raised the possibility that they can be developed against other viral pathogens, including those that cause pneumonia [6]. Thus, despite significant progress, it is clear that viral pneumonia remains a major threat to human health and further advances in its diagnosis, treatment, and prevention are needed.

One paradigm that holds significant promise in the management of viral pneumonia is precision medicine. It has been defined as "medical care designed to optimize efficiency or therapeutic benefit for particular groups of patients using genetic or molecular profiling" [7]. More pragmatically, precision medicine involves rapidly identifying altered biology within an individual and using the findings to guide treatment. There is an increasing amount of research underway on precision medicine across a multitude of medical conditions including cancer, rheumatoid arthritis, psoriasis, and asthma [8–10]. Furthermore, precision medicine approaches have been investigated for several infectious processes including sepsis [7], community-acquired pneumonia [11], urinary tract infections [12], intra-abdominal infections [13], diabetic foot infections [14], meningitis [15], and endocarditis [16]. Patients with viral pneumonia often present to the emergency department with broad phenotypes. Viral etiologies and outcomes are unique to individuals, making it difficult to cohort patients with viral pneumonia. But this presents a prime target for testing and developing tools for precision medicine. Thus, precision medicine might help differentiate viral from bacterial pneumonia thereby reducing unnecessary antibiotic usage, guide appropriate antiviral therapy such as optimal drug dosing, and determine which patients with viral pneumonia might benefit from adjunctive therapies, such as corticosteroids or other immune modulators (Fig. 1).
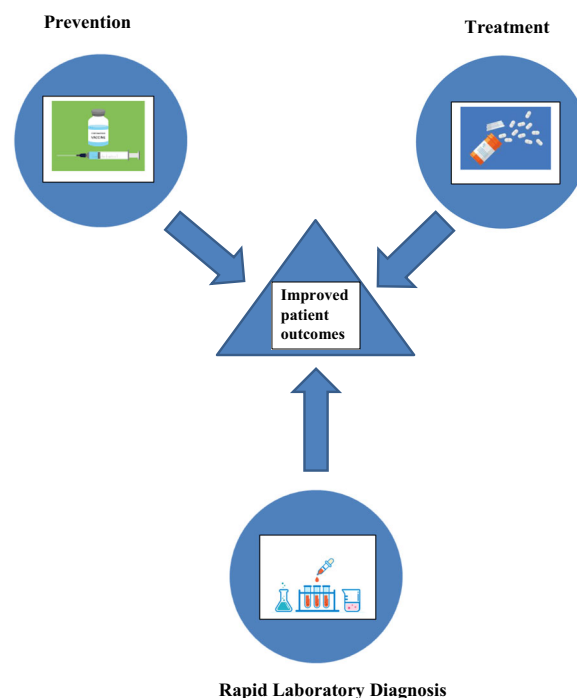

Fig. 1 Components of a precision medicine approach to viral pneumonia. A comprehensive approach to viral pneumonia using precision medicine involves rapid laboratory testing and biomarkers, with the main goal of differentiating bacterial from viral etiologies. Treatment includes effective antiviral medications and anti-inflammatory therapies (e.g., steroids and immunomodulators) that are preferentially prescribed early in the course of illness. Prevention occurs through vaccines and prophylactic antiviral medications, when appropriate. These combine to optimize the care of patients with viral pneumonia by improving outcomes and reducing overall health care costs

The microbiome of the upper airways and, to a lesser extent, the lower airways host a large number of commensal viruses (i.e., the virome) that is often disrupted during an acute episode of viral pneumonia [17]. For example, increased COVID-19 severity has been shown to correlate with greater colonization and higher titers of *Anelloviridae* and *Redondoviridae* in the respiratory tract [18]. Each individual has their own unique virome, which is impacted by opportunistic viral pathogens in myriad ways. Further understanding of these complex interactions may lead to novel diagnostic and therapeutic approaches targeting the pathogens that cause viral pneumonia, as well as ways to reconstitute the virome post-infection.

In this review, the latest advances in the use of precision medicine for diagnosing and treating viral pneumonia in adults will be discussed, with an emphasis on pragmatic approaches that clinicians treating patients at the bedside will find useful. It will also identify gaps in our current understanding of the pathophysiology of viral pneumonia, particularly from a genomic standpoint, and offer suggestions for further research. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

CLINICAL MANIFESTATIONS OF VIRAL PNEUMONIA

There are many viruses that have the potential to cause pneumonia in humans. The most commonly encountered ones in clinical practice are listed in Table 1. Symptoms of viral pneumonia range from mild with fever, cough, and shortness of breath to severe, including sepsis and acute respiratory failure [19]. The severity of symptoms is due to local and systemic immune responses and varies for each individual. Hypoxemia can occur as a result of impairment in alveolar gas exchange [20]. Although fever higher than 38.5 °C, a respiratory rate greater than 50 breaths per minute, and chest recession are suggestive of bacterial rather than viral pneumonia, clinical

Table 1 Common etiologies of viral pneumonia in adults

SARS-CoV-2
Influenza A
Influenza B
Respiratory syncytial virus
Human metapneumovirus
Adenovirus 4 and 7
Parainfluenza
Rhinovirus
Herpes simplex virus*
Cytomegalovirus*
Varicella zoster virus*

Adapted from reference [68]
*More frequent in immunocompromised patients

manifestations alone are not reliable for differentiating the two conditions [21].

Influenza remains the clinically most significant viral cause of community-acquired pneumonia in adults, with annual epidemics in the USA occurring during the fall and winter months. Risk factors for influenza infection progressing to pneumonia include advanced age, malignancy, delayed influenza diagnosis, an absolute lymphocyte count less than 200 cells/mL, and not receiving influenza-directed antiviral therapy [20]. A study that included 579 adults hospitalized for influenza found those with acute respiratory failure and who presented with a productive cough had a higher likelihood of pneumonia [22]. Multiplex nucleic acid amplification tests (NAATs) that include influenza in a panel of other respiratory viruses are commonly used for diagnosis and are preferred over rapid influenza tests for better accuracy. Chest radiographs often demonstrate diffuse infiltrates, with no one feature differentiating it from other viral etiologies.

Respiratory syncytial virus (RSV) is primarily an infection of infants and young children. When adults are infected, it usually causes mild illness although immunocompromised individuals are at higher risk for severe disease.

Patients with RSV often report a longer time from the beginning of symptoms to hospital admission when compared to other causes of viral pneumonia, and bacterial superinfection occurs in approximately 12% of cases [23]. Human metapneumovirus (HMPV) was detected in 3% adult patients with pneumonia in a population-based surveillance study. Clinical features did not reliably differentiate HMPV-associated pneumonia from other pathogens. HMPV-associated pneumonia was less severe than bacterial and adult RSV pneumonia, but apart from that was comparable to other etiologies [24]. Adenovirus usually causes mild illness in immunocompetent adults but can sometimes lead to acute respiratory distress syndrome (ARDS). A prospective observational study found younger age, lower $CD3^+CD4^+$ T cells, and high serum creatinine were associated with adenovirus-induced ARDS in adults who required mechanical ventilation [25]. There are four types and two subtypes of parainfluenza virus (PIV), with PIV-3 the most common cause of clinically significant infections. The clinical presentation of PIV in adults (i.e., cough, sore throat, and rhinorrhea) is indistinguishable from other respiratory illnesses. Typical chest computed tomography (CT) findings for PIV pneumonia are multifocal patchy consolidation with ground glass opacities and centrilobular nodules with bronchial wall thickening [26]. Recently a case of ARDS in an immunocompetent 48-year-old man due to PIV was reported [27]. Rhinoviruses typically cause pneumonia in immunocompromised adults and appear to cause septic shock less often than other respiratory pathogens [28]. Co-infections of rhinoviruses with influenza virus or *Streptococcus pneumoniae* can occur and there is an increased incidence of rhinovirus infections in autumn [29]. As with influenza, RSV, parainfluenza, HMNV, adenovirus, and rhinovirus are often included in multiplex NAAT panels and it not advised to use viral cultures for diagnostic purposes because of the long turnaround time.

Numerous risk factors for COVID-19 pneumonia have been identified. These include age 65 years or older, male sex (which may be related to lower T cell activation than in female individuals), diabetes, hypertension, obesity, viral hepatitis, HIV disease, and chronic kidney disease [5]. Obesity and insulin resistance in people with diabetes predisposes to metabolic syndrome and can lead to vascular damage, impaired tissue repair, and a dampened immune response early in the course of COVID-19 infection. The result can be impaired viral clearance, causing further immune cell activation and vascular injury. Notably, it may be possible to modify some of these risk factors, such as improving glycemic control in people with diabetes and weight loss in those with obesity, using a precision medicine approach [30]. For example, combining clinical information with genomics and metabolomics data might identify more accurate predictors that lead to optimized therapy for individual patients.

COVID-19 pneumonia usually develops around 7 days after the initial onset of symptoms. Dyspnea is the most common symptom and hypoxia is often present. Most patients have lymphopenia, and some develop thromboembolic complications, disorders of the central or peripheral nervous system, cardiac arrhythmias, rhabdomyolysis, coagulopathy, and shock [31]. Chest radiographs frequently show bilateral consolidations or ground glass opacities. A study that included 88 patients with severe COVID-19 pneumonia found alveolar macrophages in the lungs containing SARS-CoV-2 and T cells form a positive feedback loop that drives persistent alveolar inflammation [32]. This sheds light onto the complex immunopathogy occurring in the lungs, as does another study by Verma et al., which reported low monocyte/lymphocyte ratio levels among nonsurvivors of COVID-19 pneumonia [33]. Sex-specific biological differences in COVID-19 pneumonia require further elucidation and are an area of active investigation. As previously mentioned, male individuals tend to have lower T cell activation in the lungs. Recent data shows that estrogen impacts angiotensin-converting enzyme 2 (ACE-2) expression and lowers the available binding sites for SARS-CoV-2 [34]. Further understanding of sex-related differences in viral pneumonia in general and COVID-19 in particular will advance precision medicine and

may lead to improvements in diagnostic methods and treatments.

There are radiographic features that may help to differentiate viral from bacterial pneumonia. The most common pattern observed of viral pneumonia on CT scans of the chest is multifocal patchy consolidation with ground glass opacities. Radiographic findings common in influenza include bilateral reticulonodular areas of opacity with or without focal areas of consolidation, usually in the lower lobes, and poorly defined patchy or nodular areas of consolidation that become rapidly confluent and resolve after 3 weeks [26]. Patients who progress to diffuse lung damage can demonstrate findings of ARDS or, in cases of influenza H1N1, organizing pneumonia. Adenovirus pneumonia can show lobar or segmental distribution that indicates bronchopneumonia resembling bacterial pneumonia [26].

BIOMARKERS AND THE DIAGNOSIS OF VIRAL PNEUMONIA

Antiviral therapies are most effective if given soon after the onset of infection, making it imperative that a rapid diagnosis occurs [35]. The main challenge in diagnosing viral pneumonia is differentiating viral from bacterial pneumonia. A misdiagnosis can have a number of deleterious consequences, including the unnecessary use of antibiotics and delaying or missing the chance to use antivirals. Thus, improving diagnostic capabilities for viral pneumonia is an important objective and precision medicine approaches have the potential to achieve this goal. For example, measuring host gene expression is a promising diagnostic strategy for discriminating viral from bacterial infection. Bodkin et al. did a systematic comparison of 28 host gene expression signatures and found that performance improved with larger signatures, viral classification was easier than bacterial classification, and performance was decreased in pediatric subjects [36]. Moreover, signature performance differed on the basis of age, specific pathogen, sample type, and the cohort's heterogeneity. One caveat with this study is that subjects adjudicated as having a

rhinovirus infection, which is frequently a colonizer, may actually have had non-viral infections leading to errors in the clinical label. The results will hopefully inform the development and translation of host gene expression signatures into clinical practice.

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [37]. Biomarkers are key factors in precision medicine because they can be an effective tool for better stratification, prognosis, and therapeutic selection. While their use first became common in oncology [38], biomarkers have since moved into the realm of infectious diseases such as sepsis [7], intra-abdominal infections [39], and pneumonia [40]. Perhaps the most extensively studied biomarker in pneumonia is procalcitonin (PCT), a peptide produced by the parafollicular cells of the thyroid. During a bacterial infection, an inflammatory cascade triggers the extra-thyroidal production of PCT from adipocytes and neuroendocrine cells in the lungs and intestine. In contrast, viral infections cause an increase in interferon-γ, which inhibits production of PCT. High PCT levels have been shown to strongly correlate with an increased probability of bacterial community-acquired pneumonia (CAP) [41]. However, the sensitivity of the test ranges from 38% to 91% making it unreliable for important clinical decisions such as withholding antibiotics [42]. The latest guidelines on the management of CAP from the Infectious Diseases Society of America and the American Thoracic Society state "we recommend that empiric antibiotic therapy should be initiated in adults with clinically suspected and radiographically confirmed CAP regardless of initial serum procalcitonin level (strong recommendation, moderate quality of evidence)" [43]. PCT levels can be elevated in severe COVID-19, calling its diagnostic usefulness into further question [44]. Thus, clinicians need more accurate biomarkers for pneumonia than PCT, whose prominence appears to be fading.

The primary role of vitamin D in humans is the maintenance of bone homeostasis, but it

also plays a role in regulating innate and adaptive immunity. Vitamin D deficiency is associated with worse outcomes in a number of infections including pneumonia [45]. The role of vitamin D deficiency and COVID-19 severity has been controversial, with some studies showing higher severity [46–48], while others showed no significant difference between patients with low and normal vitamin D levels [49]. Although the role of vitamin D deficiency in viral pneumonia including COVID-19 remains to be fully elucidated, measuring serum vitamin D is relatively rapid, widely available, and inexpensive, making it axiomatic for precision medicine.

Nucleic acid amplification tests (NAATs) have been the mainstay for diagnosing viral pneumonia over the past decade [50]. The COVID-19 pandemic has led to an outpouring of research on novel biomarkers for viral pneumonia, several of which have the potential to be used in a precision medicine approach. Using multi-cohort analysis, Sweeney et al. derived a set of seven genes to discriminate bacterial from viral infections, and then validated them in 30 independent cohorts [51]. Next, they used a previously identified 11-gene set along with the new bacterial/viral classifier to design an integrated antibiotics decision model. A pooled analysis of 1057 samples from 20 cohorts found the integrated antibiotics decision model had a sensitivity and specificity for bacterial infections of 94.0% and 59.8%, respectively. Although the turnaround time of the technique (4–6 h) is too long for clinical applications, further refinements may shorten the timeframe and allow it to be useful in the diagnosis of pneumonia.

Levels of the hormone MR-proadrenomedullin were shown to predict non-survival and risk for intensive care unit (ICU) admission in patients with influenza A pneumonia [52]. This study also found that ferritin levels greater than 830 ng/mL reflected a significant risk of mortality. Notably, patients with bacterial co-infection were excluded from the analysis. Another potential biomarker for influenza pneumonia is influenza interferon-induced protein 35 (IFP35). Yu et al. reported that IFP35 was released by macrophages and

lung epithelial cells after influenza virus infection [53]. Administration of IFP35 neutralizing antibodies reduced severe pneumonia and lowered the fatality rate in influenza-infected mice. However, some severely ill individuals (15 of 83) had low serum IFP35 and the investigators hypothesized that it may have been caused by degradation from serum proteases in the bloodstream. Further investigation of IFP35 in patients with varying degrees of influenza pneumonia seems warranted.

A plethora of biomarkers for COVID-19 pneumonia have been recently reported (Table 2). Using metabolomic data generated from the blood of COVID-19 patients, Rendeiro et al. found substantial changes in serum metabolome composition that correlated with disease severity and treatment with tocilizumab [60]. They generated high-dimensional metabolomic and joint immune-metabolic readouts that provide meaningful information to understand the host's response to infection. For example, tocilizumab partially rescued the effect of disease severity at the metabolic level and biomarkers for liver function (e.g., AST and ALT) did not show significant association with disease severity. The immune–metabolic cross talk that occurs during COVID-19 progression highlights the potential use of metabolites to control disease by direct modulation of specific steps of lipid metabolism at the immune level. Having accurate methods for disease monitoring that captures both metabolism and immune system states would be an important advancement in precision medicine.

TREATMENT OF VIRAL PNEUMONIA

It has been known for several decades that viral infections can be effectively treated with medications that interfere with viral replication. All RNA viruses encode a common set of enzymes (e.g., RNA polymerases and proteases) that are essential for replication and thus potential targets for antiviral compounds. All three of the approved drugs for COVID-19 target SARS-CoV-2 replication. Remdesivir and molnupiravir act on SARS-CoV-2 polymerase, while nirmatrelvir inhibits SARS-CoV-2 M^{pro} protease. The three

Table 2 Biomarkers for COVID-19 pneumonia

Biomarker	References
Cell free DNA (cfDNA)	[54]
Growth differentiation factor 15 (GDF-15)	[55]
Actin-aortic smooth muscle (ACTA2)	[56]
α-1-acid glycoprotein 1 (ORM1)	
α-1-antichymotrypsin (SERPINA3)	
β-2-microglobulin (B2M)	
Carbonic anhydrase 1 (CA1)	
Complement component C9 (C9)	
C-reactive protein (CRP)	
Cystatin-c (CST3)	
Follistatin-related protein 1 (FSTL1)	
Fructose–bisphosphate aldolase b (ALDOB)	
Haptoglobin (HP)	
Hemoglobin subunit α (HBA1; HBA2)	
Insulin-like growth factor-binding protein 2 (IGFBP2)	
Leucine-rich α-2-glycoprotein (LRG1)	
Lipopolysaccharide-binding protein (LBP)	
Matrix metalloproteinase-9 (MMP9)	
Neutrophil gelatinase-associated lipocalin (LCN2)	
Osteopontin (SPP1)	
Peroxiredoxin-2 (PRDX2)	
Plasma protease c1 inhibitor (SERPING1)	
Pregnancy zone protein (PZP)	
Protein s100-A12 (S100A12)	
Protein s100-A9 (S100A9)	
Protein deglycase DJ-1/parkinson disease	
Protein 7 (PARK7)	
Serum amyloid A-1 and A-2 proteins (SAA1; SAA2)	
Serum amyloid P-component (APCS)	
Secreted protein acidic and rich in cysteine (SPARC)	
Thrombospondin-1 (THBS1)	
Vascular cell adhesion protein 1 (VCAM1, vascular cell adhesion molecule 1)	
von Willebrand factor (VWF)	
S100A-9	
S100-A12	
Apolipoprotein(a) (LPA)	
sPD-L1	[57]
sTIM-3	
sMMP-7	
sTREM-1	[58]
Serum NO_2^- and NO_3^-	[59]
Procalcitonin	
D-dimer	
LDH	
Albumin	

antiviral drugs recommended for treating influenza (oseltamivir, zanamivir, and peramivir) inhibit the neuraminidase enzyme, which facilitates viral release from infected cells.

The development of effective therapies against COVID-19 is a marvel of scientific progress and human ingenuity. Equally remarkable as the new antiviral drugs has been the progress made in creating monoclonal antibodies (mAbs) against SARS-CoV-2. The first mAb approved was in 1998 for the prevention of RSV in neonates. The technology made significant strides during the Ebola outbreak of 2018–2019, where both a fixed-dose combination of three monoclonal antibodies and a monotherapy directed against a single protein on the Ebola virus surface reduced deaths by approximately 50% in patients with symptoms [61]. This experience allowed manufactures to quickly identify mAbs that tightly bind to the SARS-CoV-2 S protein and neutralize the virus when the pandemic first began. Promising antibodies were then rapidly advanced to clinical studies [35]. Hopefully the development of mAbs against SARS-CoV-2 can serve as a blueprint for designing effective mAbs against other viral pathogens that cause pneumonia.

The finding that steroids improve outcomes in COVID-19 yet are harmful in the treatment of influenza underscores the crucial role of the inflammatory response in mediating the pathogenesis of viral pneumonia [5]. Moreover, when other anti-inflammatory drugs (e.g., interleukin-6 inhibitors and JAK-STAT blockers) are given to less ill patients or too late in the course of illness, there is evidence of harm. Further understanding of these complex immunopathological processes is needed to identify which patients with viral pneumonia might benefit from immune modulating therapy. A precision medicine approach for dealing with the heterogeneity of using anti-inflammatory agents for viral pneumonia could match therapies to subgroups of patients that are anticipated to most likely benefit, which initially could be identified by assessing for heterogeneity of treatment effect in clinical trials [62].

PREVENTION OF VIRAL PNEUMONIA

The development of mRNA vaccines has been one of the most important advances from the COVID-19 pandemic. They have proven to be highly effective in preventing serious disease and death. This is mainly because mRNA sequences can be altered to encode nearly any protein without significantly altering its chemical properties [63]. It is therefore hoped that mRNA vaccines can be developed against the multitude of other viral pathogens that cause pneumonia. Recent advances in omics technologies that measure the behavior of genes, mRNA (single-cell transcriptomics), proteins (proteomics), metabolites (metabolomics), cells (mass cytometry), and epigenetic modifications (ATAC-seq), coupled with computational approaches, have facilitated the investigation of the immune response to vaccination in myriad ways [64]. Coupling these with computational approaches has led to the emerging field of systems virology, which aims to comprehensively evaluate the immune response to vaccination with a view towards defining new mechanisms and correlates of protective immunity [65]. Thus, combining systems virology with precision medicine approaches holds immense promise for designing vaccines against respiratory viruses, especially as the threat of future pandemics looms [66]. Additional research on integrating these approaches is warranted.

CONCLUSIONS AND FUTURE DIRECTIONS

The first-ever sequencing of a complete human genome is a groundbreaking accomplishment that is very exciting from a precision medicine standpoint [67]. It may facilitate the development of more accurate diagnostic tests and therapies for many infections, including viral pneumonia. One current limitation in the management of viral pneumonia is the time it takes to make a diagnosis. This unmet clinical need could be solved by further advances in omics technologies and computational algorithms. Immunotherapy is another area where the promise of precision medicine will be actualized after further understanding of the complex role the immune system plays in contributing both to the protection against and the pathogenesis of viral pneumonia. Elucidating the obligatory determinants of the underlying biological processes in viral pneumonia will require considerable effort. We must invest further in basic and applied research on viral evolution, pathogenesis, human immunology, and how they intersect in order to mitigate the effects of viral pneumonia on human health, the world economy, and health care systems.

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