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**Research Article**

# CO-AFFECT OF SARS-COV-2 WITH OTHER RESPIRATORY VIRUSES

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**A B S T R A C T**

The earth is brimming with viruses. Co-infection with respiratory viruses and SARS-CoV-2 raising danger bells around the world. The world is living on the brink.COVID-19, an exciting outstanding pandemic co-infected with respiratory viruses, which demands crucial public health Intervention. The extent of co-infections of SARS-CoV-2 with other respiratory viruses remains unknown. Data on the prevalence and outcomes of co-infection and super infection are limited. The most significant challenge raised by co infection is perhaps the unsuitable propagation of recombination viruses through the interchange of genetic material amidst different strains. Influenza virus is a habitual pathogen that causes pneumonia in winter. It was found clinically that very few patients were diagnosed with both COVID-19 and influenza virus Rhinoviruses and coronaviruses are perceived as the significant source of the common cold syndrome.



## INTRODUCTION

Identifying co-infections of more than one respiratory virus can help with understanding the various clinical symptoms, long-lasting effects on health, and appropriate methods of prevention (1)

Hospitalization in children under 3 years of age, following simultaneous infection with RSV and Human metapneumovirus (hMPV) (2) Furthermore, patients with viral respiratory tract coinfections are more likely to be admitted to the hospital than individuals with a single respiratory virus infection (3) Moreover, due to the similarity of common clinical symptoms of COVID-19 with that of the diseases caused by other respiratory viruses, it has become quite challenging to precisely distinguish SARS-CoV-2 infection from other viral infections (4) It is thought that co-infection with common respiratory viruses can still occur in individuals infected with other respiratory-specific strains (5)

Human infections with zoonotic corona viruses (CoVs), including severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV, have raised great public health concern globally.(6)

The virus, referred to as severe acute respiratory syndrome corona virus-2 (SARS-CoV-2), is transmitted through

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respiratory tract and could induce pneumonia (7)

Influenza virus has similar transmission characteristics with COVID-19, including direct contact (human-to-human transmission) and transmission via airborne droplets (8,9)

COVID-19 and influenza co-infection is limited. Co-infections with viral respiratory pathogens, including corona virus-influenza co-infections (10) and influenza-Middle East respiratory syndrome coronavirus infection, have been reported in a substantial number of patients.(11) CMV can predispose individuals to severe cases of COVID-19 through disruption of peripheral blood T-cell differentiation, and upregulation of inflammatory cytokines, including IL-6, especially in the elderly(12)

DENV,116 which is more prevalent in rainy seasons, causing conditions varying from mild dengue fever (DF) to severe hemorrhagic DF and dengue shock syndrome (13,14)

An investigation conducted by Yan et al. suggested the possibility of DENV and SARS-CoV-2 co infection, characterized by prolonged fever (15)

***History***

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The first known case was identified in Wuhan, China, in December 2019 (16) The disease has since spread worldwide, leading to an ongoing pandemic (17)

The first confirmed human infections were in Wuhan, Hubei, China. A study of the first 41 cases of confirmed COVID-19, published in January 2020 in The Lancet. (18,19)

Official publications from the WHO reported the earliest onset of symptoms as 8 December 2019 (20)

Human-to-human transmission was confirmed by the WHO and Chinese authorities by 20 January 2020 (21,22)

According to official Chinese sources, these were mostly linked to the Huanan Seafood Wholesale Market. (23)

In May 2020 George Gao, the director of the CDC, said animal samples collected from the seafood market had tested negative for the virus, indicating that the market was the site of an early super spreading event, but that it was not the site of the initial outbreak (24) Possibly the first influenza epidemic occurred around 6,000 BC in China, and possible descriptions of influenza exist in Greek writings from the 5th century BC (25) In both 1173–1174 and 1387, epidemics occurred across Europe that were named "influenza".

Whether these epidemics and others were caused by influenza is unclear since there was no consistent naming pattern for epidemic respiratory diseases at that time. (26)

Influenza may have been brought to the Americas as early as 1493, when an epidemic disease resembling influenza killed most of the population of the Antilles (27,28) The flu pandemic in 1557 was potentially the first time influenza was connected to miscarriage and death of pregnant women (29) The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from the Jin Dynasty (266–420) which referred to a "water poison" associated with flying insects (30)

There have been descriptions of epidemics in the 17th century, but the most plausible early reports of dengue epidemics are from 1779 and 1780.(31) In 1953, when a cluster of nurses developed a mild respiratory illness, Winston Price, from the Johns Hopkins University, took nasal passage samples and isolated the first rhinovirus, which he called the JH virus, named after Johns Hopkins.His findings were published in 1956 (32)

***Different types of human corona viruses***

229E (alpha coronavirus) NL63 (alpha coronavirus) OC43 (beta coronavirus) HKU1 (beta coronavirus)

***Influenza amidst Covid-19***

Influenza, commonly called "the flu", and caused by influenza viruses. Fever, runny nose, sore throat, muscle pain, headache, coughing, and fatigue are the common symptoms. These symptoms begin 1–4 days after exposure to the virus and last for about 2–8 days..

Influenza and Corona viruses have similar transmission and clinical manifestations. The details of COVID-19 and influenza co infection is limited (33) laboratory findings Skiagraphy and other imaging studies, show similar clinical characteristics both in Influenza and COVID-19 patients Nasal tampon and pharyngalgia may be more prone to appear for those coinfection patients (34) The influenza season and the COVID-19 pandemic has created a similar and strenuous challenge. COVID-19 and influenza are both contagious respiratory illnesses With the ongoing winter season in the northern hemisphere, it is expected that the seasonal influenza virus will be in circulation along with SARS-CoV-2 (35)

***Dengue amidst COVID-19***

The mystery of plummeting cases Classical dengue fever is characterized by the onset of fever, malaise, headache, facial flushing, retrobulbar pain that worsens on eye movements, conjunctival suffusion and severe back ace, which is a prominent symptom.

Lymphadenopathy, petechiae on the soft palate and transient morbilliform skin rashes may also appear on the limbs with subsequent spread to involve the trunk Desquamation occurs. Cough is uncommon. Dengue fever syndrome is characterized by capillary leak syndrome, thrombocytopenia, hemorrhage, hypotension, and shock. It is characteristically a disease of children occurring most commonly in South-East Asia. Warning Signs of Dengue are stomach pain, tenderness, Vomiting (at least 3 times in 24 hours),Bleeding from the nose or gums, Blood in vomit or stool, Feeling tired, restless, or irritable but Trouble breathing, Persistent pain or pressure in the chest, are the signs of Covid-19 (36)

***Rhinovirus amidst Covid-19***

How the common cold can boot out Covid The viruses of this group are responsible for the most frequent of all human infections, the common cold. Most people suffer from 2-4 colds every year and, although the primary infection is not a severe one, secondary bacterial infection often follows with temporary incapacity. These viruses cause the loss of many million man hours of work. When rhinoviruses are instilled into nose of human volunteers a mild sore throat and cough are the pulmonary signs which precede the profuse nasal

discharge of typical common cold. Chimpanzees are the only other creatures known to be susceptible to these viruses. The viruses can be recovered from the secretions of the nose and throat but only rarely from the faeces.

The virus settles on the ciliated nasal epithelial cells, enters the cells and spreads from cell to cell the epithelium. The cilia become immobilized and both cilia and cell degenerate as the virus replicates. Although it is often suggested that bacterial invasion of the damaged tissue occurs and is responsible for the purulent nasal discharge which is a feature, the engulfing of dead or virus damaged epithelial cells by phagocytes of various sorts may be primary cause of this discharge. The cells lining the throat and lower airways are exposed to the environment making them a prime target for co-infection by respiratory viruses.

***Corona viruses and Acute Respiratory Syndromes MERS, and SARS***

Fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste are the common symptoms of Covid-19 (37) 30%-40% of people who are infected do not develop noticeable symptoms (38) Of those people who develop symptoms noticeable enough to be classed as patients, most (81%) develop mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and 5% suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction (39) MERS-CoV is a coronavirus believed to be originally from bats.Typical symptoms include fever, cough, diarrhea, and shortness of breath. The disease is typically more severe in those with other health problems (40) Middle East respirator syndrome coronavirus, or MERS-CoV) was first diagnosed in Saudi Arabia in 2012.

Middle East respiratory syndrome (MERS) is a viral respiratory disease caused by novel coronaviruses. Coronaviruses can cause diseases fluctuating from common cold to Severe Acute Respiratory Syndrome (SARS). 35% of patients died with MERS-CoV infection. Middle East respiratory syndrome is caused by the MERS coronavirus (MERS-CoV), a species with single-stranded RNA belongs to the genus beta corona virus which is distinct from SARS coronavirus and the common-cold corona virus (41).

COVID-19 is correlated with an acute respiratory distress syndrome (ARDS) and severe pneumonia (42)

COVID-19 was the first severe disease to make an appearance in the 21st century and spread all over the globe. The receptor binding domain (RBD) in S protein of this virus gets attached with the ACE2 receptors present on human cells.

MERS CoV was first reported in 2012 in Middle East, originated from bat and transmitted to humans through camels (43)

COVID-19 virus produces mild to moderate respiratory illness. The COVID-19 virus spreads primarily through droplets of saliva or when an infected person coughs or sneezes.

***Bird flu outbreak amidst COVID-19***

Pandemic South Africa has testimony for several outbreaks of avian influenza (H5N1) in dissimilar poultry farms.

It is a shock that was already suffering from the deadly COVID-19 pandemic. South Africa is facing the economic COVID-19 crisis, the bird flu causing a significant incision in the economy, as well as severely impacting people's day-to-day life. Bird flu-also called avian influenza-is a viral infection that can infect not only birds but also humans and other animals

Unavailability of suitable vaccines, correct treatment, and deficiency of public health measures are major setbacks.(44)

***COVID-19 and Zika association***

Zika virus was first identified in Uganda in 1947. WHO announced Zika virus disease as a "Public Health Emergency of International Concern".

Till last year it was a concern of Latin America and Africa but now it sporadically spread in India too, where pregnant mothers usually have no history of traveling to an affected area of foreign nations. Zika virus disease is caused by Zika virus which belongs to the Flavivirus. Zika virus is transmitted through the bite of an infected Aedes mosquito. Ades mosquito which is known to transmit infections like dengue and chikungunya. It is associated with severe neurological complications, particularly congenital Zika virus syndrome and Guillain-Barre syndrome. It is transmitted from an infected pregnant mother to her baby during pregnancy Transmitted from sexual contact with an infected person.

***Difference between corona virus and Viral fever***

COVID-19 and Influenza both cause respiratory sickness, and are caused by different viruses. COVID-19 is caused by infection with a coronavirus, and flu is caused by infection with influenza viruses. COVID-19 spreads more easily than flu. A person experiences flu symptoms from 1 to 4 days after infection, But Covid-19, symptoms can appear 2 to 14 days after infection.

***Virology***

Dengue virus (DEVN) RNA virus belongs to the family of Flavivirus genus of the Flaviviridae family. Other viruses that are related to Dengue are Japanese B encephalitis and Yellow fever.

There are four serotypes DEVN 1, DEVN 2, DEVN 3 and DEVN 4. A fifth serotype DEVN 5 has been described recently. Infection from one virus produces lifelong immunity to that strain of the virus. The viruses contain a single strand of RNA. It is enclosed by a lipoprotein and has a nucleocapsid. It is composed of three structural proteins encoding the nucleocapsid protein(C), a membrane associated protein (M) and an envelope protein (E). There are seven nonstructural proteins known as NS proteins. The NS proteins are involved in viral replication and packaging.

These processes are closely linked to host endoplasmic reticulum and secretory pathway function.

Coronaviruses belong to the family Coronaviridae. They are enveloped viruses with a positive-sense single-stranded RNA genome. The genome size of coronaviruses is one of the largest among RNA viruses. They have club-shaped spikes that project from their surface, Middle East respiratory syndrome is caused by the MERS coronavirus (MERS-CoV), It has single-stranded RNA belonging to the genus betacoronavirus. Its genomes are

phylogenetically classified into two clades, A and B. Influenza viruses have a negative-sense, single-stranded RNA genome. The negative sense of the genome means it can be used as a template to synthesize messenger RNA (mRNA). IAV and IBV have eight genome segments that encode 10 major proteins. ICV and IDV have seven genome segments that encode nine major proteins. Rhinoviruses belong to the genus Enterovirus in the family Picornaviridae. The three species of rhinovirus (A, B, and C) include around 160 recognized types of human rhinovirus that differ according to their surface proteins, and are the smallest viruses.

***Research on viral infection of the lung: Host Response and Sequelae***

The recognition of pathogen-associated molecular patterns by the pattern recognition receptors such as the stromal cells (CD45-) and cells in the lung (CD45+) is the key to initiate the host immune response to the microbial invasion. As well as the recognition of damage-associated danger signals are important to activate the intracellular innate protein complex, the inflammasome, which are responsible in the organization of both the innate and adaptive immune responses.

In response to a viral respiratory tract infection, interferon (type I and III) are produced by the recognition of: The melanoma differentiation-associated protein 5 and the retinoids acid-inductively gene I, both cytotoxic receptors, will recognize the double-stranded RNA. Unknown cytosolic DNA receptors or DAI will recognize the double-stranded DNA. Retinoids acid-inductively gene I is also triggered by 5'-pppRNA from the transcription of double-stranded DNA, using an RNA polymerase III. After the recognition has been made, the interferon regulatory transcription factors will be activated through the kinase TANK-binding kinase; which then leads to the production of interferon type I and III in the site of the viral infection.

Viral molecules arrive at their respective TLR3, TLR4, TLR7, and TLR9 which will then stimulate through the adaptor protein molecules for the production of interferon type I; leading to the transcription of interferon genes and pro-inflammatory cytokines. Type I interferons (IFN-a, IFN-ß) and type III (IFN-?) share many functions, including induction by viral infection, activation of shared signaling pathways, and transcriptional programs. Interferon type I binds to the receptor IFNAR2 with high-affinity, which then activates a low-affinity IFNAR1 to form a signaling complex.

***How the Corona virus Attacks Lungs***

The genetic material of viruses enveloped by protein and fat.

They are connecting links between life and death. As long as the virus is present in the cell,they are living,but when present outside the cell they are non-living.

***Lung macrophages challenged with respiratory viruses***

Most of the cells of the immune system derived from the hematopoietic system. Phagocytic cells are found in the circulation (Monocytes and granulocytes) and reside in the tissues (macrophages).Each cell type expresses characteristic surface molecules ( CD3,CD4,CD8.) Alveolar or pulmonary macrophages present freely on the outer surface of the lung.These cells scavenging the dust particles, microorganisms and other debris.The primary function of macrophage is phagocytosis. The macrophages, by their property of amoeboid movement, put forth pseudopodia which help in engulfing any solid particle such as the invading microorganisms. The macrophages have lysosomal granules, containing acid hydrolases and degradative enzymes with which it destroys the phagocytosed substances. The attachment of antigens to macrophage is specific.

All the macrophages have surface receptors for the C3 component of complement as well as for Fc component of antibody. The macrophages are involved in processing of antigens before they are presented to the T and B cells. (45) Lower respiratory tract infection due to RSV is a complicated process and several cell types are implicated in the disease progression (46) Disease severity due to extensive lung tissue damage correlates with enhanced pro-inflammatory cytokine secretion and inflammation. (47).

Pulmonary macrophage cells may behave differently with respect to RSV infection (48)

***Laboratory Findings***

Early detection may help to use appropriate antiviral agents. 1. Complete blood count may reveal leukocytosis with mild left shift. 2. Gram stains of the sputum may show few too many polymorphonuclear leukocytes.

***Radiographic Findings***

Chest X ray shows perihilar pulmonary edema, or dense opacities.

***Diagnosis***

Culture- Influenza virus can be isolated from upper and lower respiratory samples. However, because of the long turnaround time of reports, they are not used routinely. 2. Serology- Complement fixation and hemagglutinin inhibition during the acute phase of the illness and repeat test at 2-3 weeks during the convalescent phase to demonstrate a fourfold rise in antibody titer may be used. 3. Rapid antigen assays- less sensitive in detecting Influenza A infections as compared to RT-PCR assays. 4. Molecular diagnosis- Molecular methods like multiplex PCR / RT PCR are increasingly useful for the detection of H1N1, H3N2, and novel swine H1N1v.

The retrospective study included 461 patients who had been hospitalized with acute Covid-19 within four days of development of symptoms and positive RT PCR test for SARS-CoV-2 using a nasopharyngeal sample. (49)

***Treatment and prevention***

Influenza patients should be kept in bed until the fever has subsided. A mild analgesic usually relieves the head and backache. The vaccine is administered in cold countries to protect elderly people with preexisting cardiopulmonary or nasal disease and to other high-risk individuals with influenza outbreak is imminent.

RSV is worldwide in distribution and causes a winter epidemic in infants and children below one year of age Both formalin-inactivated crude whole-virus vaccine as well as a live vaccine have been tried but none is found satisfactory. Attempts to prepare vaccines with purified F and G surface glycoproteins of RSV are in progress.

***COVID-19 Vaccine***

The specific immune response against the pathogen is the key element stimulated by vaccine administration, Nanomaterial-based vaccines have proven prodigious prophylaxis of various infectious and non-infectious diseases of human and animal concern. The control of the spread of the virus and preventing severe fatal illness are the primary goals of the COVID-19 vaccine. It is widely accepted that neutralizing antibodies are key for the protection, which prevents the viruses from attacking the cells by blocking the SARS-CoV-2 spike protein interaction domain from binding with the ACE To control the pandemic, a constructive vaccine candidate should achieve immunity around 60–70% of the population to the infection to accomplish the concept of "herd immunity". The prominent genomic homology of the SARS-CoV2 virus with other beta coronaviruses like SARS-CoV and MERS-CoV supported the vaccine researchers to immensely accelerate the development of efficacious vaccine formulations to the status of a global healthcare issue. On January 11, 2020, the sequence of the SARS-CoV-2 RNA genome was published, which boosted in designing various varieties of innovative vaccine technologies, including modified or recombinant proteins, peptide fragments, particle mimicking the virus, viral vectors, nucleic acids (RNA and DNA), and complete virus vaccines (inactivated or live attenuated virus). Development of vaccines typically takes decades, but overwhelming demand of vaccination, knowledge on years of previous studies on relevant diseases which made significant achievements, sufficient funding for vaccine developers to run multiple trials simultaneously, and regulators decision making at unprecedented speed. Attenuated vaccine pathogens are known for their complexities. Even if considering tremendous advancements in rDNA technology in recent times empower broad exploration of antigen (protein or peptide) encoded recombinant vaccines, subunit vaccines, and nucleic acid-based vaccines.

***Research programs for the next generation world***

The main goal of most vaccination strategies is to be able to induce a strong and healthy virus-specific neutralizing antibody response in the host.

By doing so through the induction of virus-specific CD8 T-cell response and its humoral immunity. This dual approach may allow optimal viral control. Nowadays with viruses such as Respiratory Syncytial Virus, Parainfluenza Virus, Influenza Virus, Human Metapneumovirus, Rhinovirus, Parainfluenza Virus and Coronavirus. Researchers are exploring different technologies to tackle these respiratory infections. Virus vaccines: by using the virus in a weakened form or inactivated. Viral-vector vaccines: by genetically engineering the measles of adenovirus (weakened) to produce coronavirus proteins in the body.

Two types are those that can still replicate within the cells without producing a disease and the other one that cannot reproduce in the cells by disabling key genes. Nucleic-acid vaccines: by using genetic instructions, in the form of DNA or RNA, for a coronavirus protein that will encourage in the host the immune response. The nucleic acids are inserted into human cells that will churn out copies of the virus protein. Protein-based vaccine: injection of the virus proteins, fragments or protein shells that mimics the virus outer coat, directly into the host. (50)

## CONCLUSION

Advances in immunology, immunopathology, and immunopharmacology have already opened a way to a clearer understanding of the nature of certain respiratory diseases. Immunology has a further contribution to make in the field of respiratory infection Coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases.

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