COVID-19 INFECTION OR VACCINATION DOES NOT PROVIDE CROSS-PROTECTION AGAINST HUMAN METAPNEUMOVIRUS INFECTION

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ABSTRACT

Human metapneumovirus (HMPV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are major respiratory pathogens. This study investigates whether prior SARS-CoV-2 infection or COVID-19 vaccination provides cross-protection against HMPV. Nucleotide sequences of HMPV, SARS-CoV-2, and mRNA vaccines (Moderna and Pfizer-BioNTech) were retrieved from the NCBI database. Multiple sequence alignment, BLAST analysis, sequence dot plot and phylogenetic tree construction were performed to assess genetic and structural similarities. Results revealed no significant sequence homology between SARS-CoV-2 genome, structural proteins, mRNA vaccine sequences, and HMPV. HMPV does not share any common linear peptide epitope with SARS-CoV-2. This indicates a complete lack of cross-immunity. Phylogenetic analysis confirmed the distinct evolutionary divergence between these viruses. The resurgence of HMPV infections following the relaxation of COVID-19 restrictions further underscores the need for independent surveillance and vaccine development. These findings highlight the necessity for targeted immunization strategies against HMPV to mitigate future outbreaks.

KEYWORDS: HMPV, SARS-CoV-2, COVID-19, Cross-Protection.

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Introduction

Acute Respiratory Infections (ARIs) remain a significant global health concern, especially among children under five years in developing countries, e.g. pneumonia alone is claiming over 700,000 lives of children under five years every year, or around 2,000 every day (O'Brien et al., 2019). A new epidemic of Human metapneumovirus (HMPV) was noticed in late 2024 in China and has swamped healthcare institutions, notably in the northern regions, which saw an inflow of people suffering from severe respiratory distress (Verma et al., 2025). This epidemic sparked global alarm following five years of the SARS-CoV-2 pandemic and widespread vaccination against SARS-CoV-2 around the world. It also raised the question of the relationship between these two diseases. Since they have comparable symptoms and are both respiratory disorders, should they share certain preventive systems? The question is whether COVID-19 infection or the delivery of COVID-19 vaccinations protects against HMPV infection.

HMPV is a major cause of ARIs, especially in children (Yousafzai et al., 2018, Van den Hoogen et al., 2001), immunocompromised people, and the elderly. HMPV, which belongs to the Metapneumovirus genus within the Paramyxoviridae family, was discovered in 2001 (Van den Hoogen et al., 2001) and is connected to avian metapneumovirus subtype C, which has been around for at least 65 years and infects virtually all children by the age of five. However, this protection is imperfect in the sense that infections occur throughout life. HMPV symptoms vary from minor (cough, fever, rhinorrhea) to severe (bronchiolitis, pneumonia). It spreads through close contact and as HMPV is difficult to grow, RT-PCR is the best method for diagnosis. Despite advances in research, there are no FDA-approved HMPV antivirals or vaccines (Shafagati and Williams, 2018). HMPV is a negative sense, non-segmented, single-stranded RNA virus of approximately 13,000 nucleotides in length. The virus encodes eight genes that produce nine proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), matrix-2 proteins (M2-1 and M2-2), small hydrophobic protein (SH), glycoprotein (G), and large polymerase protein (L). Like other paramyxoviruses, HMPV contains a replication complex composed of the N, L, and P proteins. HMPV and avian metapneumovirus genomes have some similarities with RSV genome, however HMPV and avian metapneumovirus have distinct gene orders and lack the NS1 and NS2 proteins. These NS1 and NS2 proteins possess anti-interferon activity (Bossert and Conzelmann, 2002). HMPV morphologically resembles other paramyxoviruses, having an enveloped shape, short protein spike projections, and sizes ranging from 150 to 600 nm (Van den Hoogen et al., 2001,

Shafagati and Williams, 2018). HMPV is separated into genetic groups A and B, with lineages A1, A2.1, A2.2.1, A2.2.2, B1, and B2 based on the F gene sequence, indicating high antigenic diversity. New subtypes, including A2.2.1 and A2.2.2, have been discovered, demonstrating the genetic heterogeneity (Groen et al., 2023).

The COVID-19 pandemic has impacted the propagation of seasonal respiratory viruses, particularly HMPV, highlighting the necessity for rigorous epidemiologic investigations (Agca et al., 2021). SARS-CoV-2 is from the Coronaviridae family, specifically the Sarbecovirus genus. It has 79% genomic similarity with SARS-CoV-1 and has a close genetic link with bat coronaviruses. It arose in late 2019 in Wuhan, China, sparking a global pandemic. In recent decades, three major zoonotic coronaviruses have impacted humans: SARS-CoV-1 (2002-2003 outbreak), MERS-CoV (sporadic outbreaks since 2012), and SARS-CoV-2 (which causes COVID-19). The SARS-CoV-2 virion contains four structural proteins: spike protein (S), nucleocapsid protein (N), membrane protein (M), and envelope protein. The spike glycoprotein, which forms trimers on the surface of viruses, is the primary factor that determines coronavirus tropism (Hulswit et al., 2016). The S1 subunit of the spike binds ACE2, while the S2 subunit mediates fusion with the host cell membrane. TMPRSS2 and cathepsin L are key proteases involved in viral entry. SARS-CoV-2 can enter cells via direct fusion or through endosomal pathways. Structural proteins include - membrane (M) protein – shapes the viral envelope, envelope (E) protein – plays a role in viral assembly, and nucleocapsid (N) protein – binds to viral RNA for packaging. Clinical manifestations include fever, cough, sore throat, and fatigue in mild cases. Again, pneumonia, shortness of breath, mild hypoxia, acute respiratory distress syndrome (ARDS), respiratory failure, and multi-organ damage can happen in moderate and severe cases. RT-PCR is the gold standard for detecting viral RNA and other rapid diagnostic tests include rapid antigen test. For treatment, antivirals like Remdesivir, Molnupiravir, Paxlovid are used. Dexamethasone and Tocilizumab are used as anti-inflammatory treatments (Lamers and Haagmans, 2022). Different anticoagulants and monoclonal antibodies are also used. SARS-CoV-2 has developed into several variations, each with unique genetic alterations that impact transmissibility and immunological response. The first Wuhan variety (Wuhan-Hu-1) was discovered in Wuhan, China, in December 2019, signaling the start of the COVID-19 pandemic. The Alpha version (B.1.1.7) was discovered in the United Kingdom in September 2020, followed by the Beta variant (B.1.351) in South Africa in December 2020. The Gamma version (P.1) appeared in Brazil in January 2021, with greater transmissibility. The extremely infectious Delta variant (B.1.617.2) was first discovered in India in May 2021, resulting in an increase in worldwide infections. Later, in November 2021, the Omicron variety (B.1.1.529) was discovered in South Africa, which is characterized by widespread mutations that allow immunological escape (Erkihun et al., 2024). The rapid development of COVID-19 vaccines has been a crucial step in combating the pandemic. Various vaccines have been developed using different technologies, each with varying efficacy, storage requirements, and potential side effects (Mascellino et al., 2021). mRNA vaccines (Pfizer-BioNTech and Moderna) have shown the highest efficacy (~95%) in preventing infection and severe disease. They use lipid nanoparticles to deliver genetic instructions for the spike protein which promotes an immune response. Viral vector vaccines (AstraZeneca, Janssen, and Sputnik V) use modified adenoviruses to introduce the spike protein gene into human cells. Protein subunit and inactivated virus vaccines (Novavax, Sinovac) provide alternative approaches by using viral protein fragments or inactivated virus particles to trigger immunity. According to the World Health Organization (WHO), as of February 15, 2025, there have been more than 777.37 million confirmed cases and 7.08 million deaths from the COVID-19 pandemic. 13.64 billion doses of the COVID-19 vaccine were administered worldwide, with 67% of the population having received the whole main series and 32% having received at least one booster dose (2025).

Because of their similar respiratory tract tropisms, one question that come up is whether infection by SARS-CoV-2 or vaccination against COVID-19 provide any immunity against HMPV. The purpose of this study is to determine whether vaccination or past COVID-19 infection confers any immunity against HMPV through multiple sequence alignment of the nucleotide and protein sequences of the SARS-COV-2 variants and mRNA vaccines with HMPV sequences.

Methods

Retrieving Nucleotide Sequences

Viral nucleotide sequences were obtained from the NCBI Virus portal of the National Institutes of Health (NIH). For human metapneumovirus (HMPV, taxid 162145), a search was conducted using the term "HMPV," and the dataset was filtered based on the collection date (31-10-2024 to 23-03- 2025) with sequence length set at minimum 13000. The collection date was selected with regard to the recent outbreak of HMPV that happened in the late 2024 and early 2025 (Verma et al., 2025). Accession numbers of the identified sequences were recorded, and the corresponding FASTA-format genome sequences were retrieved. Additionally, major HMPV variants (A1, A2, B1, B2, A2.2.2) sequences were obtained using the genotype filter.

Similarly, for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), genome sequences were retrieved from the NCBI Virus portal using the isolate name filter and directly from the NCBI Nucleotide database using relevant accession numbers. These sequences were also downloaded in FASTA format for further analysis.

Genome Alignment and Dot Plot Construction

To find any similar sequence stretches, HMPV whole genome sequences were aligned to SARS-CoV-2 whole genomes using BLAST. Representative HMPV whole genome was given as query sequence and SARS-CoV-2 representative sequences were given as subject sequences. Representative sequences of the two viruses were also aligned to produce dot plots using Sequence Dot Plot tool in VectorBuilder (https://en.vectorbuilder.com/tool/sequence-dot-plot.html).

Phylogenetic Tree Construction

The retrieved HMPV and SARS-CoV-2 sequences were subjected to multiple sequence alignment (MSA) using the Clustal Omega tool in MEGA using default parameters. Phylogenetic trees were constructed using Neighbor Joining method in MEGA with the number of bootstrap replications set to 1000. All other settings were kept at default (Tamura et al., 2021). Percent Identity Matrix was produced from the aligned sequences using MView (Madeira et al., 2024). Heatmap was

prepared from the percent identity matrix using matrix2png web interface (Pavlidis and Noble, 2003).

BLAST Analysis of SARS-CoV-2 and HMPV Structural Proteins

To assess potential protein-level similarities between SARS-CoV-2 structural proteins and human metapneumovirus (HMPV) proteins, a BLASTp (protein BLAST) analysis was conducted using the NCBI BLAST tool. The protein sequences of SARS-CoV-2 structural proteins were retrieved from the NCBI database, with the following GenBank accession numbers: Spike Protein (S): YP_009724390.1, Nucleocapsid Protein (N): YP_009724397.2, Membrane Protein (M): YP_009724393.1, Envelope Protein (E): YP_009724392.1. These sequences were used as queries in BLASTp to compare them against HMPV proteins (TaxID: 162145) using the Non-Redundant Protein Sequences (nr) database. The analysis aimed to determine whether SARS-CoV-2 structural proteins share sequence homology with HMPV proteins, which could suggest potential functional or immunological similarities. The BLASTp parameters included standard protein-protein BLAST, with HMPV as the target organism, ensuring specificity in the comparison.

Retrieval of epitope sequences and comparison

All available linear peptide epitope sequences of SARS-CoV-2 and HMPV were retrieved from the Immune Epitope Database and Tools (IEDB) (https://www.immuneepitope.org). Presence of any common epitope was searched using Venny (Oliveros, 2007).

Retrieval and BLAST Analysis of mRNA Vaccine Sequences

To analyze the genetic similarities and differences between, human metapneumovirus (HMPV), and mRNA vaccines of SARS-CoV-2, the nucleotide sequences of the two widely used COVID-19 mRNA vaccines – Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) – were retrieved from the NCBI nucleotide database. The GenBank accession numbers for the retrieved sequences are Moderna (mRNA-1273): OK120841.1 and Pfizer-BioNTech (BNT162b2): OR134577.1.

To determine sequence similarity between SARS-CoV-2 mRNA vaccine sequences and HMPV, NCBI's BLASTn tool were used, applying the following parameters: Program Selection: Optimized for highly similar sequences (MEGABLAST); Database: Core Nucleotide Database (Core Nucleotide [nt]); Organism: Human Metapneumovirus (HMPV) [TaxID: 162145].

Results

Twenty-nine HMPV and seven SARS-CoV-2 genome sequences were retrieved

Twenty-four nucleotide sequences of HMPV genome were retrieved whose collection dates were between 31-10-2024 to 23-03-2025 (Table 1). In addition, representative sequences of the five main subgroups of HMPV, namely A1, A2, B1, B2, and A2.2.2 were retrieved from NCBI nucleotide database with accession numbers PP086007.1 (A1, USA), PP315925.1 (A2, China), PP315926.1 (B1, China), MZ221203.1 (B2, China), and PP763212.1 (A2.2.2, Taiwan). Seven SARS-Cov-2 sequences representing the major variants were retrieved which include OL689430.1 (Alpha, Switzerland), OP295757.1 (Delta, India), OR575560.1 (Omicron, Belgium), OR936774.1 (Beta, South Africa), OR578389.1 (Zeta, Switzerland), OM366054.1 (Kappa, Canada) and NC_045512.2 (Wuhan variant, China) (Table 2).

Table 1. Particulars of retrieved HMPV genomes.

Accession	Length	Subgroup	Geolocation	Collection Date
PV260518.1	13198		USA: Massachusetts	2025-01-23
PV260519.1	13257		USA: Massachusetts	2025-01-20
PV081662.1	13358	A	Brazil: Sao Paulo	2024-12-30
PV081663.1	13085	B	Brazil: Sao Paulo	2024-12-26
PV081664.1	13091	B	Brazil: Sao Paulo	2024-12-30
PV081665.1	13358	A	Brazil: Sao Paulo	2025-01-03
PV081666.1	13358	A	Brazil: Sao Paulo	2025-01-13
PV081667.1	13085	B	Brazil: Sao Paulo	2025-01-13
PV206817.1	13198		USA: Massachusetts	2024-12-18
PV178224.1	13276		USA: Massachusetts	2024-12-11
PV178241.1	13309		USA: Massachusetts	2024-11-18
PV052135.1	13444		USA: Washington	2025-01-03
PV052140.1	13434		USA: Washington	2024-12-06

Accession	Length	Subgroup	Geolocation	Collection Date
PV052155.1	13065		USA: Washington	2024-12-12
PV052192.1	13236		USA: Washington	2024-12-25
PV052201.1	13435		USA: Washington	2024-11-30
PV052224.1	13068		USA: Washington	2024-11-01
PV052225.1	13445		USA: Washington	2024-11-01
PV052226.1	13086		USA: Washington	2024-11-01
PV052227.1	13436		USA: Washington	2024-12-01
PV052228.1	13088		USA: Washington	2024-12-01
PV052229.1	13104		USA: Washington	2024-12-01
PV052230.1	13320		USA: Washington	2024-12-01
PV052231.1	13103		USA: Washington	2024-12-01
PP086007.1	13331	A1	USA	1994
PP315925.1	13387	A2	China	2023
PP315926.1	13235	B1	China	2023
MZ221203.1	13281	B2	China	2014
PP763212.1	13430	A2.2.2	Taiwan	2023-07-15

Table 2. Particulars of retrieved SARS-Cov-2 genomes.

Accession	Length	Variant	Geolocation	Collection Date
OL689430.1	29839	Alpha	Switzerland	2020-12-23
OP295757.1	29798	Delta	India	2022-01-23
OR575560.1	29684	Omicron	Switzerland	2021-12-08
OR936774.1	29816	Beta	South Africa	2021-04-23
OR578389.1	29825	Zeta	Switzerland	2021-03-04
OM366054.1	29804	Kappa	Canada	2021-07-30
NC_045512.2	29903	Wuhan-Hu-1	China	2019-12

HMPV and SARS-CoV-2 genomes have no significant sequence similarity

In order to identify any stretch of sequence with high similarity, representative sequences of HMPV genome were subjected to BLAST nucleotide search against SARS-CoV-2 genomes of different variants. No significant local sequence similarity was found both when the search was performed using megablast and discontiguous megablast using expect threshold 0.05. To visualize the difference, dot plots were generated using HMPV genome (PP086007.1) and SARS-CoV-2 genome (NC_045512.2) using the Sequence Dot Plot Tool in VectorBuilder. Dot plot with window size 10 and mismatch limit 0 had randomly arranged dots throughout the plot with no lines eliminating the presence of any identical long sequence stretches (Figure 1). When the window size was increased to 15 there appeared only two dots. At window size 18, there were no remaining dots. The two viral genomes carry highly dissimilar sequences apparently having no significant similarity.

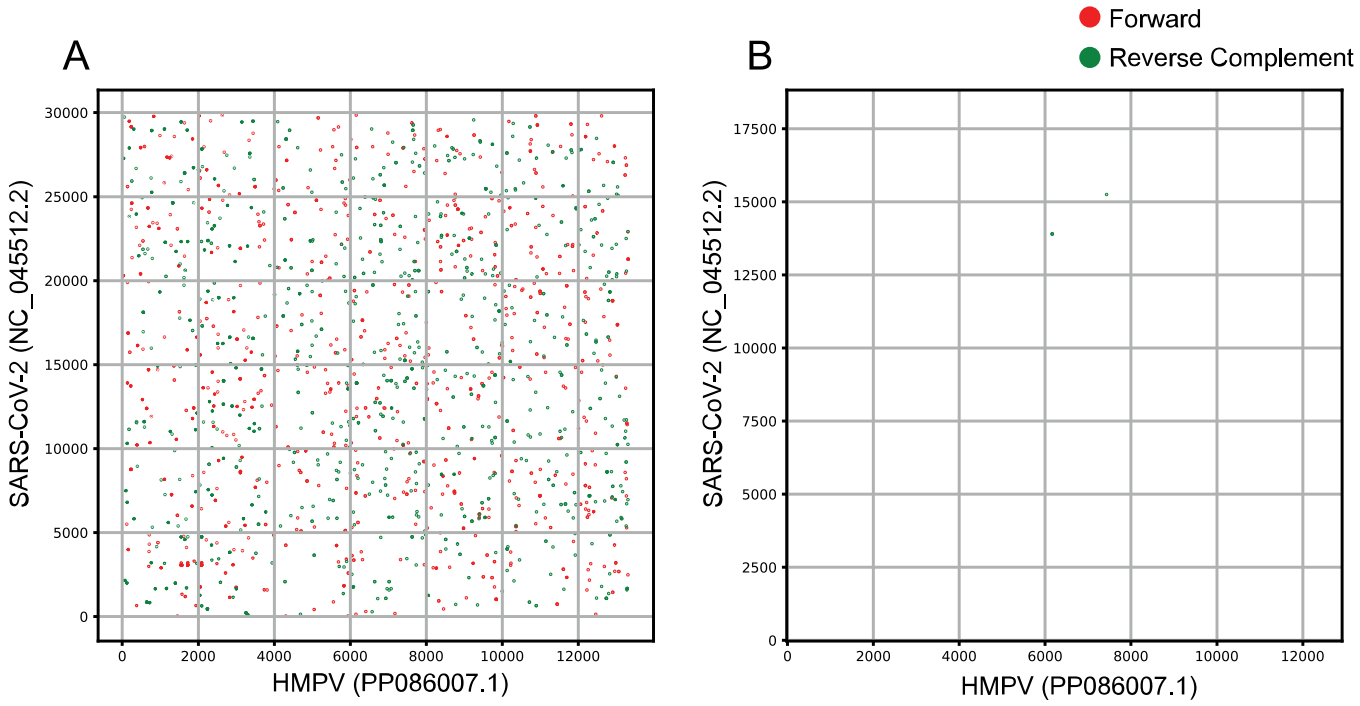

Figure 1. Sequence dot plots showing the absence of any significant similarity between HMPV and SARS-CoV-2 whole genomes. In (A), the window size was set at 10 and the mismatch limit was 0. In (B), the window size was increased to 15 and the mismatch limit was 0.

HMPV and SARS-CoV-2 genomes were aligned using Clustal Omega to produce a multiple sequence alignment (Supplementary File 1). Phylogenetic tree prepared from this alignment show no significant similarities which can be evident by the fact that they form different and very distant clusters in the phylogenetic tree constructed with various HMPV and SARS-CoV-2 sequences (Figure 2). The tree represents different HMPV isolates from USA, Brazil, Taiwan, and China which were mostly collected during the 2024-2025 outbreak and seven representative SARS-CoV-2 sequences from different variants. Within the HMPV cluster, there is a clear division into two subclades. The upper subclade consists of HMPV subgroup A sequences whereas the lower subclade contains the HMPV subgroup B sequences. We observed no significant difference among sequences that were collected before and during the 2024-2025 outbreak. Importantly, there is no intermixing of SARS-CoV-2 and HMPV sequences. Thus, it strongly suggests the genetic separation between these respiratory pathogens.

From the multiple sequence alignment, a percent identity matrix was calculated using MView (Figure 3, Supplementary File 2). The SARS-CoV-2 genomes had high sequence identity among themselves ranging from 99 to 100 percent. Sequence identity among the HMPV and SARS-CoV-2 genomes were comparatively very low ranging from 43 to 46 percent. The genomes of HMPV formed two distinct subgroups A and B. Sequence identity within the subgroups ranged from 91 to 100 percent whereas between the two subgroups in ranged from 77 to 82 percent.

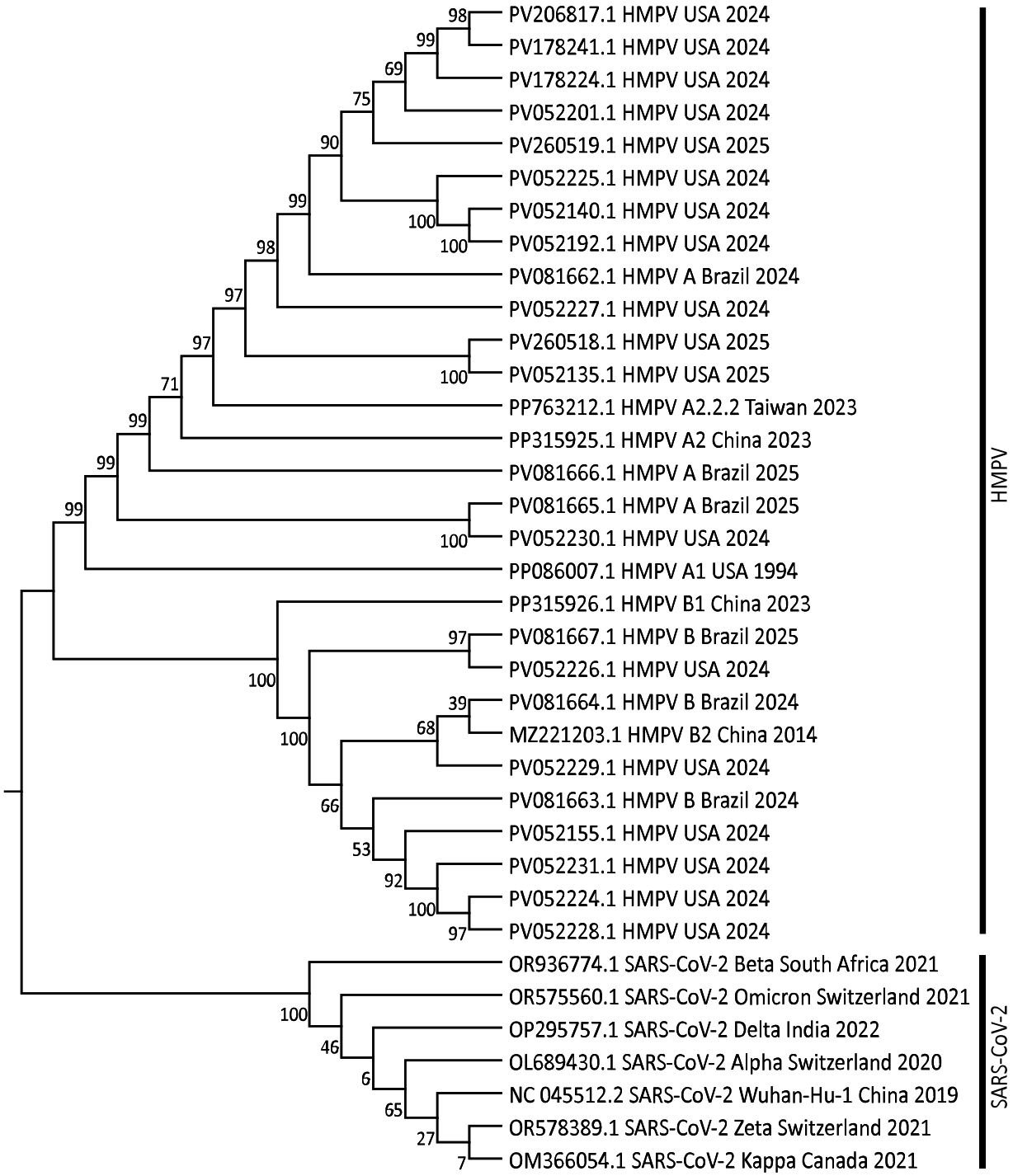

Figure 2. Phylogenetic Tree showing distinct genetic difference between SARS-CoV-2 and HMPV sequences. Node names include accession number followed by the name, subgroup or variant, geolocation and isolation year of the viruses. Value at the left of each node represents the bootstrap frequency.

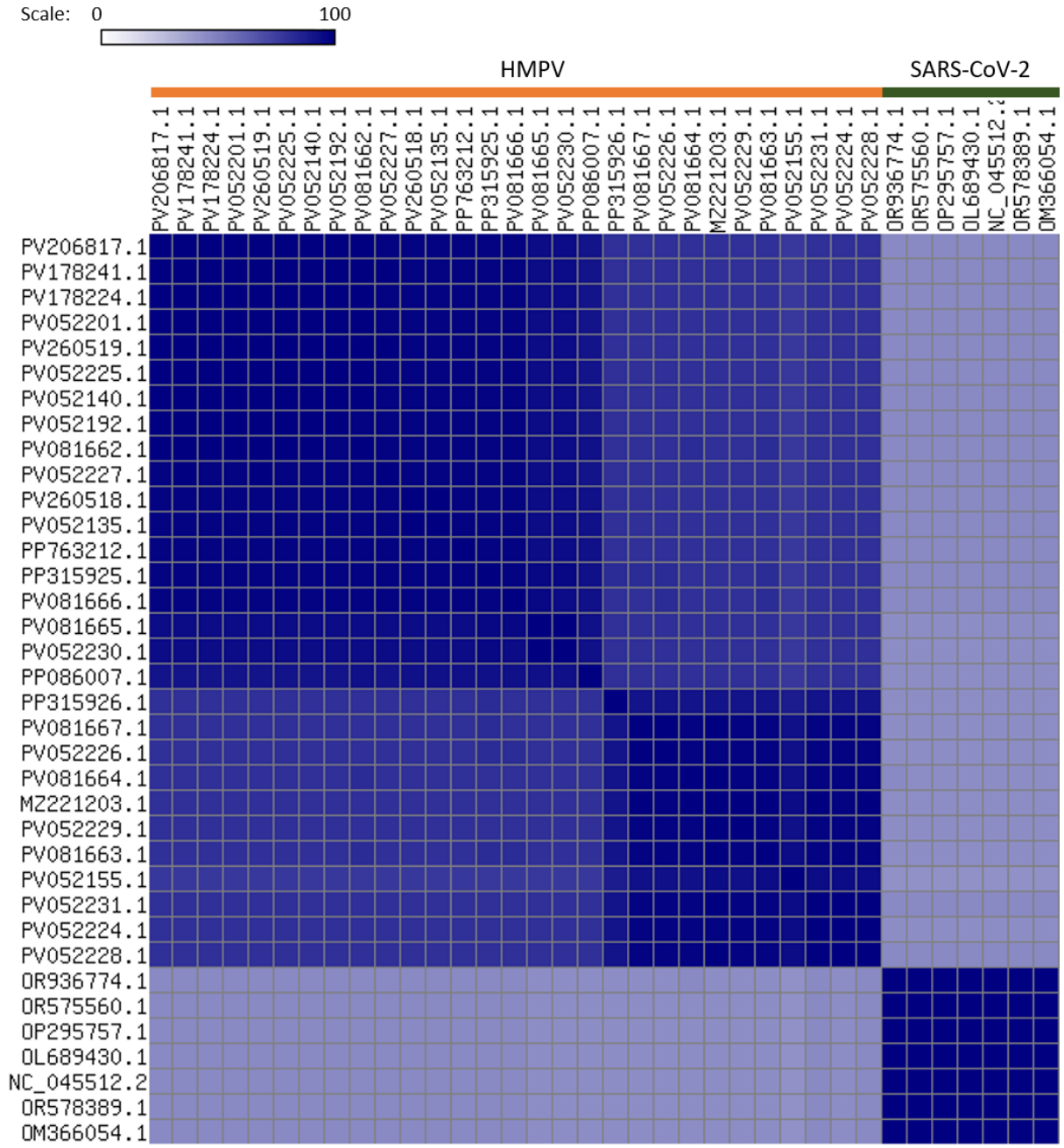

Figure 3. A heatmap showing percent identity among HMPV and SARS-CoV-2 genomes. The color-coded scale indicates percent identity where white indicate 0% and deep blue indicates 100%. The sequences are sorted as they clustered in Figure 2.

Lack of Protein Sequence Homology Between SARS-CoV-2 and HMPV

The BLASTp analysis revealed no significant sequence similarity between the SARS-CoV-2 structural proteins (S, N, M, E) and HMPV proteins. No alignment met the significance threshold (Expect value 0.05), indicating a complete lack of homology between the structural components of the two viruses. The absence of conserved regions or functional similarities suggests that SARS-CoV-2 and HMPV do not share common structural protein features.

HMPV and SARS-CoV-2 share no common linear peptide epitope

Linear peptide epitope sequences were retrieved from the IEDB database. For SARS-CoV-2 a total of 16685 linear peptide epitopes were available in the database. For HMPV the number was 113. However, comparison of the epitope sequences with Venny yielded no common epitope between the two viruses (Figure 4).

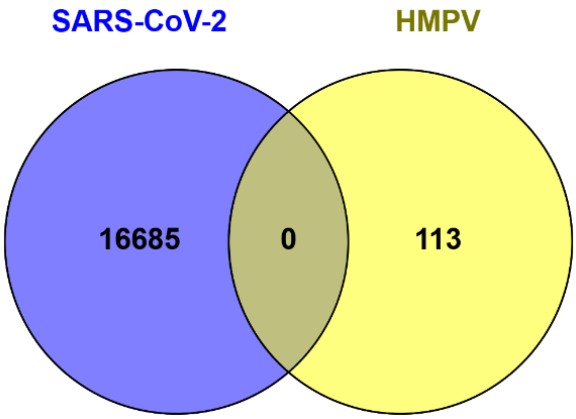

Figure 4. Venn Diagram showing the absence of any common epitope between SARS-CoV-2 and HMPV.

There is no sequence similarity between COVID-19 mRNA vaccines and HMPV genome

Local alignment using BLAST revealed a complete lack of sequence similarity between the Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) mRNA vaccine sequences and HMPV genome.

Discussion

The genetic dissimilarity between SARS-CoV-2 and HMPV directly explains the lack of cross-protection observed in our study. Immune responses generated by SARS-CoV-2 infection or by introducing vaccine primarily target the viral spike (S) protein and other SARS-CoV-2-specific antigens (Dai and Gao, 2021). Since HMPV completely lacks sequence similarity and hence structural or antigenic similarities with these proteins, pre-existing immunity to SARS-CoV-2 does not confer protection against HMPV infections.

HMPV infections surged globally following the relaxation of COVID-19 restrictions. It highlights the absence of protective immunity against this virus. Lockdown measures implemented to curb SARS-CoV-2 transmission also suppressed other respiratory pathogens, including HMPV. As these restrictions eased, HMPV re-emerged at high incidence rates along with other common respiratory pathogens. It underscores continued ability of the virus to cause outbreaks (Liu et al., 2025).

Several case reports and studies have documented co-infections of SARS-CoV-2 and HMPV, further demonstrating the lack of immune cross-protection. Individuals diagnosed with COVID-19 have also tested positive for HMPV, suggesting that prior SARS-CoV-2 infection does not confer immunity against concurrent or subsequent HMPV infections (Touzard-Romo et al., 2020, García-García et al., 2023). These findings reinforce the need for independent surveillance and targeted vaccine development strategies for HMPV.

Conclusion

Our analysis demonstrates that prior SARS-CoV-2 infection does not provide immunity against HMPV due to antigenic and immune response differences. Likewise, COVID-19 vaccines, designed specifically against SARS-CoV-2, do not confer protection against HMPV. Given the persistent burden of HMPV infections, it is essential to develop specific vaccines and antiviral strategies for this pathogen. Future research should focus on targeted immunization approaches and understanding the interplay between viral co-infections in respiratory diseases.

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