

Respiratory Viruses Dynamics and Interactions: Ten Years of Surveillance in Central Europe

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Abstract

Background: Lower respiratory tract infections are among the main causes of death. Although there are many respiratory viruses, diagnostic efforts are focused mainly on influenza. The Respiratory Viruses Network (RespVir) collects infection data, primarily from German university hospitals, for a high diversity of infections by respiratory pathogens. In this study, we computationally analysed a subset of the RespVir database, covering 217,150 samples tested for 17 different viral pathogens in the time span from 2010 to 2019.

Methods: We calculated the prevalence of 17 respiratory viruses, analysed their seasonality patterns using information-theoretic measures and agglomerative clustering, and analysed their propensity for dual infection using a new metric dubbed average coinfection exclusion score (ACES).

Results: After initial data pre-processing, we retained 206,814 samples, corresponding to 1,408,657 performed tests. We found that Influenza viruses were reported for less than half of all infections and that they exhibited the highest degree of seasonality. Coinfections of viruses are frequent, the most prevalent coinfection was rhinovirus/bocavirus and most of the virus pairs had a positive ACES indicating a tendency to exclude each other regarding infection.

Conclusions: The analysis of respiratory viruses dynamics in monoinfection and coinfection contributes to the prevention, diagnostic, treatment, and development of new therapeutics. Data obtained from multiplex testing is fundamental for this analysis and should be prioritized over single pathogen testing.

Background

The current COVID-19 pandemic prominently demonstrates the serious threat posed by respiratory infections, not only for the health of individuals, but also for the stability of modern society, in general. While SARS-CoV-2 infections are currently extensively recorded and analysed, future studies must encompass the full breadth of respiratory viruses as has been done in the past. Even before the pandemic, lower track respiratory infections were among the main causes of death in children and adults [1, 2]. Influenza infection killed between 250,000 and 500,000 people annually, 152,000 deaths were reported in Europe in the 2017-2018 season [3]. In Germany, during the 2018-2019 season, 182,000 influenza-positive tests were confirmed, including 40,000 from inpatients [4].

In 2009 the Respiratory Viruses Network (RespVir www.clinical-virology.net) was founded as an initiative of a Clinical Virology group within the German Virology Society (GfV). The purpose of RespVir is to record respiratory infections in an online database [5], providing clinicians with up-to-date information about circulating pathogens. The RespVir database contains mainly registries from inpatients data reported by 47 laboratories from university hospitals and a few private. These institutions are located primarily in Germany, Austria, and Switzerland. Over 12 years, RespVir has analysed more than 280,000 samples with respect to 25 respiratory pathogens (17 viruses and 8 bacteria). Among these years RespVir had obtained data on causal agents of respiratory infections.

RespVir includes records of samples from all patients with respiratory symptoms, sent in by clinicians requesting a diagnosis. Independent of the diagnostic hypothesis of the clinician, each sample was tested in a multiplex manner covering a maximum of 17 respiratory viruses, depending on test availability of each laboratory.

In this study, our aims were (i) to describe the prevalence and seasonal variation (seasonality) for each pathogen, (ii) to assess the prevalence of coinfections and (iii) to determine the rate of exclusion or affinity for pairwise coinfections.

After filtering registries with incomplete data and a post-hoc data quality control. To accomplish our objectives, we performed the analysis in a subset of the RespVir database including 17 different viral pathogens covering the time span from 2010 to 2019.

We observed that 48.64% of all respiratory infections are caused by influenza virus. We found four general seasonality patterns. Each of the 17 viruses belongs to one of these patterns. Stratification across years shows biennial seasonality patterns for some viruses, indicating infection peaks every other season. We further observed that coinfections do not occur statistically independently, but that for most virus pairs coinfection is far less frequent than expected by chance.

Methods

Samples and Data Collection

Since November 2009, the RespVir network (Figure 1) has collected multiplex test records for 17 virus infections from patients that showed respiratory infection symptoms. The records stem from various 47 sites, according to the sites' test availability. The tests used by some sites do not differentiate between certain virus types or subtypes: (i) FLUA-generic, which cannot distinguish between influenza A H1N1 and H3N2, (ii) HPIV-generic, which cannot differentiate between parainfluenzas 1, 2, 3 or 4, (iii) HCoV-generic which cannot differentiate between the human coronaviruses HCoV-OC43, HCoV-NL63, HCoV-229E, and HCoV-HKU1, and (iv) RV/EV which does not differentiate between rhinovirus and enterovirus (Table 1). Each RespVir member site submitted a file that includes the date of sampling, the tests performed and their results to a data base manager, who fed the data to the database.

Database Pre-processing

The database required a pre-processing of the data. This process consisted in 1) filtering all incomplete data records before further analysis, and 2) a post-hoc curation.

After manual inspection of the data records, we found that most of the sites reported coinfection rates below 0.01 of any virus pairs. There were few sites (up to 4 out of 47, depending on the analysed virus pairs) reporting coinfection rates above 0.01. Due to the possibility of typographic errors and to avoid overestimation of the coinfection rates, we analysed only coinfections for each virus pairs reported below 0.01 threshold per site. Of note, this threshold also did not significantly affect the results.

After the pre-processing we split the database in two for the analysis. The first part of the analysis was performed on data records from monoinfections. Therefore, we filtered the data records for monoinfection. The second analysis was coinfections. For the coinfection analysis we took the records from samples tested for multiple viruses and exclusively evaluated coinfections with two viruses.

Seasonality profiles

We computed the *seasonality profile* of a virus by stratifying the number of positive tests from 2010 to 2019 by month and normalizing these month-specific infection counts. To quantify the *degree of the seasonality* of each virus, we computed the Kullback-Leibler divergence (KLD) of the seasonality profile to a uniform distribution [6]. Hence, a value of zero corresponds to uniform prevalence over the year, i.e., no seasonal variation. To compare the seasonality profiles of the 17 pathogens among each other, we computed the Jensen-Shannon divergence (JSD) [7] and applied agglomerative clustering with average linkage.

We also computed *year-specific seasonality profiles* for each year from 2010 to 2019. We clustered these profiles according to their JSD to compare the seasonality profiles over different years. In addition, we repeated the year-specific analysis using the positivity rate instead of the absolute counts of positive tests.

Coinfections Prevalence and Virus Pair Relations

For studying coinfections, we considered the 17 viruses corresponding to 21 tests including the non-differentiating tests (FLUA-generic, HPIV-generic, RV/EV and HCoV-generic). While theoretically 210 combinations of the 21 tests are possible, we excluded combinations of non-differentiating tests with their more specific counterparts, such as FLUA(H3N2) combined with FLUA-generic. Finally, 197 valid combinations remained.

For assessing the tendency of each virus pair to exclude each other or coinfect the patient, we created a *coinfection exclusion score* (CES), see Supplementary material, Section 1.1, for the precise definition.

To exclude bias due to seasonal effects, we carried out this procedure for the entire data set stratified by months and averaged the resulting values over the statistically significant CES per virus pairs and months (Supplementary material, Section 1.2), yielding the *average coinfection exclusion score* (ACES). The CES and ACES scores assume a value of 1 if coinfections are ten times less likely than expected by chance and a value of -1 if they are ten times more likely.

Results

Database Pre-processing

From 2010 to 2019, RespVir database registered 217,150 samples. After the initial filtering of the records with incomplete data, we retained 213,131 (98.14%) sample records.

To the monoinfection analysis, we selected samples with one or no positively tested pathogen. Regarding coinfections we selected all samples tested for at least two pathogens. To filter out sample records that are likely erroneous, for the coinfection analysis, we performed an additional post-hoc curation by setting a coinfection rate threshold of 0.01, for each of the virus pair per site. We discarded all coinfection patient records that yielded coinfection rates above this coinfection rate threshold.

After all filters were applied to the data base, we retain 206,814 sample records, of which 126,808 (61.31%) were monoinfections, 6781 (3.27%) coinfections, and 72,335 (34.97%) negatives. The retained samples correspond to 1,408,657 tests performed. For coinfection, we analysed 7,790,879 tests results combinations corresponding to the 197 senseful viral pairs (Supplementary table S1).

Infections Prevalence.

The 17 different respiratory viruses were not tested equally frequently. For example, while the 30.15% of the samples were tested only for the *Orthomyxoviridae* family, consisting of with FLUA (18.18%) and FLUB (11.97%). Members of the *Coronaviridae* family were tested significantly less frequently, with 4.51% HCoV-OC43, 4.36% HCoV-NL63, 4.21% HCoV-229E, 1.21% HCoV-HKU1, and 0.54% HCoV-generic (Table 1).

Influenza viruses represent 48.64% of all positive outcomes, of which 31.90% pertain to FLUA, and 16.74% to FLUB. The remaining 51.36% cover the remaining 14 viruses.

FLUA-generic test become the test with the highest positivity rate (32.89%), followed by rhinovirus (28.23%), RV/EV (20.70%), human respiratory syncytial virus (HRSV) (20.37%), and influenza B (15.19%). The tests for coronaviruses and parainfluenza families were the ones with the lowest positivity rate (Table 1).

Seasonal Variations of Viruses Circulation

To study the seasonality of the respiratory viruses, we excluded the four tests that do not differentiate virus subtypes. The influenza viruses (FLUB, FLUA(H3N2), and FLUA(H1N1)) exhibit the highest degree of seasonality, whereas RV, HPIV-3, enterovirus, and adenovirus exhibit the lowest (Figure 2a).

We determined the similarity of the seasonality profiles among the 17 viruses and carried out hierarchical clustering with average linkage. After applying a cut-off of 0.05 to the dendrogram, we obtained four groups (Figure 2b), each of which we assigned an interpretive label: (1) "Winter Peak" comprises FLUB, FLUA(H3N2) and FLUA(H1N1)), (2) "Winter/Spring Peak" comprises HRSV, HCoV-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, HMPV, and HBoV, (3) "Autumn Peak" comprises HPIV-1, HPIV-2, and HPIV-4, and (4) "Perennial" comprises HAdV, EV, HPIV-3, RV (Figure 2c and Supplementary figure S1). We repeated this analysis using the positivity rate, obtaining similar results. (Supplementary figure S2)

To analyse seasonality variation of each virus among the 10 years of the study, we stratified the frequency of positive tests for each pathogen by year and calculated their year-specific seasonality

profiles (Supplementary figure S3). We found that HCoV-OC43, exhibiting a clear biennial pattern, that is, high infection numbers at the end of even and beginning of odd years (Figure 3a). To obtain a more concise representation, we applied hierarchical clustering with average linkage to the ten profiles of each virus (Supplementary figure S4). We found that the year-specific seasonality profiles of HCoV-OC43 resolve into two groups that contain the odd and even years respectively (Figure 3b), and a similar biennial variation becomes apparent for HPIV-1, HPIV-3, and HRSV (Supplementary figure S4). For FLUA(H3N2) (Figure 3c) and FLUA(H1N1) (Figure 3d) a biennial pattern can be presumed, but it is not consistently true all years.

Coinfections Prevalence and Virus Pair Relations

To describe the coinfection prevalence, we analysed 7,790,879 tests results for the 197 virus test pairs.

We found that RV/HBoV, RV/HAdV, HRSV/HBoV, HRSV/HAdV and HRSV/HCoV-OC43 coinfections were the most prevalent coinfections, and together with HRSV/RV had the highest positivity rate. For 19 out of the 197 studied virus pairs, we did not find any coinfection case (Supplementary table S1).

For 73 of the 197 virus pairs, we obtained a coinfection exclusion score (CES), which implies a statistically significant dependence of both test results, for at least one month. The great majority of test pairs yield a positive ACES (Average coinfection exclusion score), indicating coinfection exclusion. The pair FLUA(H3N2)/FLUB shows the highest coinfection exclusion (ACES=1.67), followed by FLUA(H3N2)/FLUB (ACES=1.39), FLUB/HPIV-3 (ACES=1.34), FLUA-generic/HMPV (ACES=1.30), and FLUA(H1N1)/RV and FLUA(H3N2)/FLUA(H1N1) with an ACES=1.29 for both cases. We found negative ACES values in only five test pairs, indicating affinity of the viral pairs like FLUA(H3N2)/HPIV-4 with ACES=-1.39 (Figure 4 and Supplementary table S2).

Discussion

In the present study, we present data from the respiratory pathogens network that has been in place since 2009, based on multicenter, wide-spectrum collection rather than collection based on narrowly defined selection criteria.

Filtering and post-hoc curation was required. This was partly necessary due to non-curved data entering the database. To overcome this disadvantage, it is important to establish quality control mechanisms during data collection in the future to reject the collection of false data mainly regarding coinfections.

We analysed the frequency of 17 respiratory pathogens with respect to monoinfections and coinfections, their seasonal variation, and the affinity to coinfect with other viruses, spanning 10 years (2010-2019). To our knowledge, this study reports on the largest volume of data of its kind [4, 8–15].

Our results confirm previous reports that influenza A viruses, HRSV, and RV are most commonly found [4, 13, 14, 16, 17]. Nevertheless, almost one quarter (24.65%) of the infections are caused by other respiratory viruses. Even influenza tests are the most frequently performed, 51.36% of all positive test were other

respiratory viruses. Altogether supports the importance of testing for multiple pathogens for diagnostic purposes [18–20].

To properly detect patterns of seasonal variation long-term studies are needed [18, 19]. Our study is robust and covers a long-term period. This study allow us to confirm previously reported seasonal patterns [18–22], but also to proposed a new seasonal classification of the studied viruses into four groups. Furthermore, we found a typical seasonal pattern repeated every other year for HPIV-1, HPIV-3, HMPV, HRSV, and HCoV-OC43; also, for FLUA(H3N2) except for years 2010 and 2018 as well as for FLUA(H1N1) except for years 2010 and 2012, respectively. This confirms the constancy of the biennial patterns except for years near to a pandemic event due to new viruses appearance.

The SARS-CoV-2 outbreak has raised questions regarding the seasonal pattern of this virus. Studies on seasonal patterns of endogenous viruses could help to solve these questions. We found a slight difference in the seasonal profile within the coronaviruses (Figure S1). SARS-CoV-2 belongs to beta-coronaviruses which season starts in November-December and has its peak in December-January. Thus, a similar seasonality could be expected for SARS-CoV-2 in the future.

Coinfection modifies the natural history of diseases. Thus, deeper understanding of coinfections, especially the exclusion mechanisms could help the development of antivirals [23]. Only a few large-scale data analyses on virus-virus interactions exist, in contrast to numerous studies on bacterial coinfections and virus-bacteria studies [24–28]. We characterized the coinfection prevalence and the interactions between 17 different viruses and analysed 7,790,879 tests combinations, among ten years. To our knowledge, our study provides the analysis of virus-virus interaction with the largest diversity of respiratory viruses, the longest surveillance period, and the largest number of tests performed.

As expected, the most prevalent coinfection virus pairs and the highest positivity rate (Table S1) had a high mono-infection prevalence and a seasonal overlap. To compare the propensity of a virus pair to coinfect, we introduced a coinfection exclusion score (CES). To exclude bias due to seasonal effects, we calculated an average coinfection exclusion score (ACES).

One of the most relevant studies of virus-virus interaction has been performed by Nickbakhsh et al. [29], who analysed 44,230 respiratory illness cases tested for 11 viruses over nine years and classified the viral pairs interactions. Our data confirms a strong exclusion of any of the influenza A strains (H1N1 or H3N2) to coinfect with rhinovirus. This exclusion has been confirmed also in an animal model [30]. Our data also confirm an exclusion between FLUB and HAdV. Contrary to Nickbakhsh et al. [29], our data suggests strong exclusion for HRSV and HMPV coinfection and no significant interaction between HPIV-2 with HPIV-3. Nickbakhsh et al. [29] did not report any other interaction, while our data shows the strongest exclusion for FLUA(H1N1) and FLUB as well as for FLUA(H3N2) and FLUB.. For the other virus pairs exist partly too small number of tests for significant results in the present study. So further studies are needed to get more insight into the frequency and role of mixed virus infections.

Conclusions

The deeper understanding on virus dynamics will contribute to improve the prevention, diagnostic, and development of therapies for viral infections. We show the advantages of multiplex testing to identify the causative agent and a reliable approach and results for collecting and analyse data on (co-) infections, seasonality, and interactions of viruses. Our results and future studies of its kind could improve the clinical handling.

Abbreviations

RespVir: Respiratory Viruses Network; ACES: average coinfection exclusion score; COVID-19: Coronavirus disease 2019; SARS-CoV-2: severe acute respiratory disease-coronavirus-2; GfV: German Virology Society; FLUA- generic: influenza A generic test; HPIV- generic: human parainfluenza virus-generic test; HCoV: human coronavirus; HCoV-OC43: human coronavirus OC43; HCoV-NL63: human coronavirus NL63; HCoV-229E: human coronavirus 229E; HCoV-HKU1: human coronavirus HKU1; RV/EV: rhinovirus/enterovirus; KLD: Kullback-Leibler divergence; CES: coinfection exclusion score; FLUA: influenza A; FLUB: influenza B; HRSV: human respiratory syncytial virus; HMPV: human metapneumovirus; HBoV: human bocavirus; HPIV-1: human parainfluenza virus 1; HPIV-2: human parainfluenza virus 2; HPIV-4: human parainfluenza virus 4; HAdV: human adenovirus; EV: enterovirus; HPIV-3: human parainfluenza virus 3; RV: rhinovirus.

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Availability of data and materials

Data and source code are available upon reasonable request from Rolf Kaiser and Gibran Horemheb-Rubio (data) and Ralf Eggeling (source code).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GHR*: concept of the current analysis, analysis of the data, and, writing the manuscript, RE*: bioinformatics analysis, Writing of supplementary appendix, NP: bioinformatics analysis, NS: database management, TL: interpretation of the data, and preparation of the manuscript, BG: co-coordination of the RespVir network and data collection, CP: co-coordination of the RespVir network and data collection, MK: patient recruitment and clinical validation of the RespVir network, CS: patient recruitment and clinical validation of the RespVir network, OA**: concept and coordination of the network, database structure, analyses of the virologic results; contributed RK**: concept and coordination of the network, database structure, analyses of the virologic results and concept of the current analysis.

All authors contributed to the writing of the manuscript and accepted the final version

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Table

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures



Figure 1

Distribution of RespVir Network. The figure shows a European map with the location of the 47 laboratory members of RespVir Network. These laboratories are located in the following countries: Germany, Austria, Switzerland, Netherlands, and Spain.

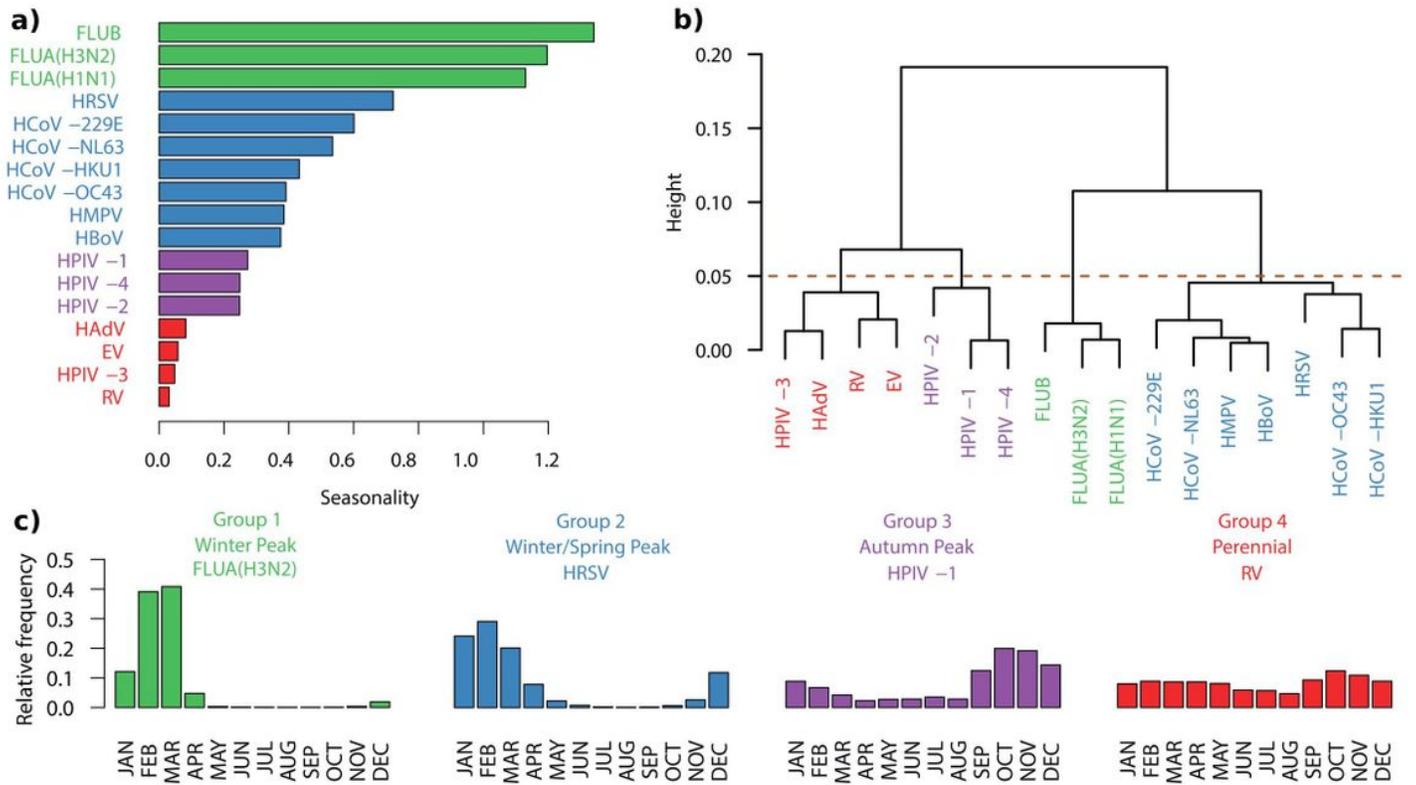


Figure 2

Seasonality Profile of the Respiratory Viruses. The figure shows the seasonality profile of the 17 respiratory viruses studied. a) Degree of seasonality of each virus calculated by Kullback-Leibler divergence, where zero indicates no seasonality. b) Average linkage clustering of the 17 viruses according to their seasonality profile. c) The seasonal four groups according to the similarities of the 17 viruses, the figure shows the seasonal profile of one virus per group and the group name.

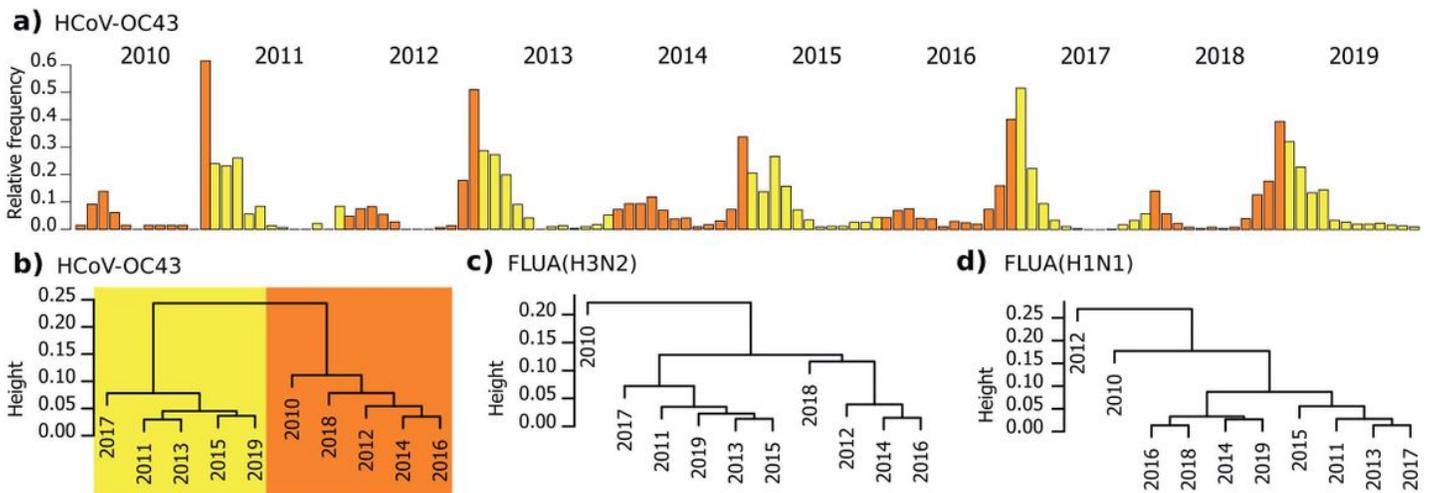


Figure 3

Annual variation of seasonality. The figure shows the annual variation of seasonality and the biennial pattern discovered. a) Biennial pattern of HCoV-OC43 exhibiting high infection numbers at the end of even and beginning of odd years, but low infection numbers at the end of odd and beginning of even years. b) Hierarchical clustering with average linkage of the annual variation of seasonality of HCoV-OC43. c) Hierarchical clustering with average linkage of the annual variation of seasonality of FLUA(H3N2). d) Hierarchical clustering with average linkage of the annual variation of seasonality of FLUA(H1N1).

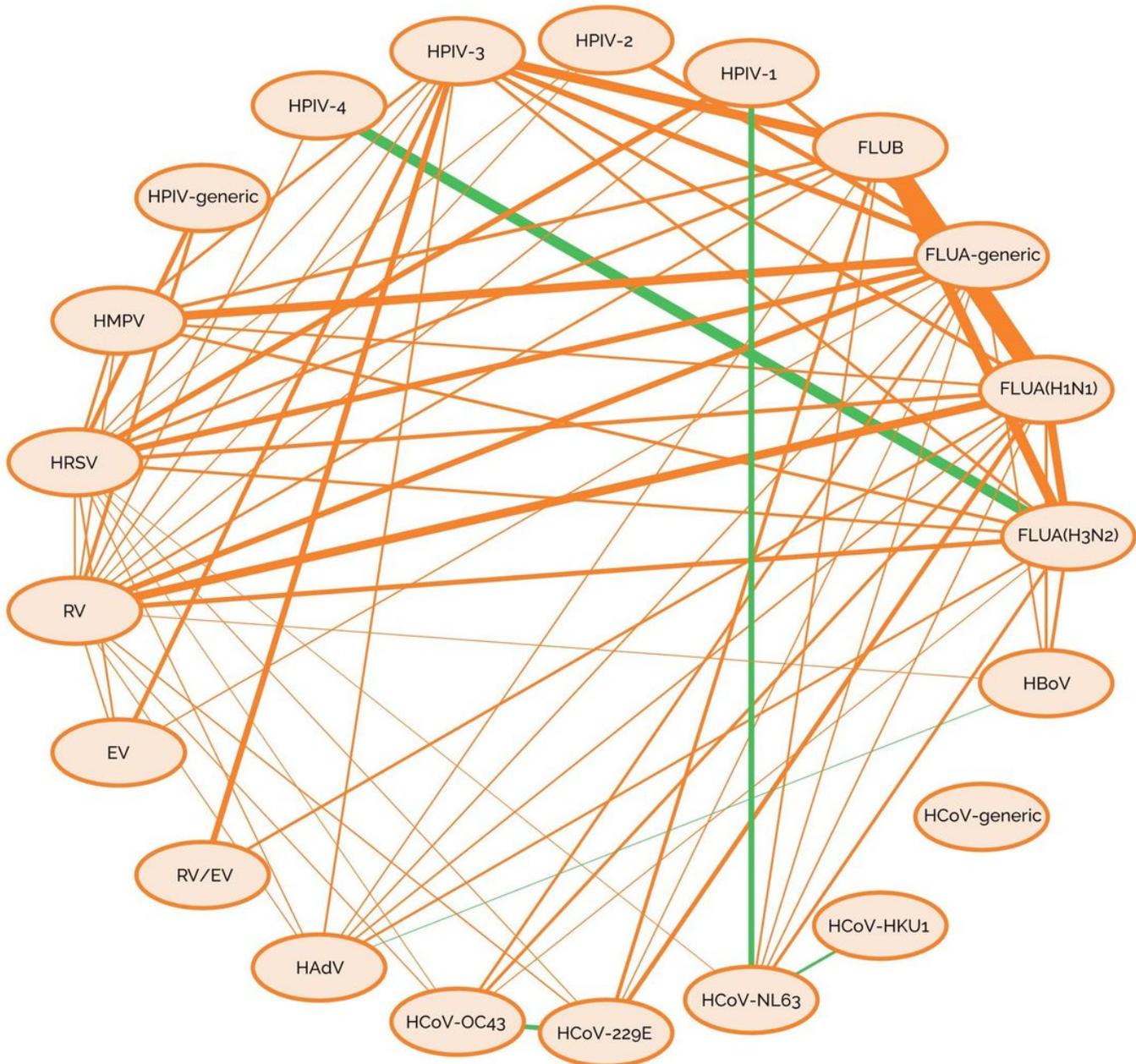


Figure 4

Interaction strength between the 17 virus pairs regarding coinfection. The figure shows the 17 studied viruses linked by lines. Orange lines indicate an exclusion interaction while green lines an affinity interaction. The thickness of the lines indicates the strength of the interaction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.pdf](#)
- [AdditionalFile1.pdf](#)