OpenSAFELY Protocol: Comparison of disparities in RSV, Influenza, and COVID-19

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Version	*Notes*
0.1	*Initial draft*
1	*Protocol finalised to align with code being run against data*
1.5	*Edit to add detail to secondary analysis*
2	*Edit to add detail to outcome phenotypes table*
3	*Edit to add detail to sensitivity analysis regarding season definitions*
4	*Edit to add detail regarding participants who join age cohorts mid season*
5	*Edit to add detail regarding figures and tables to be created*
6	*Edit to tweak infants subgroup analysis plan (move maternal vaccinations to main models as opposed to additional models)*
7	*Edit to remove mortality related analyses as cause-specific mortality unavailable before 2019. Also add clarification regarding all-season analysis*
8	*Edit to add information on ethnicity recording for infants*
9	*Edit to make sensitive phenotypes, for severe outcomes, more stringent*
10	*Edit to reduce registration period requirement to 3 months*
11	*Edit to update links for codelists in line with newest versions*
12	*Edit to update links for covariate codelists in line with newest versions*

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Background

- Low socio-economic status and minority ethnicity were both identified as risk factors for Influenza, when data from the A/H1N1 epidemic was examined it shows that overall "incidence per 100k in the most deprived 20% was 2.83 times higher than the most affluent 20%" (1). These disparities were also likely to vary amongst children, with overall Influenza admissions being highest amongst healthy children under five (2).
- Similar disparities were identified during the COVID-19 pandemic (3) and were explored using OpenSAFELY (4). It is uncertain whether these disparities exist amongst children as they make up a small number of COVID-19 outcomes.
- Finally, it is thought that disparities within RSV infections exist amongst children in the UK, with studies showing the existence of disparities in both Scotland (5) and the US (6,7)
- This raises the question about how these disparities compare to one another, do characteristics influence these respiratory conditions in the same way

Objectives

1. Describe ethnic and socioeconomic health disparities in RSV, Influenza, and COVID-19
2. Compare disparities between the three respiratory conditions
3. Determine whether certain comorbidities mediate these associations

Methods

Data Source

Primary care records managed by the GP software provider, TPP were linked to ONS death data through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (https://opensafely.org). OpenSAFELY provides a secure software interface allowing the analysis of pseudonymized primary care patient records from England in near real-time within the EHR vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymized patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimises any risk of re-identification. Similarly pseudonymized datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data. The dataset analysed within OpenSAFELY is based on 24 million people currently registered with GP surgeries using TPP SystmOne software. It includes pseudonymized data such as coded diagnoses, medications and physiological parameters. No free text data is included. Further details on our information governance can be found here.

Outputs are accessed by researchers as aggregated data with suppression of small numbers and rounding of counts in compliance with re-identification minimisation requirements for OpenSAFELY.

Information Governance

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment, which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant (8,9); patient data have been pseudonymized for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymized datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is through a virtual private network (VPN) connection; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; and only aggregate statistical outputs leave the platform environment following best practice for anonymization of results such as statistical disclosure control for low cell counts (10). The OpenSAFELY research platform adheres to the data protection principles of the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure (11). Together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Study Design and Population

Study Period

The first date of entry to the study cohort will be 1 September 2016, with the last potential date of inclusion in the study being 1 September 2022. 'Recruitment' will be performed at the beginning of each season (1 September yearly), participants will be included in multiple seasons as long as they meet the inclusion criteria for each season. Individuals will be followed up until the date of death, practice deregistration, or end of the study period (31 August 2023 or 31 August 2024 if data available). The study start date coincides with the first year of availability of HES records in OpenSAFELY and the beginning of that year's respiratory virus season. The study end date has been chosen due to this being the last date of a full season available.

Inclusion Criteria

Four cohorts will be defined in the OpenSAFELY data: infants (up to 2 years old), children and adolescents (aged 2 to 17), adults (ages 18 to 64), and older adults (aged 65 years or over). An individual in the relevant age group will be included in the relevant cohort on the first date they meet the following criteria: registered with a primary care practice in England for whom electronic health records were available through the OpenSAFELY platform, with at least 3 months of continuous registration. All infants will be included from birth, a subgroup analysis will then be conducted on infants with linkage to their birth parent. Infants will be included in this subgroup when the linked birth parent has at least 1 year of continuous registration prior to the index date in order to capture information about the pregnancy relating to the infant. The characteristics of the subgroup will be investigated to determine missingness type of linkage. The four age cohorts will be analysed separately but will include the same participants for all three viruses.

Exclusion Criteria

We will exclude people with missing data on age, sex, or index of multiple deprivation, since these are likely to indicate poor data quality. Infants eligible for treatment using Palivizumab will be excluded from the study due to their high risk of complications due to RSV. This will be infants who meet the following criteria (12):

- children under 2 years of age with severe combined immunodeficiency syndrome
- children under 1 year of age who require long-term ventilation
- children 1–2 years of age who require long-term ventilation and have an additional co-morbidity (including cardiac disease or pulmonary hypertension)

Study Measures

Exposures

Socioeconomic status

Defined using quintiles of the English Index of Multiple Deprivation, and based on postcode of residence:

- 1 (least deprived)
- 2
- 3
- 4
- 5 (most deprived)

Ethnicity

Depending on outcome counts this may be separated out further into 16 categories following the census categories:

- White
- Mixed
- Asian
- Black
- Other
- Unknown

In infants, ethnicity recording in primary care is much less frequent. To improve this, ethnicity from primary care will be the most recent recording in the patient record - irrespective of start of follow-up - and records will be supplemented with Secondary Use Services (SUS; in-patient, out-patient, and emergency care attendances) recordings of ethnicity. We will explore the differences between those with and without a SUS recording of ethnicity.

Household size and composition

Defined in terms of numbers of household members and the age groups of household members:

- living alone: *participant* living alone (single occupancy household); this is not possible for infants, children, or adolescents
- multiple of the same generation: *participant* living with others of the same generation (reference category);
- one other generation: *participant* and other(s) of the same generation living with people from just ONE other generation;
- two other generations: *participant* and other(s) of the same generation living with people from TWO other generations;
- three other generations: *participant* and other(s) of the same generation living with people from all THREE other generations.

Outcomes

A report of any of the following in primary care or secondary care, or listed as cause of death:

- RSV
- Influenza
- COVID-19
    - COVID-19 will be included in seasons which begin after September 1st 2019, however, any outcomes identified before March 2020 will be censored to align with when testing became established

- Overall respiratory virus (RSV, Influenza, COVID-19, unspecified respiratory virus)

I will use multiple measures for these outcomes, which indicate different levels of severity as a result of each infection type. The measures will be split into mild and severe as indicated by diagnosis received in primary or secondary care. For severe outcomes, diagnosis codes in secondary care will be included if in either the first or second position on the patient record. If a participant initially falls into the mild category, but within the same episode transitions into the severe category, they will be included in the mild category until that transition.

Due to testing data being sparse for RSV we will use a diagnosis of Bronchiolitis as a proxy. Bronchiolitis is considered a good proxy for RSV in infants (13) and is defined as a condition affecting those under 2 years of age (14), hence does not indicate other viruses in adults and therefore can be included in the RSV phenotype (see 'Outcome Phenotypes' below). To capture the burden which would be placed on primary care during out of office hours I will look at emergency attendances for bronchiolitis.

Defining Infection 'Episodes'

To ensure that outcomes from the same episode are accurately captured, we needed to define episode lengths. This way when codes occur within a certain period they can be assigned to a single infection. This will be defined as 14 days as shown in literature to be the shortest time period recorded where re-infection has not occurred prior to for all viruses (15–18).

Outcome Phenotypes

RSV	*Mild (Primary Care, Emergency Attendances)*	*Severe (Secondary Care)*
Primary	• At least one RSV diagnosis code, or bronchiolitis diagnosis code, in SNOMED CT (codelist), OR, • In infant population, bronchiolitis diagnosis code (4120002), in SNOMED CT, in first or second position in ECDS (A&E)	At least one ICD-10 diagnosis code for RSV or bronchiolitis in the first or second position in the HES APC (codelist)
Sensitivity	*Inclusion Criteria* • Meets criteria for 'Primary' phenotype, OR, • At least two of the following respiratory symptoms recorded in SNOMED CT within a two-week period (two on the same day is acceptable): rhinitis, cough, fever, breathing abnormalities, viral infections, sepsis, and septicaemia OR, • (codelist for above) • In infant population, at least one bronchiolitis (4120002) or viral wheeze (276191000000107) diagnosis code, in SNOMED CT, in first or second position in ECDS (A&E), OR, • At least one prescription for antibiotics (amoxicillin, doxycycline, trimethoprim, clarithromycin, phenoxymethylpenicillin, azithromycin, erythromycin, cefalexin, ciprofloxacin, amoxicillin / clavulanic acid (co-amoxiclav), levofloxacin, co-trimoxazole, ceftriaxone or moxifloxacin) or antivirals (oseltamivir or zanamivir) in Pseudo BNF relevant for the treatment of infectious respiratory diseases (codelist), with the presence of at least one diagnosis code from maximally sensitive codelist *Exclusion Criteria*	*Inclusion Criteria* • Meets criteria for 'Primary' phenotype, OR, • ~~At least one ICD-10 diagnosis code for RSV or bronchiolitis in the first or second position in the HES APC (codelist), OR,~~ • ICD-10 diagnosis code for unspecified acute lower respiratory infection (J22) in the first or second position in the HES APC *Exclusion Criteria* ICD-10 diagnosis code in the first or second position in HES APC for influenza, pneumonia, human metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia, bronchitis, sinusitis, tonsillitis, laryngitis, pertussis, or coronavirus, including COVID-19, within the one-month period (±) of respiratory symptoms (codelist)

	Diagnosis code in SNOMED CT for Influenza, pneumonia, human metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia, bronchitis, sinusitis, tonsillitis, laryngitis, pertussis, or coronavirus, including COVID-19, within the one-month period (±) of respiratory symptoms or receipt of a relevant prescription as noted in the inclusion criteria above (codelist)	
Influenza	*Mild (Primary Care)*	*Severe (Secondary Care)*
Primary	At least one SNOMED CT code for Influenza (codelist)	At least one ICD-10 diagnosis code for influenza in the first or second position in the HES APC (codelist)
Sensitivity	*Inclusion Criteria* ● Meets criteria for 'Primary' phenotype, OR, ● At least one SNOMED CT code for influenza, suspected influenza, influenza-like-illness, test run for influenza (codelist), OR, ● Record of an acute respiratory illness (codelist) with a measured temperature of ≥ 38 °C (codelist) within the same episode (adapted from definition of influenza-like-illness according to WHO (19)) ● At least one prescription for antivirals (oseltamivir or zanamivir) in Pseudo BNF relevant for the treatment of infectious respiratory diseases (codelist) *Exclusion criteria* Diagnosis code in SNOMED CT for RSV, pneumonia, human metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia, tonsillitis, pertussis, or coronavirus, including COVID-19, within the one-month period (±) of respiratory symptoms or receipt of a relevant prescription as noted in the inclusion criteria above (codelist)	*Inclusion Criteria* ● Meets criteria for 'Primary' phenotype, OR, ● ~~At least one ICD-10 diagnosis code for influenza in the first or second position in the HES APC (codelist), OR,~~ ● At least one ICD-10 diagnosis code for acute respiratory illness (codelist) the first or second position in the HES APC *Exclusion criteria* ICD-10 diagnosis code in the first or second position in HES APC for RSV, pneumonia, human metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia, tonsillitis, pertussis, or coronavirus, including COVID-19, within the one-month period (±) of respiratory symptoms (codelist)
COVID	*Mild (Primary Care)*	*Severe (Secondary Care)*

Primary	At least one SNOMED CT code for COVID-19 (codelist)	At least one ICD-10 diagnosis code for COVID-19 in the first or second position in the HES APC (codelist)
Sensitivity	*Inclusion criteria* • Meets criteria for 'Primary' phenotype, OR, • At least one SNOMED CT code for COVID-19, coronavirus (without specific strain), suspected COVID-19, tests performed and referrals to support, OR, • At least two of the following symptoms of COVID-19 recorded in SNOMED CT within a two-week period (two on the same day is acceptable): fever, cough, change to sense of smell or taste, shortness of breath, fatigue, body aches/muscle aches, headache, sore throat, rhinitis, loss of appetite, diarrhoea, nausea and vomiting , OR, • (codelist for above) • At least one prescription for antivirals (nirmatrelvir plus ritonavir (Paxlovid) and molnupiravir (Lagevrio)) in Pseudo BNF (codelist) *Exclusion criteria* Diagnosis code in SNOMED CT for RSV, Influenza, pneumonia, human metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia, bronchitis, sinusitis, tonsillitis, pertussis, laryngitis, or specific coronavirus strains which are not COVID-19 within the one-month period (±) of respiratory symptoms or receipt of a relevant prescription as noted in the inclusion criteria above (codelist)	*Inclusion criteria* • Meets criteria for 'Primary' phenotype, OR, • ~~At least one ICD-10 diagnosis code for COVID-19 in the first or second position in the HES APC (codelist), OR,~~ • ICD-10 diagnosis code for Coronavirus as the cause of diseases classified to other chapters (B972) in the first or second position in the HES APC, OR, • ICD-10 diagnosis code for Coronavirus infection, unspecified site (B342), in the first or second position in the HES APC *Exclusion Criteria* ICD-10 diagnosis code in the first or second position in HES APC for RSV, influenza, pneumonia, human metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia, bronchitis, sinusitis, tonsillitis, pertussis, laryngitis, or specific coronavirus strains which are not COVID-19 within the one-month period (±) of respiratory symptoms (codelist)
Overall	*Mild (Primary Care, Emergency Attendances)*	*Severe (Secondary Care)*

Sensitive	*Inclusion criteria* • Identified from RSV maximally sensitive inclusion criteria, OR, • Identified from influenza maximally sensitive inclusion criteria, OR, • Identified from COVID-19 maximally sensitive inclusion criteria, OR, • Identified from codelist with non-specific conditions associated with respiratory viruses (codelist), OR, • At least one SNOMED CT code, in first or second position in ECDS (A&E), for LRTI (50417007) or UTRI (54150009), OR, • In older adult population, identified as having an exacerbation for COPD (codelist) or Asthma (codelist), in SNOMED CT, OR, • In older adult population, acute exacerbation of COPD diagnosis code (195951007), in SNOMED CT, in first or second position in ECDS (A&E) *Exclusion criteria* Diagnosis code in SNOMED CT for metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia or pertussis within the one-month period (±) of respiratory symptoms (codelist)	*Inclusion criteria* • Identified from RSV maximally sensitive inclusion criteria, OR, • Identified from influenza maximally sensitive inclusion criteria, OR, • Identified from COVID-19 maximally sensitive inclusion criteria, OR, • Identified from codelist with non-specific conditions associated with respiratory viruses (codelist), in ICD-10, in the first or second position in HES APC, OR, • In older adult population, identified as having an exacerbation for COPD (codelist) or Asthma (codelist), in ICD-10, in the first or second position in HES APC *Exclusion criteria* ICD-10 diagnosis code in the first or second position in HES APC for metapneumovirus, rhinovirus, adenovirus, parainfluenza, enterovirus, mycoplasma pneumonia or pertussis within the one-month period (±) of respiratory symptoms (codelist)

Covariates

For all individuals:

- Age - will be taken at the start of the season in which the participant is included. Participants will be able to *age into* the cohort, their index date will then be the date they are of the right age as opposed to the start of that season. For infants, the age will be updated monthly (see 'Statistical Analysis' section for more details). We will define age bands as follows:
    - Infants (20):
        - 0-2 months (separated further into 0-1m and 1-2m if accurate ages can be attained)
        - 3-5 months
        - 6-11 months
        - 12-23 months
    - Children and adolescents:
        - 2-5 years
        - 6-9 years
        - 10-13 years
        - 14-17 years
    - Adults:
        - 18-39 years
        - 40-64 years
    - Older Adults:
        - 65-74 years
        - 75-89 years
        - 90+ years
- Sex
- Rurality (in five categories of urban to rural density)
    - Urban major conurbation
    - Urban minor conurbation
    - Urban city and town
    - Rural town
    - Rural village

For infants a subgroup analysis will be conducted for those which can be linked to their birth parent, for these infants the following characteristics will be included:

- Gestational age of the infant where available, grouped as follows (21)
    - <35 weeks
    - 35-36 weeks
    - 37-40 weeks
    - ≥41 weeks

If gestational age is not available on infant records, we will aim to use birth weight instead.

The following maternal characteristics will also be included (where available):

- Age
- Smoking (never, former, current, no information)
- Drinking and drug usage (flag for each)
- Vaccination status against pertussis, during pregnancy of corresponding infant, as a proxy for engagement with health services. This is a per-pregnancy vaccination so for multiple children vaccinations should be linked to the correct infant
- Vaccination status against maternal Influenza vaccination, during pregnancy of corresponding infant, this will be both an indicator for health-seeking behaviour as well as a protective factor relevant for neonatal Influenza risk

And for children and adolescents, adults and older adults additional models will include:

- Prior vaccinations (e.g. COVID-19 and Influenza)
    - Influenza:
        - Vaccinated within one year prior to season start date
        - Vaccinated within current season
    - COVID-19:
        - Time since last vaccination (0-6 months, 6-12 months, 12 months plus or unvaccinated)
        - Vaccinated within current season

Covariate Codelists

Covariate	*Codelist*
Smoking	Smoking (clear) codelist, Smoking (unclear) codelist
Drinking and drug usage	Hazardous drinking codelist, Illicit substance abuse, Illicit substance abuse intervention, Illicit substance abuse - declined assessment
Exclusion Criteria	*Codelist*
Severe combined immunodeficiency syndrome	SNOMED-CT code - 31323000, in primary care record
Requiring long-term ventilation	ICD-10 code - Z99.1 for dependence on a ventilator OR ICD-10 code - P28.8 for ventilation, newborn, in secondary care record
Cardiac disease	Cardiac disease codes
Pulmonary hypertension	Pulmonary hypertension codes
Care home resident	Care home residency codes, Temporary care home residency codes, there is also a care home flag in TPP

Statistical Analysis

Exploratory Analysis

A number of exploratory feasibility counts will be conducted to explore:

- The number of participants who are infected by the same virus (RSV, Influenza, COVID-19, respectively) more than once within the same season
    - Theoretically, the number of these occurrences should be low which will mean that it is safe to explore one episode per disease per patient per season
- The differences in individuals with multiple outcomes (mild and severe respectively) within one season
    - E.g. are there differences in the individuals with more than one episode across mild and severe outcomes respectively (mild/severe: RSV, influenza, COVID-19, unspecified respiratory infection) when compared to those with only one episode
- Length of stay amongst different individuals

Primary Analysis

Rates per 1000 person-years (5,22,23) of each outcome (see 'Outcomes' section) will be estimated per season in each cohort overall and within categories of ethnicity, socioeconomic

status and household size/composition. Results will be explored across all seasons to examine how disparities have evolved over the study period. I will then perform a Poisson regression to model the rate of infection over time in different groups. Particularly for the infant cohort, two timescales are of interest: calendar time (to capture seasonality) and infant age. Initial models will use calendar time as the timescale and include infant age as a time-varying covariate, updating monthly. Models will be adjusted for age and sex, as well as the covariates given in the 'Covariates' section. Models including each of the exposures above will be explored.

After investigating risk factors individually, risk factors will be explored in pairs. Finally a full model containing all risk factors will be defined.

There will be seven seasons analysed as follows:

1. September 1st 2016 - August 31st 2017
2. September 1st 2017 - August 31st 2018
3. September 1st 2018 - August 31st 2019
4. September 1st 2019 - August 31st 2020
5. September 1st 2020 - August 31st 2021
6. September 1st 2021 - August 31st 2022
7. September 1st 2022 - August 31st 2023
8. *September 1st 2023 - August 31st 2024 (if available)*

Outcome Phenotypes

For each outcome, phenotypes which are of maximal specificity will be used in an attempt to correctly identify each disease accurately - differentiating between the conditions. These are listed in the 'Outcomes' section for each virus under 'specific'. A second set of phenotypes will be used in a sensitivity analysis to determine how often misclassification occurs when phenotypes are broader, listed in the 'Outcomes' section for each virus under 'sensitive' - see 'Sensitivity Analyses' sections for further detail.

Secondary Analysis

To determine whether there is mediation of risk occurring due to conditions which increase risk of poor outcomes I will conduct a secondary analysis to determine whether some of the disparities identified are mediated by the presence of risk factors.

The secondary analyses will be limited to older adults, this is because they are one of the primary targets for vaccination campaigns and are likely to have the comorbidities of interest. These analyses will be performed on one season of interest per pathogen, looking at a season where the pathogen of interest has had particularly high burden. This will be done using the 'specific' phenotypes outlined in the 'Outcome Phenotypes' table.

From COVID-19 and/or Influenza vaccine eligibility criteria:

- Asthma
- COPD
- Cystic fibrosis
- Other chronic respiratory diseases
- Diabetes
- Addison's disease
- Body Mass Index >40
- Chronic Heart Diseases
- Chronic Kidney Disease
- Chronic Liver Disease
- Chronic Neurological Disease
- Cancer within three years
- Immunosuppression
- Sickle cell disease

Lifestyle factors for adults and older adults:

- Smoking (never, former, current, no information)
    - These data will be missing not at random (MNAR). Current smoking is likely to be well recorded whereas former never is unlikely to be as well recorded.
- Drinking and drug usage

Additional Covariate Codelists

Covariate	*Codelist*
Asthma diagnosis	Asthma diagnosis codes, Asthma medications (inhalers), Asthma medications (oral steroids)
Reactive airway disease	SNOMED CT code - 991000119106
COPD	COPD codelist, COPD medications, COPD resolved codes
Cystic fibrosis	Cystic fibrosis codelist
Other chronic respiratory disease	Pulmonary fibrosis codelist, Chronic respiratory disease codes
Diabetes	Diabetes codes, Diabetes resolution codes
Addison's Disease	Addison's disease and hypoadrenalism codelist
BMI	BMI event, BMI stage
Chronic Heart Diseases	Chronic heart disease codelist, Heart failure, Coronary heart disease codelist

Chronic Kidney Disease	Chronic kidney disease - all stages, Chronic kidney disease - stages 3-5, Chronic kidney disease diagnosis codes (no stage)
Chronic Liver Disease	Chronic liver disease codes
Chronic Neurological Disease	Chronic neurological disease - including significant learning disability
Cancer	Cancer codes (excluding lung and haematological), Haematological cancer codes, Lung cancer codes
Immunosuppression	Immunosuppression diagnosis codelists, Immunosuppression medications codelist, Receiving chemo or radiotherapy
Sickle Cell Disease	Sickle cell disease codelists
Smoking	Smoking (clear) codelist, Smoking (unclear) codelist
Drinking and drug usage	Hazardous drinking codelist, Illicit substance abuse, Illicit substance abuse intervention, Illicit substance abuse - declined assessment

Software and Reproducibility

Data management will be performed using Python, with analysis carried out using Python/R. Code for data management and analysis as well as codelists archived online.

Power Calculations

OpenSAFELY contains records for approximately 45% of England and is broadly representative, hence power calculations are extraneous detail.

Sensitivity Analyses

To determine whether results are due to decisions made during the analysis process (as detailed above) a number of sensitivity analyses will be conducted.

Outcomes

For the primary analysis, a phenotype which is highly specific will be used to detect each disease (RSV in particular due to the lack of testing available). A more sensitive phenotype will be used as a sensitivity analysis, this phenotype will be broader and have more room for error, so there will be specific exclusion criteria to attempt to prevent incorrect identification.

Subsequently I will conduct an analysis on an overall respiratory outcome using a phenotype combining all maximally sensitive phenotypes with a reduced exclusion criteria codelist.

Season Definition

For the season by season analyses, data will be extracted for one year periods between September-September. Sensitivity analyses will be conducted to determine the impact of 'out-of-season' infections, this will be done by extracting data for October-March for each year. primary targets for vaccination campaigns and are likely to have the comorbidities of interest.

These analyses will be performed on one season of interest per pathogen (excluding COVID-19), looking at a season where the pathogen of interest has had particularly high burden. This will be done using the 'specific' phenotypes outlined in the 'Outcome Phenotypes' table.

Example Table Shells

Characteristics (table 1)

Infants

Characteristic	Category	Number of individuals (col %) 2016/17	Number of individuals (col %) 2017/18	Number of individuals (col %) 2018/19	Number of individuals (col %) 2019/20	Number of individuals (col %) 2020/21	Number of individuals (col %) 2021/22	Number of individuals (col %) 2022/23	Number of individuals (col %) 2023/24
Total									
Age	0-2m								
	3-5m								
	6-11m								
	12-23m								
Sex	Female								
	Male								
Ethnicity	White								
	Mixed								
	Asian or Asian British								
	Black or								

	Black British								
	Other Ethnic Groups								
	Unknown								
IMD Quintile	1 (least deprived)								
	2								
	3								
	4								
	5 (most deprived)								
Rurality	Urban major conurbation								
	Urban minor conurbation								
	Urban city and town								
	Rural town								
	Rural village								

	Unknown								
Subgroup for Which Maternal Linkage is Available									
Total									
Age	0-2m								
	3-5m								
	6-11m								
	12-23m								
Sex	Female								
	Male								
Ethnicity	White								
	Mixed								
	Asian or Asian British								
	Black or Black British								
	Other Ethnic Groups								
	Unknown								
IMD Quintile	1 (least deprived)								

	2								
	3								
	4								
	5 (most deprived)								
Rurality	Urban major conurbation								
	Urban minor conurbation								
	Urban city and town								
	Rural town								
	Rural village								
	Unknown								
Gestational Age	<35w								
	35-36w								
	37-40w								
	≥41w								

	Unknown								
Maternal Age									
Maternal Smoking Status	Never								
	Former								
	Current								
	Unknown								
Maternal Drinking	Yes								
	No								
Maternal Drug Usage	Yes								
	No								
Maternal Pertussis Vaccination Status	Vaccinated during pregnancy								
	No								
Maternal Influenza Vaccination Status	Vaccinated during pregnancy								
	No								

Children and Adolescents

Characteristic	Category	Number of individuals (col %) 2016/17	Number of individuals (col %) 2017/18	Number of individuals (col %) 2018/19	Number of individuals (col %) 2019/20	Number of individuals (col %) 2020/21	Number of individuals (col %) 2021/22	Number of individuals (col %) 2022/23	Number of individuals (col %) 2023/24
Total									
Age	2-5y								
	6-9y								
	10-13y								
	14-17y								
Sex	Female								
	Male								
Ethnicity	White								
	Mixed								
	Asian or Asian British								
	Black or Black British								
	Other Ethnic Groups								

	Unknown								
IMD Quintile	1 (least deprived)								
	2								
	3								
	4								
	5 (most deprived)								
Rurality	Urban major conurbation								
	Urban minor conurbation								
	Urban city and town								
	Rural town								
	Rural village								
	Unknown								
Time since last COVID-19 vaccination	0-6m								

	6-12m								
	12m+								
Vaccination against COVID-19 in current season	Yes								
	No								
Vaccinated against flu in previous season	Yes								
	No								
Vaccinated against flu in current season	Yes								
	No								

Adults

Characteristic	Category	Number of individuals (col %) 2016/17	Number of individuals (col %) 2017/18	Number of individuals (col %) 2018/19	Number of individuals (col %) 2019/20	Number of individuals (col %) 2020/21	Number of individuals (col %) 2021/22	Number of individuals (col %) 2022/23	Number of individuals (col %) 2023/24
Total									
Age	18-39y								
	40-64y								
Sex	Female								
	Male								
Ethnicity	White								
	Mixed								
	Asian or Asian British								
	Black or Black British								
	Other Ethnic Groups								
	Unknown								
IMD Quintile	1 (least deprived)								

	2								
	3								
	4								
	5 (most deprived)								
Rurality	Urban major conurbation								
	Urban minor conurbation								
	Urban city and town								
	Rural town								
	Rural village								
	Unknown								
Time since last COVID-19 vaccination	0-6m								
	6-12m								
	12m+								
Vaccination	Yes								

against COVID-19 in current season									
	No								
Vaccinated against flu in previous season	Yes								
	No								
Vaccinated against flu in current season	Yes								
	No								

Older Adults

Characteristic	Category	Number of individuals (col %) 2016/17	Number of individuals (col %) 2017/18	Number of individuals (col %) 2018/19	Number of individuals (col %) 2019/20	Number of individuals (col %) 2020/21	Number of individuals (col %) 2021/22	Number of individuals (col %) 2022/23	Number of individuals (col %) 2023/24
Total									
Age	65-74y								
	75-89y								
	90y+								
Sex	Female								
	Male								
Ethnicity	White								
	Mixed								
	Asian or Asian British								
	Black or Black British								
	Other Ethnic Groups								
	Unknown								

IMD Quintile	1 (least deprived)								
	2								
	3								
	4								
	5 (most deprived)								
Rurality	Urban major conurbation								
	Urban minor conurbation								
	Urban city and town								
	Rural town								
	Rural village								
	Unknown								
Time since last COVID-19 vaccination	0-6m								
	6-12m								

	12m+								
Vaccination against COVID-19 in current season	Yes								
	No								
Vaccinated against flu in previous season	Yes								
	No								
Vaccinated against flu in current season	Yes								
	No								

Older Adults - Additional Characteristics

Characteristic	Category	Number of individuals (col %) 2016/17	Number of individuals (col %) 2017/18	Number of individuals (col %) 2018/19	Number of individuals (col %) 2019/20	Number of individuals (col %) 2020/21	Number of individuals (col %) 2021/22	Number of individuals (col %) 2022/23	Number of individuals (col %) 2023/24
Smoking Status	Never								
	Former								
	Current								
	Unknown								
Drinking	Yes								
	No								
Drug Usage	Yes								
	No								
Asthma	Yes								
	No								
COPD	Yes								
	No								
Cystic Fibrosis	Yes								
	No								
Other Chronic	Yes								

Respiratory Diseases									
	No								
Diabetes	Yes								
	No								
Addison's disease	Yes								
	No								
BMI > 40	Yes								
	No								
Chronic Heart Diseases	Yes								
	No								
Chronic Kidney Disease	Yes								
	No								
Chronic Liver Disease	Yes								
	No								
Chronic Respiratory Disease	Yes								

	No								
Chronic Neurological Disease	Yes								
	No								
Cancer within 3 years	Yes								
	No								
Immunosuppression	Yes								
	No								
Sickle cell disease	Yes								
	No								

Primary Analysis - For Example Season e.g. 2021/22

Infants

Characteristic	Category	Mild RSV Outcomes (Rate per 1000 person-years)	Severe RSV Outcomes (Rate per 1000 person-years)	Mild Influenza Outcomes (Rate per 1000 person-years)	Severe Influenza Outcomes (Rate per 1000 person-years)	Mild COVID-19 Outcomes (Rate per 1000 person-years)	Severe COVID-19 Outcomes (Rate per 1000 person-years)
Total							
Age	0-2m						
	3-5m						
	6-11m						
	12-23m						
Sex	Female						
	Male						
Ethnicity	White						
	Mixed						
	Asian or Asian British						
	Black or Black British						
	Other Ethnic Groups						

	Unknown						
IMD Quintile	1 (least deprived)						
	2						
	3						
	4						
	5 (most deprived)						
Rurality	Urban major conurbation						
	Urban minor conurbation						
	Urban city and town						
	Rural town						
	Rural village						
	Unknown						
Subgroup for Which Maternal Linkage is Available							
Total							
Age	0-2m						
	3-5m						
	6-11m						

	12-23m						
Sex	Female						
	Male						
Ethnicity	White						
	Mixed						
	Asian or Asian British						
	Black or Black British						
	Other Ethnic Groups						
	Unknown						
IMD Quintile	1 (least deprived)						
	2						
	3						
	4						
	5 (most deprived)						
Rurality	Urban major conurbation						
	Urban minor conurbation						

	Urban city and town						
	Rural town						
	Rural village						
	Unknown						
Gestational Age	<35w						
	35-36w						
	37-40w						
	≥41w						
	Unknown						
Maternal Age							
Maternal Smoking Status	Never						
	Former						
	Current						
	Unknown						
Maternal Drinking	Yes						
	No						
Maternal Drug Usage	Yes						

	No						
Maternal Pertussis Vaccination Status	Vaccinated during pregnancy						
	No						
Maternal Influenza Vaccination Status	Vaccinated during pregnancy						
	No						

Children and Adolescents

Characteristic	Category	Mild RSV Outcomes (Rate per 1000 person-years)	Severe RSV Outcomes (Rate per 1000 person-years)	Mild Influenza Outcomes (Rate per 1000 person-years)	Severe Influenza Outcomes (Rate per 1000 person-years)	Mild COVID-19 Outcomes (Rate per 1000 person-years)	Severe COVID-19 Outcomes (Rate per 1000 person-years)
Total							
Age	2-5y						
	6-9y						
	10-13y						
	14-17y						
Sex	Female						
	Male						

Ethnicity	White						
	Mixed						
	Asian or Asian British						
	Black or Black British						
	Other Ethnic Groups						
	Unknown						
IMD Quintile	1 (least deprived)						
	2						
	3						
	4						
	5 (most deprived)						
Rurality	Urban major conurbation						
	Urban minor conurbation						
	Urban city and town						
	Rural town						

	Rural village						
	Unknown						
Time since last COVID-19 vaccination	0-6m						
	6-12m						
	12m+						
Vaccination against COVID-19 in current season	Yes						
	No						
Vaccinated against flu in previous season	Yes						
	No						
Vaccinated against flu in current season	Yes						
	No						

Adults

Characteristic	Category	Mild RSV Outcomes (Rate per 1000 person-years)	Severe RSV Outcomes (Rate per 1000 person-years)	Mild Influenza Outcomes (Rate per 1000 person-years)	Severe Influenza Outcomes (Rate per 1000 person-years)	Mild COVID-19 Outcomes (Rate per 1000 person-years)	Severe COVID-19 Outcomes (Rate per 1000 person-years)
Total							
Age	18-39y						
	40-64y						
Sex	Female						
	Male						
Ethnicity	White						
	Mixed						
	Asian or Asian British						
	Black or Black British						
	Other Ethnic Groups						
	Unknown						
IMD Quintile	1 (least deprived)						
	2						

	3						
	4						
	5 (most deprived)						
Rurality	Urban major conurbation						
	Urban minor conurbation						
	Urban city and town						
	Rural town						
	Rural village						
	Unknown						
Time since last COVID-19 vaccination	0-6m						
	6-12m						
	12m+						
Vaccination against COVID-19 in current season	Yes						
	No						
Vaccinated	Yes						

against flu in previous season							
	No						
Vaccinated against flu in current season	Yes						
	No						

Older Adults

Characteristic	Category	Mild RSV Outcomes (Rate per 1000 person-years)	Severe RSV Outcomes (Rate per 1000 person-years)	Mild Influenza Outcomes (Rate per 1000 person-years)	Severe Influenza Outcomes (Rate per 1000 person-years)	Mild COVID-19 Outcomes (Rate per 1000 person-years)	Severe COVID-19 Outcomes (Rate per 1000 person-years)
Total							
Age	65-74y						
	75-89y						
	90y+						
Sex	Female						
	Male						
Ethnicity	White						
	Mixed						
	Asian or Asian						

	British						
	Black or Black British						
	Other Ethnic Groups						
	Unknown						
IMD Quintile	1 (least deprived)						
	2						
	3						
	4						
	5 (most deprived)						
Rurality	Urban major conurbation						
	Urban minor conurbation						
	Urban city and town						
	Rural town						

	Rural village						
	Unknown						
Time since last COVID-19 vaccination	0-6m						
	6-12m						
	12m+						
Vaccination against COVID-19 in current season	Yes						
	No						
Vaccinated against flu in previous season	Yes						
	No						
Vaccinated against flu in current season	Yes						
	No						

Sensitivity Analysis (out-of-season infections)

- Table to show change in number of episodes identified (2017-18 for RSV and 2018-19 for influenza), broken down by characteristic

For an example season e.g. 2017-18 for an example cohort e.g. infants

Characteristic	Category	Change in RSV Mild	Change in RSV Severe
Age	0-2m		
	3-5m		
	6-11m		
	12-23m		
Sex	Female		
	Male		
Ethnicity	White		
	Mixed		
	Asian or Asian British		
	Black or Black British		
	Other Ethnic Groups		
	Unknown		
IMD Quintile	1 (least deprived)		
	2		
	3		

	4		
	5 (most deprived)		
Rurality	Urban major conurbation		
	Urban minor conurbation		
	Urban city and town		
	Rural town		
	Rural village		
	Unknown		

Exploratory Tables

- Table to show number of multiple episodes of different viruses within a season within one individual broken down by characteristics (specific phenotypes to begin)

For an example season e.g. 2022-23 for an example cohort e.g. infants

Characteristic	Category	RSV + influenza	RSV + COVID-19	Influenza + COVID-19	RSV + influenza + COVID-19
Age	0-2m				
	3-5m				
	6-11m				
	12-23m				
Sex	Female				
	Male				
Ethnicity	White				
	Mixed				
	Asian or Asian British				
	Black or Black British				
	Other Ethnic Groups				
	Unknown				
IMD Quintile	1 (least deprived)				
	2				

	3				
	4				
	5 (most deprived)				
Rurality	Urban major conurbation				
	Urban minor conurbation				
	Urban city and town				
	Rural town				
	Rural village				
	Unknown				

- Table to show multiple infections of same virus within a season within one individual (specific phenotypes to begin)

For an example cohort, e.g. adults

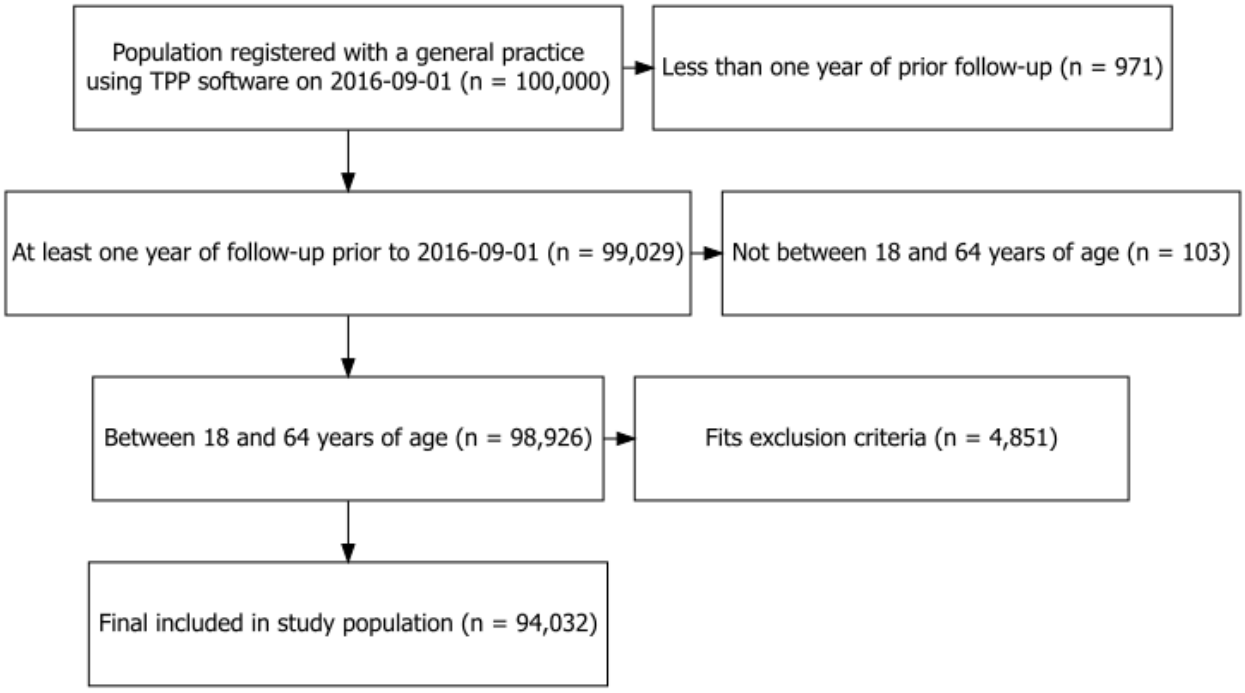
Season	Prop. RSV 2nd	Med. time to 2nd infection	Prop. with 2nd infection under 15-28 days	Prop. COVID-19 2nd	Med. time to 2nd infection	Prop. with 2nd infection under 15-28 days	Prop. influenza 2nd	Med. time to 2nd infection	Prop. with 2nd infection under 15-28 days
2016-17									
2017-18									
2018-19									
2019-20									
2020-21									
2021-22									
2022-23									

- Proportion of those with one episode that go on to have a second

Example Figures

Methods

- Flow diagram of the cohort
  https://www.nature.com/articles/s41586-020-2521-4/figures/1



(Adult cohort: created using dummy data)

Results

Primary Analysis

- Graphs indicating rates in subgroups (e.g. figures 3 and 5)
  - Outcome by IMD
  - Outcome by ethnicity
  - Outcome by household size/composition
  - Outcome by pairs
  - Outcome by all three exposures
- Rate ratios for each patient characteristic
  (https://www.nature.com/articles/s41586-020-2521-4/figures/3)

Secondary Analysis

- Graphs indicating rates in subgroups (e.g. figures 3 and 5)
    - Outcome by IMD
    - Outcome by ethnicity
    - Outcome by household size/composition
    - Outcome by pairs
    - Outcome by all three exposures

Sensitivity Analysis

For one season per pathogen:

- Graphs indicating rates in subgroups (e.g. figures 3 and 5)
    - Outcome by IMD
    - Outcome by ethnicity
    - Outcome by household size/composition
    - Outcome by pairs
    - Outcome by all three exposures
- Rate ratios for each patient characteristic (https://www.nature.com/articles/s41586-020-2521-4/figures/3)

Exploratory Figures

- Figure to show number of multiple viruses within a season within one individual
- Venn diagram showing overlap in outcomes identified dependent on phenotype
- Venn diagram showing how the overall respiratory outcome overlaps with the three viruses
- Stacked bar graph to show increase in cases identified by sensitive phenotype, both respectively for each virus and for identification of multiple viruses within one episode

Strengths and Limitations

Strengths

This is the first analysis of its kind, looking at differences in potential - and already identified - disparities in the three most resource intensive respiratory viruses. In addition to comparing disparities in these three viruses, this analysis will also explore how these disparities are characterised in different age cohorts.

Limitations

Differentiating between these respiratory viruses, especially in primary care, is particularly difficult and relies on the definition of phenotypes (given in the 'Outcome Phenotypes' section). Determining how much the definition of these phenotypes impacts the results I will conduct a sensitivity analyses using less specific phenotypes which contain more overlap for the three viruses.

Another limitation of this analysis is that it relies on testing in secondary care settings, access to which differs depending on the disease in question, the time period, and location. This will influence how many cases are identified for each virus, especially when using the most specific outcome phenotype.

Administrative

Ethics

Local ethical approval application will be submitted once protocol accepted, as according to LSHTM procedure

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

Funding

Project undertaken as part of an NIHR funded doctoral fellowship

Conflict of Interests

None

References

1. Munday JD, Pebody R, Atkins KE, van Hoek AJ. Changing socio-economic and ethnic disparities in influenza/A/H1N1 infection early in the 2009 UK epidemic: a descriptive analysis. BMC Infect Dis. 2021 Dec 11;21(1):1243.
2. Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: A statistical analysis to inform vaccine policy. J Infect. 2014 Apr 1;68(4):363–71.
3. GOV.UK [Internet]. [cited 2023 Oct 10]. Chapter 2: disparities. Available from: https://www.gov.uk/government/publications/technical-report-on-the-covid-19-pandemic-in-the-uk/chapter-2-disparities
4. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430–6.
5. Hardelid P, Verfuerden M, McMenamin J, Smyth RL, Gilbert R. The contribution of child, family and health service factors to respiratory syncytial virus (RSV) hospital admissions in the first 3 years of life: birth cohort study in Scotland, 2009 to 2015. Eurosurveillance. 2019 Jan 3;24(1):1800046.
6. Wang L, Davis PB, Berger NA, Kaelber DC, Volkow ND, Xu R. Disruption in seasonality, patient characteristics and disparities of respiratory syncytial virus infection among young children in the US during and before the COVID-19 pandemic: 2010-2022 [Internet]. medRxiv; 2022 [cited 2022 Dec 30]. p. 2022.11.29.22282887. Available from: https://www.medrxiv.org/content/10.1101/2022.11.29.22282887v1
7. Holmen JE, Kim L, Cikesh B, Kirley PD, Chai SJ, Bennett NM, et al. Relationship between neighborhood census-tract level socioeconomic status and respiratory syncytial virus-associated hospitalizations in U.S. adults, 2015–2017. BMC Infect Dis. 2021 Mar 23;21(1):293.
8. NHS Digital [Internet]. [cited 2023 Oct 16]. NHS digital, data and technology standards. Available from: https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/nhs-digital-data-and-technology-standards
9. NHS Digital [Internet]. [cited 2023 Oct 16]. Data Security and Protection Toolkit assessment guides. Available from: https://digital.nhs.uk/cyber-and-data-security/guidance-and-assurance/data-security-and-protection-toolkit-assessment-guides
10. NHS Digital [Internet]. [cited 2023 Oct 16]. ISB1523: Anonymisation Standard for Publishing Health and Social Care Data. Available from: https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/isb1523-anonymisation-standard-for-publishing-health-and-social-care-data
11. Coronavirus (COVID-19): notification to organisations to share information - GOV.UK [Internet]. 2020 [cited 2023 Oct 16]. Available from: https://web.archive.org/web/20200421171727/https://www.gov.uk/government/publications/coronavirus-covid-19-notification-of-data-controllers-to-share-information
12. Respiratory syncytial virus | Treatment summaries | BNF content published by NICE [Internet]. [cited 2023 Nov 20]. Available from:

https://bnf.nice.org.uk/treatment-summaries/respiratory-syncytial-virus/
13. Rybak A, Cohen R, Kramer R, Béchet S, Delobbe JF, Dagrenat V, et al. Respiratory Syncytial Virus in Outpatient Children with Bronchiolitis: Continuous Virus Circulation During the Nonepidemic Period. Pediatr Infect Dis J. 2023 Dec;42(12):e488–90.
14. nhs.uk [Internet]. 2017 [cited 2024 Feb 5]. Bronchiolitis. Available from: https://www.nhs.uk/conditions/bronchiolitis/
15. Wishaupt JO, van der Ploeg T, de Groot R, Versteegh FGA, Hartwig NG. Single- and multiple viral respiratory infections in children: disease and management cannot be related to a specific pathogen. BMC Infect Dis. 2017 Jan 11;17(1):62.
16. Price O, Birrell FA, Mifsud EJ, Sullivan SG. Epidemiology of repeat influenza infection in Queensland, Australia, 2005–2017. Epidemiol Infect. 2022 Jan;150:e144.
17. Molecular Analysis of Respiratory Syncytial Virus Reinfections in Infants from Coastal Kenya | The Journal of Infectious Diseases | Oxford Academic [Internet]. [cited 2024 Jan 4]. Available from: https://academic.oup.com/jid/article/193/1/59/870060
18. Tang CY, Wang Y, McElroy JA, Li T, Hammer R, Ritter D, et al. Reinfection with two genetically distinct SARS-CoV-2 viruses within 19 days. J Med Virol. 2021;93(10):5700–3.
19. Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. Bull World Health Organ. 2018 Feb 1;96(2):122–8.
20. Noble M, Khan RA, Walker B, Bennett E, Gent N. Respiratory syncytial virus-associated hospitalisation in children aged ≤5 years: a scoping review of literature from 2009 to 2021. ERJ Open Res. 2022 May 30;8(2):00593–2021.
21. Zylbersztejn A, Pembrey L, Goldstein H, Berbers G, Schepp R, Klis F van der, et al. Respiratory syncytial virus in young children: community cohort study integrating serological surveys, questionnaire and electronic health records, Born in Bradford cohort, England, 2008 to 2013. Eurosurveillance. 2021 Feb 11;26(6):2000023.
22. Wellcome Open Research | Open Access Publishing Platform [Internet]. 2021 [cited 2024 Jan 26]. Ethnic differences in the incidence of clinically diagnosed ... Available from: https://wellcomeopenresearch.org/articles/6-49/v3
23. Nab L, Parker EPK, Andrews CD, Hulme WJ, Fisher L, Morley J, et al. Changes in COVID-19-related mortality across key demographic and clinical subgroups in England from 2020 to 2022: a retrospective cohort study using the OpenSAFELY platform. Lancet Public Health. 2023 May 1;8(5):e364–77.