National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Surveillance of acute respiratory infections in the Netherlands: winter 2024/2025 - Background and methods

RIVM

A. van Leeuwenhoeklaan 9
3721 MA Bilthoven
Postbus 1
3720 BA Bilthoven
www.rivm.nl

T 088 689 89 89

Center: Centre for Epidemiology and surveillance of infectious diseases
Contact:
anne.teirlinck@rivm.nl
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1. Respiratory season, respiratory year and calendar year

The aim of this annual report is to describe the surveillance of respiratory infections and their causative agents in the Netherlands. Since respiratory illnesses mainly occur in winter, the results are usually presented for the respiratory season or the respiratory year. A respiratory season is defined as the period from week 40 through week 20 of the next calendar year and the respiratory year is defined as the period from week 40 through week 39 of the next calendar year. In this report, data on the respiratory year 2024/2025 is limited to the respiratory season to allow a timely reporting.

2. Background on COVID-19, influenza and RSV surveillance

COVID-19

COVID-19 is caused by SARS-CoV-2 virus infection. The disease often presents with respiratory symptoms, shortness of breath, and/or fever. SARS-CoV-2 was declared as a public health emergency of international concern (PHEIC) by the WHO from the 30th of January 2020 until the 5th of May 2023. After SARS-CoV-2 Wildtype, several Variants of Concern (VoC) were declared by the WHO (Alpha, Delta, and Omicron). Since January 2022, different subvariants were established for the Omicron SARS-CoV-2 variant. The COVID-19 surveillance overview in this report includes results from community-based surveillance (Infectieradar), wastewater-surveillance, general practitioner (GP) sentinel surveillance, virological laboratory surveillance, and hospital surveillance (through LCPS). For more information about COVID-19 vaccination effectiveness and coverage, see the annual report of the national immunisation programme in the Netherlands.

Influenza

Influenza is an acute respiratory disease caused by infection with an influenza virus. Most patients recover quickly, although an influenza virus infection can cause severe illness, especially in the elderly and in patients with an underlying medical condition. Human seasonal influenza viruses cause yearly epidemics, usually in winter of the Northern and Southern hemisphere.
Most influenza virus infections in humans are caused by the influenza virus types A and B. Influenza virus type C infection causes hardly any or very mild symptoms and is usually not tested for. Influenza type A viruses are divided into subtypes, based on proteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). Different combinations of HA and NA proteins result in various subtypes, for example H1N1pdm09 and H3N2, which are the subtypes currently causing seasonal epidemics. Influenza type B viruses are divided into genetic lineages based on their gene coding for the HA. While two influenza B virus lineages (B/Yamagata/16/88 and B/Victoria/2/87) have co-circulated, B/Yamagata-lineage circulation has not been confirmed since March 2020 (1). Both type A and B influenza viruses
are constantly mutating, which might result in small antigenic changes that may result in escape from existing natural or vaccine induced immunity,

a process known as antigenic drift. Influenza surveillance in the Netherlands includes GP and nursing home sentinel surveillance, virological laboratory surveillance, and participatory community-based surveillance. See paragraph 3 for a detailed explanation of the surveillance sources. The influenza-like illness (ILI) surveillance performed by sentinel general practitioners (GPs) of Nivel Primary Care Database (Nivel-PCD) combines the reporting of clinical diagnoses of ILI and other ARI with virological testing of a subset of ILI and other ARI patients, to give insights into the main causes of ILI and other ARI, and into influenza virus circulation. Virological testing is performed by a combined nose/throat swab. These samples are further analysed at the National Influenza Centre (NIC), see paragraph Surveillance of circulating viruses. This also applies to the participatory community-based surveillance (Infectieradar). The NIC is a collaboration between RIVM, Nivel, and the Erasmus Medical Centre (Erasmus MC). A large number of hospital laboratories in the Netherlands send in influenza virus positive clinical samples to the NIC. For the majority of these samples, as well as for the influenza virus positive samples in the GP sentinel and Infectieradar surveillance, the type, subtype or lineage, and genetic characteristics are determined in order to assess the match between the circulating viruses and those included in the influenza vaccine and the presence of antiviral reduced susceptibility markers. In addition, for a subset of influenza viruses the antigenic properties are characterized, and the phenotypic antiviral susceptibility profile is determined.

RSV

Respiratory Syncytial Virus (RSV) infection causes respiratory disease and is commonly contracted by children and frail elderly in temperate countries, mostly in the winter season. During their first two years of life, most children are infected with this virus (2). Re-infections later in life are very common. Especially in risk groups, such as new-borns and preterm infants, infection can lead to severe illness, hospitalisation and even death. RSV is also a common cause for respiratory infections in the elderly (3) and causes outbreaks in elderly care facilities (4).

RSV is subdivided into RSV-A and RSV-B, based on the different antigenic properties of their attachment glycoprotein G. These two serotypes may circulate simultaneously in the population, and either type can be dominating during the season (5). Reports are conflicting in their conclusions on the correlation of RSV infection severity with RSV serotype and specific genotypes (6).

The RSV surveillance in this report includes GP (sentinel) surveillance, virological laboratory surveillance, and community-based surveillance. Primary care surveillance of RSV is based on virological testing of a sample of patients consulting with an acute respiratory infection (ARI), as well as consultation rates for acute bronchitis/bronchiolitis (ICPC-code R78).

In September 2025, RSV immunization with the monoclonal antibody nirsevimab will be introduced in the national immunization program in the Netherlands. Children born from October 2025 up to March 2026 will be offered immunization within 14 days after birth. Children born from April up to September 2025 will be offered immunization in September and October 2025. Several studies and surveillance structures are being set up to monitor the effect and impact of this program.

For adults aged 60 years and older three vaccines (Arexvy, Abrysvo and mResvia) are registered by the EMA. In March 2025, the Dutch Health Council advised positively on offering RSV vaccination to persons aged 75 years and older and for persons aged 60-75 years who have a medical risk condition or live in a long-term care facility. However, they suggest to wait with implementation until more information on the duration of protection becomes available. Also, the current cost-effectiveness is unfavourable for a general vaccination program.

3. Data sources

Wastewater Surveillance
Individuals infected with the SARS-CoV-2 virus can shed the virus into the wastewater though faeces. Therefore, measuring the amount of coronavirus particles in wastewater provides an indication of the amount of circulation of the virus among the population. Since 2020, the national wastewater surveillance department (NRS) has worked together with the 21 Dutch water authorities to collect (multiple) weekly samples from all 313 public sewage treatment plants (STP's) in the Netherlands. These samples are analysed for presence and number of SARS-CoV-2 particles by the NRS. Since the beginning of 2024, one to two samples per STP per week are analysed. The results are corrected for flow and the number of inhabitants per STP care area and are published as the number of virus particles per 100.000 inhabitants per STP.

Infectieradar
The community-based surveillance system Infectieradar has been operational since March 2020. This platform provides information on self-reported respiratory symptoms in the general population. Participants complete an online application form, which contains various medical, geographical, and behavioural questions. Subsequently, participants are reminded weekly to report any symptoms they have experienced in the past week, and report other relevant information linked to these symptoms. On top participants receive a three-monthly questionnaire about long-term health and contact patterns. The symptom questionnaire is aligned with InfluenzaNet, an existing European partnership between different universities and governments. By asking similar questions it is possible to compare trends between countries and monitor symptoms of ARIs in humans in Europe. However, each of the individual studies linked to InfluenzaNet, including Infectieradar, also have their own objectives. Besides collecting information on trends and symptoms related linked to acute infections, Infectieradar was expanded in 2022 with a SARS-CoV-2 self-test study and self-sampling (swabs are send in for further testing at the RIVM). Each week around 200 participants are asked to take a nose and throat sample if they report acute respiratory symptoms. The RIVM investigates whether this sample contains the coronavirus SARS-CoV-2, influenza virus, RSV, adenovirus, rhinovirus, enterovirus, parainfluenza virus types 1-4, human metapneumovirus, adenovirus, and/or human seasonal coronavirus.

Nivel Primary Care Database
Nivel (the Netherlands institute for health services research) uses routinely recorded data from primary health care providers to monitor health and utilisation of health care services in a representative sample of the Dutch population: the Nivel Primary Care Database (Nivel-PCD) (7). Participants include over 400 general practices spread over the country, covering about 1.8 million persons (10% of the Dutch population). GPs use the ICPC coding system (International Classification of Primary Care, version 1 (8)) to record health problems of their patients. Data from the EHR are extracted on a weekly basis.

A number of participating general practices are called Sentinel Practices. They provide information that cannot be collected from routinely recorded data in electronic health records, among others for the respiratory surveillance. The population enlisted with Sentinel Practices has a coverage of about 135,000 persons (i.e. 0.8% of the Dutch population. The Sentinel Practices report on patients consulting with ILI (see Case definitions).

For the virological respiratory surveillance, about 100 of GP sentinel practices, with a coverage of about 500,000 enlisted persons (i.e. 3% of the Dutch population) collect oro-/nasopharyngeal swabs from a subset of patients with a ILI or ARI. These swabs are sent to RIVM for virological laboratory diagnostics, see paragraph Surveillance of circulating viruses.

For the surveillance of respiratory infectious diseases, the following data of Nivel-PCD is used: (see also: Case definitions)

- Weekly numbers of patients consulting for ARI.
- Weekly numbers of patients consulting for pneumonia.
- For RSV surveillance, we collect weekly numbers of patients below 5 years old consulting their GP for acute bronchitis/bronchiolitis.
- The weekly ILI incidence, calculated as the number of patients with a new episode of ILI (i.e. not reported in the previous 4 weeks), divided by the total number of enlisted patients of the participating sentinel general practices (9).
- Virological results on respiratory viruses in samples from ILI/ARI patients.

Sentinel surveillance network for infectious diseases in nursing homes (SNIV)
Nursing home residents are a vulnerable group for influenza virus-related complications but are not captured in the GP surveillance, because they receive health care from elderly care physicians. The nursing homes participating in the SNIV network serve as sentinels for the national surveillance of infectious diseases in nursing homes. In the 2024/2025 respiratory season, 6 locations from 3 different institutions participated. This respiratory season, the number of locations participating in SNIV was low, potentially hindering the ability to provide a reliable estimate of ILI incidence in nursing homes across the Netherlands. Therefore, SNIV is not further discussed in this chapter, and the results of this surveillance system were not included in the annual report of the respiratory season 2024/2025.

Virological laboratory surveillance
Over many years, about 18 medical microbiological laboratories, where members of the Working Group for Clinical Virology (NWKV) of the Dutch Society for Medical Microbiology (NVMM) work, voluntarily report the number of positive test outcomes of several viral pathogens and certain intracellular bacteria (i.e. only growing within a cell) to RIVM on a weekly basis. Results are reported by week of laboratory detection. Laboratory testing is available originating from both primary care and hospital care. However, due to aggregation of the data, no distinction can be made between the origin of samples. Positive test outcomes can be derived using a broad range of diagnostic methods, such as micro bacterial culturing, molecular diagnostics (PCR methods), serology, or rapid tests. Although no background information concerning patient status, clinical data, and type of diagnostic method is available, the weekly laboratory surveillance is useful as an additional source. It can be used to follow trends of respiratory infections over a prolonged period, because of their relative robust reporting history (over 30 years). During the COVID-19 pandemic, all laboratories in the Netherlands performing diagnostics for SARS-CoV-2 were requested to report the number of performed SARS-CoV-2 tests and the number of positive SARS-CoV-2 tests, initially on a daily basis and later weekly. Since the start of respiratory season 2023/2024, the reporting of SARS-CoV-2 has been integrated into the general virological laboratory surveillance. This allows labs to report the pathogens in one form. About 25 labs report weekly, of which 7 exclusively report SARS-CoV-2 numbers. Furthermore, laboratories are requested to additionally report the number of weekly performed tests for the reported pathogens. The number of tests performed are used to calculate a weekly percentage of positive

samples for the reported pathogens. This is a useful addition to the absolute number of detections in the real-time surveillance, as the absolute numbers are subjective to reporting delays of the labs. Furthermore, the percentage positive is less affected by changes in the number or adherence area of the reporting labs and changes in testing policy over time. Structural changes in testing (e.g. a more strict testing policy) could however still influence the percentage of positivity of the different pathogens. The aggregated data of all reporting laboratories of the previous 27 weeks can be accessed at the website of the Virological respiratory surveillance.

SARS-CoV-2 hospital surveillance
The *Landelijk Coördinatiecentrum Patienten Spreiding* (LCPS) monitors hospital admissions of patients with SARS-CoV-2 infections. Up to 1 June 2024 LCPS reported national admission data from all hospitals on their website. Since 1 June 2024 data collection continued from around 50 hospitals that provide automated data. LCPS shared daily admission data (7-day moving average) with RIVM which is included in this report. Data from LCPS do not include patient characteristics and cannot be used for e.g. monitoring background characteristics of admitted patients or the effectiveness of vaccination.
During the COVID-19 pandemic, the National Intensive Care Evaluation (NICE) foundation facilitated the clinical registration of patients with a positive SARS-CoV-2 test admitted to hospital (including ICU admissions). The NICE COVID-19 clinical registration stopped as of 1 April 2024.

National Intensive Care Evaluation (NICE)
The Dutch National Intensive Care Evaluation (NICE) is a foundation that manages the continuous registration of all available data from adult intensive care units (ICUs). The primary goal is to monitor and optimize the quality of ICU care. The NICE registry is a well-established system for quality monitoring of ICU care in the Netherlands and has been collecting a wide range of patient data since 1996. All Dutch adult ICUs extract admission diagnoses, including SARI, from their patient data management systems (PDMS) or electronic health records (EHR) and securely upload this data to a portal. Since 2016, all Dutch ICUs have participated in this quality registry, with data from approximately 75,000 new ICU admissions being added annually.
Through the NICE registry, data is collected for surveillance of severe acute respiratory infections (SARI-surveillance), effective since January 2025. This includes admission diagnosis codes, aggregated on the week of admission. In this report data from 15 out of 70 ICUs were available.

Death notification data, Statistics Netherlands (CBS)
The Dutch weekly mortality monitoring system monitors the number of deaths reported nationwide (population size of 18.0 million in January 2025) from all causes, as information on cause of death is not available in real-time. In the Netherlands, deaths are notified to municipalities and then reported to CBS, which collects and monitors all vital statistics for the Netherlands. Weekly, RIVM receives and analyses data that includes date of death, report-delay, age-group, and region. The report-delay is the number of days between the date of death and the date that the death notification was received by CBS. Of all death reports in the past 5 years (July 2020-June 2025) on average 39% is received by CBS within 1 week after the date of death, 97% within 2 weeks after date of death and 99% within 3 weeks of date of death. The death notification data is checked for the presence of any excess all-cause mortality (i.e. mortality levels above a pre-defined threshold). Excess mortality gives an indication of the impact of any expected and unexpected events that potentially affect population

health. Examples of such events are heat waves, cold snaps, the COVID-19 pandemic, or seasonal influenza epidemics for which the morbidity and mortality burden varies due to variations in the circulation of influenza virus (sub)types.

4. Case definitions

Influenza-like illness (ILI)
Acute respiratory infections (ARI) and the subgroup of influenza-like illness (ILI) are clinical syndromes caused by a range of viruses and bacteria. However, the case definition for ILI is more specific for influenza virus infection. Two data sources estimate an ILI incidence, for different target groups: 1) Infectieradar, 2) Nivel-PCD - sentinel GP practices. These two data sources use different ILI case definitions.

The case definition of ILI used by Infectieradar is in accordance with the ECDC case definition for ILI and is as follows:

- Sudden onset of symptoms

And at least one of the following four systemic symptoms:

- Fever or feverishness
- Malaise
- Headache
- Myalgia

And at least one of the following three respiratory symptoms:

- Cough
- Sore throat
- Shortness of breath

For The Nivel-PCD sentinel GP practices, ILI is defined in accordance with the 'Pel-criteria' (10):

- Sudden onset of symptoms
- Fever (at least 38 °C)
- At least one of the following symptoms:
    - cough
    - rhinorrhoea
    - sore throat
    - frontal headache
    - retrosternal pain
    - myalgia

Acute respiratory infections (ARI)
To assess the ARI incidence in the Infectieradar community-based surveillance, any participant reporting cough, a runny nose, shortness of breath, or a sore throat is considered an ARI case.
To assess ARIs at the GP-level, weekly numbers of GP-patients consulting for an ARI (ICPC code R74), including acute/chronic sinusitis (ICPC code R75), acute laryngitis/tracheitis (ICPC code R77), acute bronchitis/bronchiolitis (ICPC code R78), or influenza(-like illness) (ICPC code R80) are obtained from the Nivel-PCD. From the 2022/2023 respiratory season onwards, SARS-CoV-2 (ICPC code R83.03) had also been included to the definition of the ARI syndrome. The weekly ARI numbers do not include pneumonia.
Please note that the ILI syndrome is a subset of, and included in, the ARI syndrome.

Severe acute respiratory infections (SARI)
In Dutch hospitals, adult ICUs utilize APACHE-IV admission diagnoses codes. The APACHE-IV system is a scoring method used to assess the severity of illness and the risk of mortality in critically ill patients. A key component of this system is the APACHE-IV diagnostic category, which assigns a code indicating the primary reason for ICU admission according to the APACHE IV model. These diagnoses are determined by the intensivist within 24 hours of admission, but can be adjusted later. In the NICE registry, there are two input fields for APACHE-IV reasons for admission: ap4diag1 and ap4diag2. The ap4diag1 field indicates the primary diagnosis for ICU admission (the most critical), while the ap4diag2 field captures a secondary diagnosis. For the selection of SARI patients, both variables are considered. There are a total of 450 different admission diagnoses in the APACHE-IV system. From these, we have selected those diagnoses with a respiratory infectious cause. The selected codes are:

- Influenza
- Pneumonia, bacterial
- Pneumonia, fungal
- Pneumonia, other
- Pneumonia, parasitic (e.g., Pneumocystis pneumonia)
- Pneumonia, viral
- Respiratory Syncytial Virus (RSV) infection
- SARS-CoV-2 infection
- Sepsis, pulmonary

These codes collectively form the definition of the SARI syndrome. If a patient is assigned a SARI related APACHE IV diagnosis upon ICU admission, it is classified as a SARI case. If a patient has two SARI codes, it is counted as a single SARI admission.

Bronchiolitis
Bronchiolitis mostly affects young children below 2 years of age and symptoms are similar to a common cold (mild fever, cough, and runny nose), but can also worsen to wheezing and shortness of breath. Bronchiolitis is commonly caused by respiratory syncytial virus (RSV) among other viruses, such as human metapneumovirus (hMPV), rhinovirus, and parainfluenzavirus. Acute bronchitis/bronchiolitis is recorded by GPs (Nivel-PCD) with ICPC-code R78. Weekly numbers of patients below 5 years old consulting their GP for acute bronchitis/bronchiolitis are obtained from the Nivel-PCD.

Pneumonia
Pneumonia is an infection of the lower respiratory tract with relatively high morbidity and mortality, especially in the elderly. Typical symptoms include cough, chest pain, fever, and difficulty breathing.
Many studies in the Netherlands and other countries show that S*treptococcus pneumoniae* is the predominant aetiological agent of community-acquired pneumonia (CAP), but CAP can be caused by many other microorganisms, mainly bacteria and viruses (11). CAP is included in the registration by GPs (Nivel-PCD). Pneumonia data are obtained from the Nivel-PCD, similarly to ARI described above, and is defined as the weekly number of patients consulting their GP for pneumonia (ICPC-code R81), regardless of being a new or already existing pneumonia episode. The total practice population of participating GP practices serves as the denominator.

5. Laboratory and data analysis

Acute respiratory infections (ARI)
Weekly ARI consultation rates are calculated as the number of patients consulting their GP in a given week, divided by the total number of enlisted patients. Cumulation of these weekly rates over the season (separately for week 40 through 20, and for week 21 through 39) is reported as the seasonal cumulative number of consultations.

Bronchiolitis
Weekly bronchitis/bronchiolitis consultation rates are calculated as the number of patients below 5 years old consulting their GP in a given week, divided by the total number of enlisted patients below 5 years old.

Pneumonia
Pneumonia data are reported as lower respiratory tract infections (LRTI).

SARS-CoV-2, Influenza virus, RSV, and other respiratory viruses
Surveillance of circulating viruses
At the National Influenza Centre (NIC) location RIVM the respiratory nose and throat swabs originating from the respiratory virus surveillance at GP sentinel practices as well as the self-sampled nose and throat samples from participants in Infectieradar are analysed. Additionally, a selection of Dutch virology laboratories submit a representative set of influenza virus positive specimens (with a requested maximum of 5-6 specimens per week), mainly to NIC-Erasmus MC (while few send to NIC-RIVM). For laboratories that continued to send all influenza virus positive specimens, the selection of 5-6 specimens per week for further characterisation is performed at Erasmus MC. Because of this restriction in samples, the trend in the specimens received by Erasmus MC is not a reflection of the course of the epidemic.

The GP sentinel practices from the Nivel-PCD are requested to take specimens (combined throat swabs and nose swabs) from ILI or other ARI patients. Since the 2021/2022 season, the GPs were instructed to swab at least the first two persons in the week with an ARI, including at least:

- one ILI patient (according to the Pel-criteria)
- one child below the age of 10 with ILI or other ARI throughout the week.

With a maximum of five samples per GP per week.

The GP specimens are analysed by NIC-RIVM. Historically, since the start in 1993 testing for all possible respiratory viruses and since the 2008/2009 season limited to influenza viruses, RSV, rhinoviruses and enteroviruses. With the COVID-19 pandemic, SARS-CoV-2 (since February 2020) was added; parainfluenza virus types 1-4, human metapneumovirus, and human seasonal coronaviruses (since January 2021); and adenovirus (since October 2023) were added again. These viruses are important causes of ARIs and have more or less similar clinical presentations. The dynamics of detections of these viruses in ARI patients allows a broad picture and enables good interpretation of respiratory epidemics. Influenza virus and RSV are genetically typed as influenza virus type A, influenza virus type B, RSV type A, and RSV type B. Influenza virus type A is subsequently subtyped, and for influenza virus type B, the phylogenetic lineage is assessed. The type of enterovirus is also determined.
Infectieradar specimens are analysed at NIC-RIVM using another test than used for the GP surveillance for influenza viruses, RSV, hMPV, rhino/enterovirus, parainfluenzaviruses, seasonal coronaviruses, SARS-COV-2, MERS-CoV, adenovirus, and bocavirus. Detected influenza type A viruses are further subtyped and type B lineage is determined.

Virus isolation

Influenza viruses are isolated from influenza virus PCR positive clinical specimens in cell culture on MDCK-SIAT, MDCK, or hCK mono culture cell lines at Erasmus MC or on mixed MDCK-SIAT and MDCK-I cell lines at RIVM. Successfully grown viruses are used for antigenic characterisation and phenotypic determination of antiviral susceptibility.

Influenza virus antigenic and genetic characterisation

Whereas subtyping and lineage determination at RIVM are performed using RT-PCR assays, in the 2018/2019 season Erasmus MC changed to nanopore next generation sequencing of the HA, NA, and polymerase acidic (PA) genes for simultaneous subtyping/lineage determination and genetic characterisation of influenza viruses. Antigenic characterisation is performed by NIC location Erasmus MC in Rotterdam for a subset of influenza viruses and influenza virus positive clinical specimens submitted by peripheral laboratories, the sentinel GP, and Infectieradar surveillance after successful virus isolation at RIVM. This provides an indication of the degree of antigenic match between the circulating influenza viruses and the vaccine viruses. Because new ferret sera have to be generated at Erasmus MC, this thorough antigenic characterisation takes some time and will be completed after this report has been published.
A subset of influenza viruses are whole genome nanopore sequenced and characterised genetically at RIVM (all 8 segments with a focus on HA, NA, PA, and M2 for seasonal viruses). The genetic characterisation is done on a systematic sample of most prevalent influenza virus types, lineage, and subtypes if the number of detections is high, and on all if the number of detections is moderate and variation is low, and on all sporadically detected types, lineages, and subtypes from the GP sentinel surveillance and Infectieradar surveillance. At Erasmus MC, genetic characterisation is done using nanopore sequencing of all received specimens with high virus load, as described above. Sequences from both locations are combined for detailed phylogenetic and amino acid substitution analysis giving information about the evolution of influenza viruses and changes that might lead to the emergence of potential antigenic variants. In addition, this type of information complements the antigenic analysis, especially when antigenic characterization is cumbersome.

Antiviral susceptibility of influenza viruses

Infection with an influenza virus with a reduced susceptibility for an antiviral agent can lead to a reduced effectiveness of treatment. The antiviral susceptibility of influenza viruses is systematically monitored. From all or a systematic sample (depending on total number positive specimen per week) of influenza virus positive clinical specimens from the GP sentinel and Infectieradar surveillance the whole genome is nanopore sequenced at NIC location RIVM in order to screen for other and new molecular markers for reduced susceptibility for antivirals (i.e. NA inhibitors and baloxavir) and markers for virulence. In case of mutations with previously unknown impact on antiviral susceptibility, the phenotypical NA inhibition test is the final proof for the degree of inhibition. Of all viruses tested at Erasmus MC, the NA and PA gene is nanopore sequenced and analysed for any markers previously associated with reduced NA inhibitor susceptibility or reduced susceptibility to baloxavir. Of the influenza virus isolates obtained from the Nivel sentinel influenza surveillance and Infectieradar surveillance, the phenotypic antiviral susceptibility for NA inhibitors (i.e. oseltamivir and zanamivir) is determined by NIC location RIVM. The phenotypic testing complements the sequencing to be able to find new amino acid changes that result in reduced susceptibility. Of viruses that appear reduced susceptible, the whole genome of the isolate is sequenced to determine the amino acid substitution that explains the reduced susceptible phenotype. This is

compared with the already obtained sequence of the virus in the clinical specimen to exclude that the reduced susceptibility substitution emerged during the virus isolation procedure. Molecular markers for resistance to adamantanes (M2 ion channel blockers: amantadine and rimantadine) are assessed in a subset of influenza virus type A positive clinical specimens by whole genome nanopore sequencing at NIC location RIVM. Data from viruses analysed at location RIVM and data from viruses analysed at location Erasmus MC are combined on a weekly basis to achieve one overall picture of the current situation.

Estimating symptomatic influenza incidence in the general population
We estimated the incidence of symptomatic infection with influenza virus by combining all relevant data sources via Bayesian evidence synthesis (12). This estimation procedure can be viewed as similar to the 'multiplier method' or 'direct method', but with appropriate propagation of the uncertainty inherent in each data source to the final estimate. The relevant data sources are: (i) ILI: number of ILI patients per season and per age-group, with catchment population size (<5, 5-14, 15-44, 45-64, 65+ years) (data from the Nivel-PCD was used); (ii) under ascertainment: age-group specific number of respondents reporting ILI and number of respondents reporting ILI and who contacted their GP (data were extracted from Infectieradar), (iii) influenza positivity rate: number of positive tests and number tested, per age-group (from GP sentinel surveillance, see paragraph Surveillance of circulating viruses); and (iv) sensitivity of virological testing: estimated at 95-100%. Analysis was restricted to the winter season (week 40 through week 20 of the next year). To show variation in symptomatic influenza incidence by virus subtype/lineage across seasons, we also fitted a model in which data were stratified by subtype A(H1N1)pdm09 and A(H3N2), and lineage (B/Victoria, B/Yamagata) rather than age-group. NB. As the number of influenza sources has expanded and the interpretation of the pre-existing sources has altered (e.g. due to changes in healthcare seeking behaviour), we are in the process of evaluating and adjusting the estimation of the influenza incidence. For the season 2024/2025, the previously mentioned methods are still used.

Impact of the influenza vaccination programme
We estimated number of GP visits averted by the influenza vaccination program in the Netherlands among those aged 65 years or older. First, the observed number of cases was estimated for GP visits based on incidence of ILI from sentinel GP surveillance, influenza virus positivity rate, and sensitivity of virological testing (i.e. the same method as described in the paragraph 'Estimating symptomatic influenza incidence in the general population', but without the correction for underascertainment based on data from Infectieradar). Secondly, the number of averted cases was calculated from the estimated number of observed cases, national vaccination coverage and VE. Vaccination coverage of the age group 65 years and older was sourced from pseudo-anonymized data from electronic medical files of general practices participating in the Nivel-PCD (15). These vaccination coverages were estimated with multilevel logistic regression analysis, in which the clustering of patients in GP practices is taken into account. Vaccine effectiveness (VE) was based on subtype specific VEBIS primary care study VEs (16), corrected for the proportion of influenza virus (sub)types circulating in the Netherlands among patient with ILI or ARI of 65 years and older who were sampled in the sentinel GP practices of Nivel. For the 2024/2025 season, we used the used proportions 0.35/ 0.61/ 0.04 for H1N1/H3N2/B (sentinel) in the Netherlands respectively.

The impact measures calculated were:
• Number of GP visits averted. This was calculated as:

$$NAE = N - n = \frac{n}{1-(VC*VE)} - n = n * (\frac{VC*VE}{1-(VC*VE)})$$

where NAE = number of averted events,
N = Expected number of events without the vaccination programme
n = Observed number of events
VC = vaccination coverage
VE = Vaccine effectiveness
• Prevented fraction (PF), which was calculated as:
PF = NAE/N
• Number needed to vaccinate to prevent one event, which was calculated as:
NVN = 1/(VE*N/population size).

95% CIs were derived through Monte Carlo simulation

Moving Epidemic Method (MEM) for RSV and ILI seasonality
Since season 2018/2019, we use the Moving Epidemic Method (MEM) to define the RSV season. The MEM was originally developed to assess influenza seasonality (17), to establish the epidemic thresholds for RSV, using the virological laboratory surveillance data of the previous 12 seasons (18). MEM was applied with the Moving Epidemic Method Web Application (19) and absolute detection numbers per week for all 12 seasons in the fixed criterium model and a manually optimised slope parameter of 1.4 that had been established previously (18). We calculated the mean length, timing and coverage of the epidemic period by calculating pre-and post-epidemic thresholds using the arithmetic mean and its one-sided 95%-point confidence interval (CI). The start of the RSV season is defined as the first week when the number of RSV-diagnoses is above the pre-epidemic threshold, lasting for at least two consecutive weeks. The end of the RSV season is defined as the first week when the number of diagnoses is below the post-epidemic threshold, lasting for at least two consecutive weeks. We also calculated epidemic intensity levels using the geometric mean and its one sided 40% (medium), 90% (high), and 97.5% (very high) point CI. For the MEM calculations, a season was defined from week 30 through week 29 of the next year to be able to include enough data points to calculate a precise pre-epidemic threshold, as RSV circulation might start as early as week 40. The epidemic thresholds for seasons up to and including 2016/2017 were calculated based on data of seasons 2005/2006 up to and including 2016/2017 (18). The thresholds of the seasons 2017/2018, 2018/2019, 2019/2020 and 2020/2021 were calculated separately per season, based on data of the previous ten seasons. The MEM epidemic and intensity thresholds for seasons 2021/2022, 2022/2023, and 2023/2024 were based on prepandemic data and therefore similar to the thresholds that were set for season 2020/2021 (based on data of seasons 2010/2011-2019/2020). Since testing practices are likely changed since the COVID-19 pandemic, the number of RSV diagnoses and subsequent outcomes on onset and duration of the RSV season should be interpreted with caution. Because the data of the pre-epidemic seasons are less useful for setting thresholds for the post-epidemic seasons, fewer pre-epidemic seasons were used for season 2024/2025; the MEM-thresholds were calculated based on five seasons (2016/2017, 2017/2018, 2018/2019, 2022/2023 and 2023/2024), which is supposed to be the minimum number of seasons needed to calculate the MEM thresholds and were as follows: pre-epidemic threshold: 51; post- epidemic threshold: 59; medium intensity: 202, high intensity: 426; very high intensity; 593.

The MEM method is also used for determining the ILI incidence threshold. The threshold for increased ILI activity in the respiratory season 2024/2025 was set at 53 patients per 100.000 inhabitants. For more details, please refer to the Nivel website (20).

Severe Acute respiratory infections (SARI)
SARI ICU admissions per week are calculated in absolute numbers and on average numbers in a five-week moving average (two weeks before and two weeks after the week in question).

Determining excess mortality
Every Wednesday the number of reported deaths in the previous week (Monday-Sunday), as provided by CBS, is evaluated for the presence of significant excess deaths above the expected levels of death (the baseline).
The baselines and prediction limits are calculated using a Serfling type algorithm on historical mortality data from the 5 previous years (a linear regression model with a linear time trend and sine/cosine terms describing seasonal variation). In the historical data, periods with high excess mortality in winter and summer were removed so as not to influence the calculated baseline with time-periods with previous excess mortality (the 25% highest values overall and the 20% highest values in the summer months of July and August). When the observed number of deaths exceeds the upper limit of the prediction interval mortality is considered to be significantly increased. Excess deaths are calculated as the number of deaths above the baseline. Due to reporting delay the 4 most recent weeks are not complete. The total number of deaths in those 4 weeks are estimated (nowcasted) based on the delay pattern in the most recent weeks.

Burden of disease
For influenza, to estimate disease burden in DALY, an incidence- and pathogen-based approach was applied to quantify the burden due to illness, disability, and premature mortality associated with all short and long-term consequences of infection. The underlying outcome trees, disease progression probabilities, and other parameters have been previously described (21). DALY estimates incorporate both years of life lost (YLL) due to premature mortality and years lived with disability (YLD) (22). YLD were calculated by multiplying the number of acute cases, duration of a health state, and the disability weight of the health state. The disability weight is a value between 0 (perfect health) and 1 (death). We used the European disability weights collected by Haagsma et al. (23). To estimate YLL, remaining life expectancy tables were taken from the GBD 2010 study (24). We estimated the burden of influenza for respiratory seasons (week 40 to week 20) for the seasons 2020/2021 through 2024/2025, except for the 2020/2021 season, for which it was not possible to determine the influenza burden due to low case counts following the introduction of COVID-19 measures. No time discounting was applied.

Because we had direct data on the incidence of severe and critical health outcomes and mortality due to COVID-19, we did not need to rely on estimated progression (or transitional) probabilities between health outcomes, as is the case for most of the other infectious diseases for which disease burden is routinely computed and reported in the Netherlands. The notified and reported cases of COVID-19 are directly used as input to estimate the burden of COVID-19. In short, the cumulative number of mild/moderate symptomatic infections is estimated by using the ratio of between symptomatic infections (i.e. COVID-19 positive test results from OSIRIS, adjusted for underreporting based on testing behaviour) and the number of virus particles in the national wastewater surveillance from 2023, and applying it to the 2024 wastewater data, with the age-

weighting of infections based on positive COVID-19 test results from Infectieradar (25) instead of OSIRIS. The number of severe and critical cases, which are defined by the number of non-ICU and ICU hospital admissions, is based on NICE data. The cumulative number of fatal cases in 2023 is published by CBS. The burden estimate of COVID-19 is solely based on the acute phase of the disease; long-term complications such as 'post-COVID-19 syndrome' are not included. For details on the parameter values to estimate the YLD, see the State of Infectious Disease 2019 (26). To estimate YLL, remaining life expectancy tables were adopted from the GBD 2010 study (24), to allow burden to be compared with that for the other respiratory infections.

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