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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used to collect the data
Data analysis	All analyses were performed using R version 3.6.2 with the following packages: reshape2, plyr, dplyr, zoo, EnvStats, survival and survminer

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

We have provided all of the deidentified raw data used in this manuscript and figures, in the Supplementary Data. Materials are available for study via the open and ongoing Amsterdam Cohort Studies (ACS) on HIV among MSM: https://www.ggd.amsterdam.nl/beleid-onderzoek/projecten/amsterdamse-cohort/

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	This study was exploratory in nature as it was previously unknown whether and how frequently reinfections occurred. Consequently, a sample size could not be estimated or a power analysis. To increase the odds of detecting reinfections, we sought to include subjects with extensive (>10 years) follow up data. We assumed there may be slight person-to-person variation in their dynamics of seasonal HCoV reinfections, and by including 10 subjects, we allowed some variation while still being able to analyze a general trend.
Data exclusions	ELISA OD measurements with one of two replicates showing outlier OD-signals: both measurements were removed from further analysis, as an error in performance of the assay could have had an influence. In case an assay was done in triplicate and one of three showed outlier-signals then the OD measurements of only the outlier was removed from further analysis. These data exclusions were pre-established, to prevent any likelihood of over-reporting of infections which may have been influenced errors in ELISA performance.
Replication	All ELISA anlyses were performed in duplicate or triplicate. In the first half of the study samples were tested in triplicate. Due to high reproducibility of the OD-signals, the second half of the study was only done in duplicate. For each replicate new dilutions were made of the same serum sample.
Randomization	Randomization was not relevant to this study, as the aim was not to study differences between subjects or groups of subjects.
Blinding	Blinding was not relevant to this study, as knowing the subject number could not have influenced any data or interpretation of the data generated in the study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	We measured the total polyclonal antibodies in serum that are directed to the nucleocapsid protein of the seasonal coronaviruses and SARS-CoV-2. The conjugate used in the ELISA is polyclonal Alkaline Phosphatase-conjugated AffiniPure Goat Anti-Human IgG, Fc Fragment Specific (supplier: Jackson Immunoresearch), catalogue number: 109-055-170. The ELISAs have been validated (see below).
Validation	- Dijkman, R. et al. The dominance of human coronavirus OC43 and NL63 infections in infants. Journal of Clinical Virology 53, 135–139 (2012). - Severance, E. G. et al. Development of a nucleocapsid-based human coronavirus immunoassay and estimates of individuals exposed to coronavirus in a U.S. metropolitan population. Clinical and Vaccine Immunology 15, 1805–1810 (2008). - Sastre, P. et al. Differentiation between human coronaviruses NL63 and 229E using a novel double-antibody sandwich enzyme-linked immunosorbent assay based on specific monoclonal antibodies. Clinical and Vaccine Immunology 18, 113–118 (2011). - Dijkman, R. et al. Human coronavirus NL63 and 229E seroconversion in children. Journal of Clinical Microbiology 46, 2368–2373 (2008). - Lehmann, C. et al. A line immunoassay utilizing recombinant nucleocapsid proteins for detection of antibodies to human coronaviruses. Diagnostic Microbiology and Infectious Disease 61, 40–48 (2008).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	LLC-MK2 cells from an in house stock, passage number >280.
Authentication	the LLC-MK2 cells could not be authenticated.
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.

Human research participants

Policy information about studies involving human research participants

Population characteristics	- The Amsterdam Cohort Studies on HIV infection and AIDS: A total of 513 serum samples from the Amsterdam Cohort Studies on HIV infection and AIDS (van Bilsen et al AIDS 2020) were examined. The Amsterdam Cohort Studies was initially started to investigate the prevalence, incidence and risk factors of HIV-1 infection. The study population consists of men having sex with men, living mainly around the city of Amsterdam, the Netherlands. HIV-1 seronegative and HIV-1 seropositive men were enrolled, yet the subjects in our study were all from the HIV-1 negative arm of the study. At start of the study, subject age ranged from 27 to 40 years; by the end of follow-up, subjects were 49 to 66 years old. All ten subjects remained negative for hepatitis C virus, four of the ten showed infection by hepatitis B virus (subject #2 < 1984; #8 in 1998; #5 and #10 in 1999), herpes zoster virus infections were found in three subjects (#3 in 2004, #9 and #10 in 1985). Whether the study persons experienced acute infection by Epstein Barr virus was not tested. One of the subjects had had insulin dependent diabetes (subject #2). No blood-disease, cancer, autoimmune disease or neurodegenerative disease was reported during the follow up period for #2, #3, #4, #5, #8, #9 and #10. For subjects #6 and #7 these data were not available. Four subjects reported receiving a blood product in the 6 months prior to a visit (exact date, or indication not known): Subject #1 in 1991; #2 in 1994; #4 in 1987, and #5 in 1987. Serum samples were collected from 1985 till 2019, with a gap in follow up from 1996 till 2003. In the beginning of the study serum samples were collected every three months, and after 1989 every six months. Self-reported symptoms of influenza-like illnesses were documented at each study visit (see supplementary Table S1). - Sensitivity and specificity testing: A total of 59 RT-PCR confirmed coronavirus positive infections and 47 coronavirus-negative infections were investigated. The set included 11 HCoV-NL63, 16 HCoV-229E, 14 HCoV-OC43 and 18 HCoV-HKU1 infections, with Ct values < 30 for HCoV-NL63, HCoV-229E and, HCoV-OC43. Within 24 hours of first presentation (GP) a serum sample and a nasopharyngeal flocked swab (NPS; COPAN) was collected (V1). At days 28–35 after V1, serum sampling was repeated (V2). For HCoV-HKU1 (which was assayed with a separate test (Respifinder)), only POS/NEG information was available and no selection for low CT values could be done.
Recruitment	- The Amsterdam Cohort Studies on HIV infection and AIDS: Recruitment of volunteers in 1984 and 1985 was done by the Municipal Health Service Amsterdam, and established via collaboration with a support group consisting of representatives of the "gay rights movement" the "COC"(LGBT advocating organisation) and the "SAD" (Ancillary Services Department). The ACS recruited men who had sex with other men in the 6 months prior to recruitment and lived in the Amsterdam area or are involved in MSM-related activities taking place in Amsterdam. To reduce age-specific bias attributed to a uniformly aging cohort, recruitment was limited to MSM under 30 years of age during several periods of time. Recruitment entailed 'convenience sampling' (outreach activities at MSM meeting places and online advertisements on gay dating apps) and 'chain referral sampling' (participants recruiting other participants). - Sensitivity and specificity testing: The patients were recruited in 16 primary care networks. Inclusion criteria for patients were: age ≥18 years with an acute or worsened cough (≤28 days duration) as the main symptom, or any clinical presentation considered to be caused by LRTI by the general practitioner and consulting for the first time for this illness episode.
Ethics oversight	- The Amsterdam Cohort Studies on HIV infection and AIDS is approved by the Medical Ethics Committee of the Amsterdam University Medical Center of the University of Amsterdam, the Netherlands (MEC 07/182). Participation is voluntary and without incentive. Written informed consent of each participant was obtained at enrollment. - Sensitivity and specificity testing: Approved by the local ethics committees in all participating centrers and by the competent authority in each country: Cardiff and Southampton (United Kingdom): Southampton & South West Hampshire Research Ethics Committee A; Utrecht (Netherlands) Medisch Ethische Toetsingscommissie Universitair Medisch Centrum Utrecht; Barcelona (Spain) Comitè ètic d'investigació clínica Hospital Clínic de Barcelona; Mataro (Spain): Comitè d'Ètica d'Investigació Clínica (CEIC) del Consorci Sanitari del Maresme; Rotenburg (Germany) Ethik-Kommission der Medizinischen Fakultät der Georg-August-Universität Göttingen, Antwerpen (Belgium): UZ Antwerpen Comité voor Medische Ethiek; Lodz, Szeczecin, and Bialystok (Poland): Komisja Bioetyki Uniwersytetu Medycznego W Lodzi; Milano (Italy) IRCCS Fondazione Cà Granda Policlinico; Jonkoping (Sweden): Regionala etikprövningsnämnden i Linköping; Bratislava (Slovakia): Etika Komisia Bratislavskeho; Gent (Belgium): Ethisch Comité Universitair Ziekenhuis Gent; Nice (France) Comité de Protection des Personnes Sud-Méditerranée II, Hôpital Salvator; Jesenice (Slovenia): Komisija Republike Slovenije za Medicinsko Etiko. Written informed consent was obtained from each patient before inclusion.

Note that full information on the approval of the study protocol must also be provided in the manuscript.