Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Do asymptomatic respiratory viral infections occur?

Viral respiratory infections can cause wide symptom-severity ranges. Detecting community-acquired respiratory-viruses by amplified molecular methods is becoming routine and such results form components of many research studies [1]. Using these technologies, multiple respiratory-viruses can be detected simultaneously within the same symptomatic patient. However, relatively little attention has been given to the detection of respiratory-viruses within asymptomatic populations [2]. Furthermore, the data describing the detection of respiratory-viruses from "asymptomatic" individuals often fail to define "asymptomatic" or simply report studies from convenient hospital populations without respiratory diagnoses [1]. We utilized highly sensitive PCR assays to evaluate respiratory secretions of healthy adults after screening carefully to insure they did not have immune deficiencies, symptoms of upper respiratory infection (URI), or symptoms that could represent a misinterpreted URI.

To accomplish this, we leveraged our recent experience with screening healthy volunteers from our human RSV challenge models [3,4]. Healthy volunteers were carefully screened to meet strict entry criteria (Table 1) so as to avoid enrolling subjects into viral therapeutic studies who inadvertently were infected with respiratory viruses. A nasal wash was obtained which was frozen on dry ice and stored at −80 °C until batch testing using FDA-approved PCR assays with low detection thresholds.

The results of 190 subjects were evaluated (Table 2). Specimens were collected in London, UK. Two different PCR assays analyzed slightly different sets of respiratory-viruses. None of our 190 asymptomatic patients were PCR positive for respiratory-viruses with the exception of rhinovirus (12% detection).

Most respiratory-viruses are generally not detected in asymptomatic healthy adults, and when detected, generally accompany symptoms or a history of recent symptoms. It appears viral infections causing respiratory symptoms are either eradicated or drop below sensitive detection thresholds within this 2-week time frame [3,4,7–9]. This differs from respiratory-viruses in infants which as evidenced by RSV PCR data can persist much longer (> 1 month) [5].

Certain selection criteria may have reduced the exposure to respiratory viruses in our subjects. Before testing, subjects likely had limited contact with young children, hospitalized patients, and people with chronic obstructive pulmonary disease (COPD), or emphysema populations that may have been harboring frequent or prolonged viral respiratory infections [6]. These data may therefore underrepresent the true number of asymptomatic detection in the general population. Although these selection criteria may have reduced the recent exposure of our subjects to respiratory-viruses, their susceptibility and likelihood of becoming symptomatic with these infections likely reflects that of the general healthy population.

Our findings are novel because of our evaluation of completely asymptomatic healthy adults, and our findings corroborate previous data in less well-defined asymptomatic populations [1] in which extremely low PCR RSV and influenza detection rates were observed. We now extend these findings to include other common respiratory-viruses. We detected no adenoviruses within our subjects. Respiratory adenoviruses may be detectable for long periods of time in healthy humans. It is possible our sample size was not sufficient to detect them in our asymptomatic subjects. It is also possible that other adenoviruses not detectable by our assay (GenMark® PCR) were present. Rhinoviruses

Table 1
Subject Entry Criteria. This table outlines the strict inclusion and exclusion criteria used to screen for asymptomatic, healthy adults, and was derived from previous human respiratory syncytial virus challenge models [3,4]. A complete list of selection criteria can be found in supplementary materials [3,4].

Variables
Inclusion
1. Healthy males and females (no clinically significant abnormalities identified by a detailed medical history, full physical examination)
2. 18–45 years of age
3. Body mass index of 18–33 kg/m^2; total body weight ≥ 50 kg
4. Low serum RSV neutralization titers
Exclusion
1. Symptoms of hay fever
2. Abnormal clinically significant laboratory test (complete metabolic panel, urinalysis, complete blood count) or ECG
3. Significant respiratory symptoms suggestive of respiratory infection within 14 days
4. Use (within 7 days) of any medication or other product (prescription or OTC), for symptoms of hay fever, rhinitis, nasal congestion, or respiratory tract infection, with the exception of limited amounts of paracetamol
5. Systemic glucocorticoids, antiviral drugs, and immunoglobulins, or any other cytotoxic or immunosuppressive drug within 6 months prior to dosing; receipt of any systemic chemotherapy agent at any time
6. Any significant acute or chronic, uncontrolled medical illness associated with increased risk of complications of respiratory viral illness
7. Adult onset of asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, reactive airway disease, or any chronic lung condition of any etiology
8. Autoimmune disease or known impaired immune responsiveness (of any cause)
9. Human immunodeficiency virus (HIV), hepatitis B (HBV), or hepatitis C (HCV) infected
10. Significant abnormality altering the anatomy of the nose or nasopharynx
11. Any clinically significant history of epistaxis
12. Any nasal or sinus surgery within 6 months
13. Tobacco use at any time (≥ total 10-pack year history [i.e. 1 pack a day for 10 years])
14. Abnormal pulmonary function (spriometry)
15. Pregnant or nursing or male subjects whose partners are pregnant
16. Health care workers with patient contact
17. Presence of a household member or close contact with someone (for 2 weeks following study testing) who: is < 3 years of age, has any known immunodeficiency, is receiving immunosuppressant medications, is undergoing or soon to undergo cancer chemotherapy, has been diagnosed with emphysema or COPD, is elderly residing in a nursing home, has severe lung disease, or has received a transplant (bone marrow or solid organ)

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Table 2
Respiratory Virus Detection Frequency. The results of a total of 190 subjects were evaluated (one sample collection per subject). Two different PCR assays analyzed slightly different sets of respiratory viruses [Genmark® (Carlsbad, CA); Prodesse® ProFLU™+ (GenProbe, San Diego, CA)]. Manufacturer procedure assays were performed using a certified clinical molecular diagnostics laboratory (Methodist LeBonheur Molecular Diagnostics Laboratory, Memphis, TN). All assays employed closed, never-opened amplicon tubes, and counter-current sample flow – workflow directionality and other contamination prevention procedures. 124 subjects were analyzed by ProFLU™+ PCR (Influenza A & B, respiratory syncytial virus (RSV) A & B, human metapneumovirus (hMPV), and parainfluenza 1,2,3); sixty-six subjects were analyzed by Genmark® PCR (detecting the same viruses as ProFLU™ + but also detecting parainfluenza 4, rhinovirus, human coronavirus 229E, NL63, HKU1 and OC43, and adenovirus). Subjects sampled after the start of the H1N1 pandemic flu were analyzed by detection chemistries, which included this pathogen.

Assay	Month Range	Number of subjects (N)	% Pos. Freq	Type of virus N(%)						
				Influenza[a]	RSV[b]	hMPV	HCoV[c]	Rhino	Adeno[e]	Para[d]
Genmark® PCR	5/15 → 8/15	66	12	0/66 (0)	0/66 (0)	0/66 (0)	0/66(0)	8/66 (12)	0/66(0)	0/66 (0)
ProFLU™+PCR	11/06 → 11/07[f]	124	0	0/124 (0)	0/124(0)	0/124 (0)	–	–	–	0/124(0)
Total		190	12	0/190 (0)	0/190(0)	0/190(0)	0/66(0)	8/66(12)	0/66(0)	0/190(0)

[a] Influenza PCR subtypes include: influenza A (H1 and H3) and influenza B. Genmark ® detects 2009 H1N1. The studies using ProFLU™ + assay were performed prior to 2009 H1N1 pandemic.
[b] Numbers represent combined frequencies for RSV A and RSV B, which are separate PCRs.
[c] Human coronavirus subtypes include: 229E, NL63, HKU1, and OC43.
[d] Parainfluenza virus subtypes include: 1, 2, 3, and 4.
[e] Adenovirus subtypes include: B/E and C.
[f] ProFLU ™+ PCR assay includes two separate collection time points, a cohort of 36 samples were collected from 28 Nov. 2006–26 Feb. 2007 and a second cohort of 88 samples were collected from 19 June 2007–15 Nov. 2007.

appear to act differently and exist in truly asymptomatic adults. How persistent each strain is and how rhinovirus infections evolve within human hosts is not well understood.

In summary, respiratory-viruses (except for rhinoviruses) are not often detectable in asymptomatic healthy adults and the detection generally indicates a current or recent symptomatic infection.

Competing interests

None declared.

Ethical approval

Not required.

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Ryan H. Tomlinson[a,b], Lisa G. Harrison[a,b], Elizabeth A. Meals[a,b], John P. DeVincenzo[a,b,c,d,*]
[a] *Children's Foundation Research Institute, United States*
[b] *Department of Pediatrics, University of Tennessee Health Science Center, United States*
[c] *Department of Microbiology, Immunology, and Biochemistry, University of Tennessee Health Science Center, United States*
[d] *Le Bonheur Children's Hospital, Memphis, TN, United States*
E-mail address: jdevince@uthsc.edu

* Corresponding author at: Room 400R, The Children's Foundation Research Institute, Le Bonheur Children's Hospital, 50 N. Dunlap Street, Memphis TN 38103, United States.