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Air change rate and SARS-CoV-2 exposure in hospitals and residences: A meta-analysis

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ABSTRACT

As COVID-19 swept across the globe, increased ventilation and implementation of air cleaning were emphasized by the US CDC and WHO as important strategies to reduce the risk of inhalation exposure to the virus. To assess whether higher ventilation and air cleaning rates lead to lower exposure risk to SARS-CoV-2, 1274 manuscripts published between April 2020 and September 2022 were screened using key words "airborne SARS-CoV-2 or "SARS-CoV-2 aerosol." Ninety-three studies involved air sampling at locations with known sources (hospitals and residences) were selected and associated data were compiled. Two metrics were used to assess exposure risk: SARS-CoV-2 concentration and SARS-CoV-2 detection rate in air samples. Locations were categorized by type (hospital or residence) and proximity to the location housing the isolated/quarantined patient (primary or secondary). The results showed that hospital wards had lower airborne virus concentrations than residential isolation rooms. A negative correlation was found between airborne virus concentrations in primary-occupancy areas and air changes per hour (ACH). In hospital settings, sample positivity rates were significantly reduced in secondary-occupancy areas compared to primary-occupancy areas, but they were similar across sampling locations in residential settings. ACH and sample positivity rates were negatively correlated, though the effect was diminished when ACH values exceeded 8. While limitations associated with diverse sampling protocols exist, data considered by this meta-analysis support the notion that higher ACH may reduce exposure risks to the virus in ambient air.

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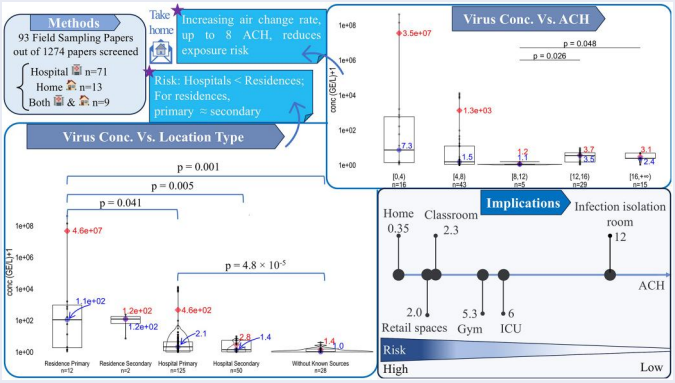

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) swept across the globe beginning in 2020 (WHO 2020) and officially ended in 2023 (WHO 2023). The COVID-19 pandemic resulted in over 774 million cases and more than 7 million deaths as of 2 Febuary 2024 (WHO 2024). Multiple measures were put forward to control the pandemic, including universal masking, physical distancing, hand hygiene, increased ventilation, and vaccination (CDC 2023b).

Person-to-person transmission of SARS-CoV-2 occurs by several pathways, including: inhalation of airborne particles and droplets containing viable virus in aerosols, direct deposition of virions in droplets emanating from coughs or sneezes onto mucus membranes, and indirect transfer of virions from fomites by touching mucus membranes with contaminated hands (CDC 2023a). Virus-laden particles can remain suspended in the air for varying time periods (Marr et al. 2019; Tang et al. 2021). Inhalation of airborne particles containing infectious virus has been recognized as the most prevalent SARS-CoV-2 transmission route (CDC 2023a; Greenhalgh et al. 2021; McNeill 2022; Tellier 2022; Zhang et al. 2020). Airborne transmission of SARS-CoV-2 has been observed in animal studies using golden Syrian hamsters (Hawks et al. 2021) and ferrets (Kutter et al. 2021). Other studies have demonstrated that laboratory-aerosolized SARS-CoV-2 can remain viable in air for three (van Doremalen et al. 2020) to sixteen hours (Fears et al. 2020). Field sampling studies have demonstrated the infectivity of airborne SARS-CoV-2 in hospitals (Fortin et al. 2023; Kitagawa et al. 2023; Lednicky et al. 2020a; Santarpia et al. 2022), a nursing home (Linde et al. 2023), and a home used for quarantine by a COVID-19 patient (Vass et al. 2022).

People spend more than 80% of their time indoors in homes, workplaces, schools, and vehicles (Nature 2023). Mounting evidence has highlighted indoor environments as important venues for SARS-CoV-2 transmission. SARS-CoV-2 RNA concentration in air, despite the variability across samples, was higher indoors compared to outdoors (Dinoi et al. 2022). An agent-based simulation showed that respiratory disease transmission can occur within 10 min of exposure (Choi and Hohl 2023). Especially, in indoor venues where intensive exercise, vocalization and interpersonal interactions occur simultaneously, the attack rate can reach 65% averagely (Huang et al. 2023). A study by Nannu Shankar et al. (2022) showed virus concentrations from air samples taken from a self-isolation room to be as high as $\sim 10^8$ genome equivalents per L (GE/L) of air. This high virus concentration might be caused by the accumulation of virus-laden particles in indoor spaces due to poor ventilation, an occurrence that can be mitigated by relatively fast air exchanges outdoors (Ding et al. 2021). Virus concentrations determined from air samples collected near and far from a virus-emitting source were found to be similar in isolation rooms without ventilation (de Man et al. 2022), suggesting that the exposure risk could be equivalently high even far from virus emission sources in poorly ventilated spaces.

Low flow rate can lead to accumulation of virus in air. Additionally, improper flow direction design can lead to the transport of viruses beyond six feet in the same room (Borro et al. 2021; Nissen et al. 2020; Tellier et al. 2019), despite the ability of air currents to dilute the virus concentration in the vicinity of the source. For instance, during a 100-minute bus ride, 23 of 67 passengers were infected by the index case when the central air conditioning system was in recirculation mode (Shen et al. 2020). The detection of SARS-CoV-2 RNA from the filters of the HVAC systems in hospitals (Horve et al. 2021; Nissen et al. 2020; Wei et al. 2020) and a nursing home (Mouchtouri et al. 2020) underscores the necessity to install proper filters in HVAC system to prevent potential for virus to circulate and transport into different rooms. SARS-CoV-2 RNA was detected in the air of a residential room serviced by the same HVAC system as a self-isolating individual but otherwise not occupied by the person (Vass et al. 2022), Furthermore, viable SARS-CoV-2 virus was isolated from air samples collected from residential spaces notwithstanding the frequency of occupancy by sick persons (Vass et al. 2023). Fecal aerosols from the bathrooms at a lower floor can be transported to bathrooms at higher floors through the drainage vent for some architecture designs (Kang et al. 2020; Wang et al. 2022a; Wang et al. 2022b). Other reviews also echo the importance of adequate ventilation and air cleaning to the reduction of airborne virus exposure risks and the maintenance of safe indoor environments (ASHRAE 2014; Dowell, Lindsley, and Brooks 2022; Li et al. 2007).

The term “ventilation” refers to the process of supplying fresh air from outdoors into an enclosed area (ASHRAE 2023) although many people define ventilation as the introduction of both outdoor air and filtered recirculated air into the space (Etheridge and Sandberg 1996). ACH is a measure of the frequency with which air within a room is added, removed, or

exchanged with treated recirculated air and outdoor air (The Lancet COVID-19 Commission 2023). In our study, we count both ventilation and air cleaning toward ACH. Since ACH is associated with the dilution and removal of target pollutants from air, it has been proposed as a parameter to assess the SARS-CoV-2 exposure risk. This assertion is supported by mass balance modeling studies (Aganovic et al. 2021; de Oliveira et al. 2021; Li et al. 2021; Miller et al. 2021), which have shown reduced exposure risk with increased ventilation. Computational fluid dynamics (CFD) simulations provide further evidence. For instance, a CFD simulation of SARS-CoV-2 transmission in a restaurant showed that poor ventilation yielded high concentrations of virus (Ho 2021b). Similarly, Mariam et al. (2021) found that increasing ventilation reduced particle number concentrations from respiratory events.

A negative association between ACH and virus concentration in the air was determined by a chamber study involving COVID-19 patients (Parhizkar et al. 2022). A laser diffraction measurement showed that increased ventilation could reduce the residence time of respiratory droplets (Somsen et al. 2020). A few field sampling studies revealed a greater proportion of air samples with positive detection of SARS-CoV-2 in isolation homes than in hospital wards, which suggests that the difference may be linked to different ACH in the two settings (de Man et al. 2022; Munoz-Price, Rivera, and Ledeboer 2022). According to Rodríguez et al. (2021), SARS-CoV-2 detection in air samples was reduced after installing air purifiers in residences housing COVID-19 patients. One study investigating the relationship between ACH and exposure risk in isolation homes where the ACH spanned from 0 to 1 concluded that a negative relationship existed between ventilation rate and exposure risk (Horve et al. 2022). However, the ACH value spans widely beyond 0 and 1 depending on the type of built environment. For example, a room-level measurement campaign reflected that ACH in universities and schools spanned from 0 to 20 (McNeill et al. 2022), while a minimum ACH value of 6 is generally required in healthcare facilities in the US (CDC 2019). As ACH is highly variable across types of structures and HVAC systems, it is important to compile the body of knowledge gained from studies that have assessed ACH and presence of viruses in various environments to depict how ACH might affect exposure to airborne pathogens like SARS-CoV-2.

In this study, we screened field sampling papers and compiled data related to SARS-CoV-2 concentrations in air samples, as well as the percentage of positive air samples by different ACH groupings. We report the impact of ACH on the abundance of airborne virus detectable in air samples to inform designers and occupants of indoor living spaces about potential exposure risks related to HVAC systems.

2. Methods

2.1. Inclusion criteria

Research studies and their evaluation compiled in this meta-analysis followed the guidelines of a Cochrane review. Application of the Cochrane review process was carried out to eliminate bias during the study selection process. Our data synthesis included papers that were either preprints or published between April 2020 and September 2022. Published papers were identified from the Google Scholar database using "airborne SARS-CoV-2" or "SARS-CoV-2 aerosol" as key words. A total of 1274 articles were captured in the initial search. The identification and selection of records using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2010) are summarized in Figure 1. Following the removal of duplicates, 877 articles were screened to select records involving field sampling for SARS-CoV-2 detection. Review papers were excluded in this step to prevent double counting of studies.

The article selection process was further refined as follows. Experimental studies conducted in laboratories and outdoors were excluded because they are not representative of built environments. The inclusion criteria for this study were limited to investigations that performed environmental sampling in either hospital or residential settings, as these locations typically guarantee the presence of infected patient(s). Sampling studies that were carried out in: (1) residential areas (community isolation facilities, nursing homes, long-term care homes, hotels, and homes) where cases of COVID-19 had been confirmed, (2) hospital wards that housed patients with COVID-19, and (3) other types of rooms within the hospital setting (hospitals and clinics), were included in this meta-analysis. Although positive air samples were detected in other public spaces, such as restaurants, schools, or buses, they were not considered in this study because little information on ACH was available for these locations. In addition, publications and preprints were excluded if sampling took place in hospital settings without clear information about the number of positive air samples and the total number of air samples collected.

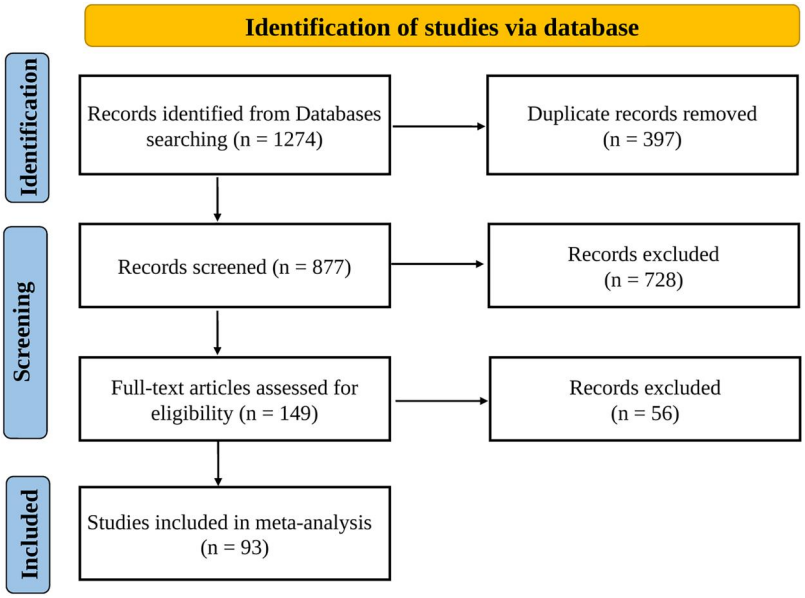

Figure 1. Flow diagram of the identification, screening, and assessment of the records based on the PRISMA method.

Ninety-three (93) papers passed these screening criteria, six of which were pre-prints at the time the screening was performed. One of the six preprints subsequently was published in 2023. Field sampling data came from 24 countries: Bangladesh (1), Brazil (1), Canada (4), China (23), Czechia (1), Germany (1), Greece (1), Hong Kong (3), India (2), Iran (10), Israel (1), Italy (3), Japan (2), Mexico (1), Netherlands (2), Korea (2), Kuwait (2), Portugal (2), Russia (1), Singapore (5), Spain (3), Sweden (2), UK (3), and USA (17). Among the 93 papers, 71 studies were in hospital settings only, 13 in residential settings only, and 9 included both types of settings.

2.2. Definition of primary and secondary rooms and rooms without known sources

The room where the COVID-19 patient spent the most time was defined as the "primary" room, and adjacent rooms or rooms less-frequented by the patient were considered "secondary" rooms. In hospital settings, primary rooms were mostly intensive care units (ICUs), isolation wards, airborne infection isolation rooms (AIIRs), and general wards housing COVID-19 patients. Secondary rooms consisted of nurse stations, corridors, rooms sharing a corridor with primary rooms, and restrooms. In residences, primary rooms were mostly bedrooms or living rooms, while secondary rooms included kitchens, bathrooms, and office spaces. Rooms without known SARS-CoV-2 emission sources in hospital settings (i.e., rooms without known sources), such as outpatient wards, radiological imaging rooms, emergency departments, and fever wards, were also included in the analysis to examine if the regular presence of infected individuals had an impact on exposure risk. Table 1 displays information related to variables that potentially impact virus concentrations in air. While this study primarily examined the impact of location type and ACH on exposure risk, other factors (e.g., the type of air sampler and patient-specific symptoms, days post infection, etc.) may serve as confounders and provide equally plausible alternative explanations for any observed relationship between location type, ACH, and exposure risk. However, the level of patient-specific and equipment-specific information spanning our selected studies did not allow detailed investigation of confounding factors.

2.3. Determination of concentration and positivity rate

Two parameters were used to assess exposure risk: SARS-CoV-2 aerosol concentration in genomic equivalents per liter of air (GE/L) and positivity rate of the air samples. The concentration information was extracted from each publication. For samplers with multiple size-fractionated stages, such as the Sioutas cascade impactor, NIOSH two-stage cyclone bioaerosol sampler (BC-251), or custom-designed Harvard Micro-Environmental Cascade Impactors (Demokritou et al. 2002), all stages within each sampler were considered one sample. For such samplers, the viral RNA concentration for each sample was considered the sum of RNA concentrations in all stages. In Ong et al. (2021), to increase the likelihood of obtaining a

Table 1. Summary of sampling location, air changes per hour, positivity rate and availability of concentration information for studies included in the meta-analysis.

Paper reference	Sampling year	Country	Location type	Room type	Primary room ACH	Conc info	Patient info	Collection device	Other info
1. (Kim et al. 2020)	2020	Korea	Hosp	P S	≥15	0	A	MD8	
2. (Faridi et al. 2020)	2020	Iran	Hosp	P	11–13	0	NA	Standard midget impinger	
3. (Cheng et al. 2020a)	2020	Hong Kong	Hosp	P	12	0	A	MD8	
4. (Ong et al. 2020)	2020	Singapore	Hosp	P S	12	0	A	PTFE filter, MD8	
5. (Cheng et al. 2020b)	2020	Hong Kong	Hosp	P	12	0	NA	SAS Super ISO 180	
6. (Wei et al. 2020b)	2020	China	Hosp	P	12	0	A	FSC-1V	
7. (Ahn et al. 2020)	2020	Korea	Hosp	P	12	0	A	BioSampler, Swab Sampler	
8. (Ma et al. 2021)	2020	China	Hosp	P S W	12	0	A	WA 15, WA 400	
9. (Li et al. 2020)	2020	China	Hosp	P S W	12 16	0	NA	BIO-Capturer-6	
10. (Song et al. 2020)	2020	China	Hosp	P S	15	0	A	Automatic sampling system	
11. (Lane et al. 2021)	2020	USA	Hosp	S	2.8–24	0	NA	BC-251	
12. (Lane et al. 2020)	2020	USA	Hosp	P S	20	0	NA	BC-251	
13. (Cai et al. 2020)	2020	China	Hosp	P	20–40	0	A	ACD-200 Bobcat	AGP
14. (Wu et al. 2020)	2020	China	Hosp	P W	6*	0	NA	Natural precipitation	
15. (Chen et al. 2020)	2020	China	Hosp	P W	6*	0	A	Coriolis μ, MD8	
16. (Zhang et al. 2020)	2020	China	Hosp	P S W	6*	0	NA	NingBo iGene Tec™	
17. (Wei et al. 2020a)	2020	China	Hosp	P S	6*-12	0	A	FSC-1V	
18. (Azizi Jalilian et al. 2022)	2020–2021	Iran	Hosp	P	NA	0	NA	PTFE filter, impinger	
19. (Dziedzinska et al. 2021)	2021	Czechia	Hosp	P	NA	0	NA	air washer LW220	
20. (Krambrich et al. 2021)	2020	Sweden	Hosp	P	NA	0	NA	Ionization device	
21. (Masoumbeigi et al. 2020)	2020	Iran	Hosp	P S W	NA	0	NA	All-glass impinger	
22. (Morioka et al. 2020)	2020	Japan	Hosp	P S	NA	0	A	MD8	AGP
23. (Vosoughi et al. 2021)	2020	Iran	Hosp	P S	NA	0	NA	Impinger	
24. (Nakamura et al. 2020)	2020	Japan	Hosp	P S	NA	0	A	MD8	
25. (Declementi et al. 2020)	2020	Italy	Hosp	P S	NA	0	A	PTFE filter	
26. (Styczynski et al. 2022)	2020–2021	Bangladesh	Hosp	P W	1.82–6.62	A	NA	BioSampler	
27. (Chia et al. 2020)	2020	Singapore	Hosp	P	12	A	NA	BC-251, PTFE filter	
28. (Ong et al. 2021)	2020	Singapore	Hosp	P	12	A	A	BioSpot, BC-251	
29. (Silva et al. 2022)	2021	Portugal	Hosp	P S W	12	A	NA	Coriolis μ, Coriolis Compact	
30. (Guo et al. 2020)	2020	China	Hosp	P S W	12 16	A	NA	SASS 2300	
31. (Santarpia et al. 2020)	2020	USA	Hosp	P S	12–15	A	NA	MD8, personal button sampler	
32. (Pochtovyi et al. 2021)	2020	Russia	Hosp	P S W	2–6	A	NA	SASS 2300, SASS 2300 + SASS 4000, Cyclone-Bio aerosol sampler	
33. (Dumont-Leblond et al. 2020)	2020	Canada	Hosp	P	3–7	A	A	IOM sampler, polycarbonate filter, SASS 3100	
34. (Lednicky et al. 2020a)	2020	USA	Hosp	P	6	A	NA	BioSpot, VIVAS	V
35. (Habibi et al. 2021)	2020–2021	Kuwait	Hosp	P W	6–10	A	NA	Custom-made sampler	
36. (Mallach et al. 2021)	2020–2021	Canada	Hosp	P	6–16	A	NA	UPAS, Coriolis μ	
37. (Liu et al. 2020)	2020	China	Hosp	P S W	6*	A	NA	Gelatin filter, Sioutas impactor	
38. (Santarpia et al. 2022)	2020	USA	Hosp	P	6*	A	A	BC-251	V
39. (Stern et al. 2021a)	2020	USA	Hosp	S W	6*	A	NA	Micro-environment cascade impactor	
40. (Hu et al. 2020)	2020	China	Hosp	P S W	6*	A	NA	WA 400	
41. (Zhou et al. 2021a)	2020	China	Hosp	P S W	6*	A	A	WA 400, WA 15	
42. (Feng et al. 2021)	2020	China	Hosp	P	6*	A	A	BC-251	
43. (Grimalt et al. 2022)	2020	Spain	Hosp	P S W	NA	A	NA	PTFE filter	
44. (Zhou et al. 2021b)	2020	UK	Hosp	S P W	NA	A	NA	Coriolis μ	AGP
45. (Lednicky et al. 2020b)	2020	USA	Hosp	W	NA	A	NA	VIVAS	
46. (Moore et al. 2021)	2020	UK	Hosp	P S W	NA	A	A	Coriolis μ, MD8	AGP
47. (Zahedi et al. 2022)	2021	Iran	Hosp	P S	NA	A	NA	Midget impinger	
48. (Stern et al. 2021b)	2020	Kuwait	Hosp	P S W	NA	A	NA	Micro-environment cascade impactor	
49. (Passos et al. 2021)	2020	Brazil	Hosp	P S W	NA	A	NA	Petri dish, CRIFFER® sampler	

(*Continued*)

Table 1. Continued.

Paper reference	Sampling year	Country	Location type	Room type	Primary room ACH	Conc info	Patient info	Collection device	Other info
50. (Munoz-Price, Rivera, and Ledeboer 2022)	2020	USA	Hosp	P	≥6	NA	A	MD8	
51. (Dietz et al. 2021)	2020	USA	Hosp	P	≥6	NA	NA	AerosolSense™ Sampler, petri dish	
52. (Nissen et al. 2020)	2020	Sweden	Hosp	P	1.5–3.2	NA	A	Petri dish	
53. (Liu et al. 2021)	2020	China	Hosp	P S W	12–16	NA	NA	WB 15	
54. (Binder et al. 2020)	2020	USA	Hosp	P	14	NA	A	BC-251	
55. (Ang et al. 2022)	2020	Singapore	Hosp	P S	14–50	NA	NA	SASS 3100	
56. (Baboli et al. 2021)	2020	Iran	Hosp	P S	3.75–27.06	NA	NA	Petri dish, all-glass impinger, PTFE filter, QuickTake30	
57. (Huang et al. 2022)	2020–2021	Hong Kong	Hosp	P	30	NA	NA	MD8	
58. (Winslow et al. 2022)	2020–2021	UK	Hosp	P	4–10	NA	NA	Coriolis μ	AGP
59. (de Man et al. 2022)	2020–2021	Netherlands	Hosp	P	6	NA	NA	vacuum cleaner	AGP
60. (Jin et al. 2021)	2020	China	Hosp	P S	6*	NA	A	WA 400	
61. (Tan et al. 2020)	2020	China	Hosp	P W	6*	NA	A	membrane	AGP
62. (Ding et al. 2021)	2020	China	Hosp	P S W	6*	NA	A	Andersen one-stage viable impactor, MD8, ASE-100, WA 15	
63. (Ge et al. 2020)	2020	China	Hosp	P S W	6*	NA	A	BC-251	
64. (Lei et al. 2020)	2020	China	Hosp	P S	6*	NA	A	BC-251, WA 15	
65. (Jiang et al. 2020)	2020	China	Hosp	P S W	6*	NA	NA	MAS-100 ECO, petri dish	
66. (Kenarkoohi et al. 2020)	2020	Iran	Hosp	P S W	NA	NA	NA	BioSampler	
67. (Kotwa et al. 2022)	2020	Canada	Hosp	P	NA	NA	NA	Polycarbonate filter, PTFE filter, gelatin filter, BC-251	
68. (Ben-Shmuel et al. 2020)	2020	Israel	Hosp	P S	NA	NA	NA	MD8	
69. (Razzini et al. 2020)	2020	Italy	Hosp	P S	NA	NA	NA	MD8	
70. (Moharir et al. 2022)	2020–2021	India	Hosp	P S W	NA	NA	NA	MD8	
71. (Ramuta et al. 2022)	2021	USA	Hosp	W	NA	NA	NA	AerosolSense™ Sampler	
72. (Mouchtouri et al. 2020)	2020	Greece	Hosp	P S W	NA	NA	A	MD8	
73. (Del Real et al. 2022)	2021	Spain	Hosp	P S W	NA	NA	NA	Personal Modular Impactor (coarse)	
74. (Seyyed Mahdi et al. 2020)	2020	Iran	Hosp	P	NA	NA	NA	Midget impinger	
75. (Dubey et al. 2021)	2020	India	Hosp	P S	NA	NA	NA	Total suspended particulate air sampler	
76. (Gharehchahi et al. 2021)	2020	Iran	Hosp	P W	NA	NA	NA	Standard midget impinger	
77. (Stern et al. 2022)	2020–2021	USA	Hosp	S W	NA	NA	A	Micro-environment cascade impactor	
78. (López et al. 2021)	2020	Mexico	Hosp	P W	NA	NA	NA	MCE filter	
79. (Hemati et al. 2021)	2020	Iran	Hosp	P S W	NA	NA	NA	Standard midget impinger	
80. (Barbieri et al. 2021)	2020	Italy	Hosp	S	NA	NA	NA	SILENT Sequential Air Sampler	
81. (Döhla et al. 2022)	2020	Germany	Resi	P	0.6*	0	NA	Coriolis μ	
82. (Mouchtouri et al. 2020)	2020	Greece	Resi	P S	NA	0	A	MD8	
83. (Xie et al. 2020)	2020	China	Resi	P W	NA	0	A	NA	
84. (Dumont-Leblond et al. 2021)	2020	Canada	Resi	P	NA	0	NA	IOM sampler	
85. (Luo et al. 2020)	2020	China	Resi	P	NA	0	A	MD8	
86. (Wong et al. 2020)	2020	Singapore	Resi	P	NA	0	NA	Coriolis μ	
87. (Vass et al. 2022)	2021	USA	Resi	P S	0.35*	A	A	BC-251, BioSpot	V
88. (Nannu Shankar et al. 2022)	2020	USA	Resi	P	0.35*	A	A	BC-251, Sioutas impactor, VIVAS, PTFE filter	
89. (Mallach et al. 2021)	2020–2021	Canada	Resi	P	2–10	A	NA	UPAS	
90. (Ma et al. 2021)	2020	China	Resi	P S	NA	A	A	WA 15, WA 400	
91. (Ong et al. 2021)	2020	Singapore	Resi	P	NA	A	NA	BioSpot	
92. (de Man et al. 2022)	2020–2021	Netherlands	Resi	P	0	NA	NA	vacuum cleaner	
93. (Rodríguez et al. 2021)	2021	Spain	Resi	P	0–26.8	NA	A	MD8	†
94. (Laumbach et al. 2022)	2020–2021	USA	Resi	P S	0.35*	NA	A	PTFE filter	
95. (Robie et al. 2021)	2020–2021	USA	Resi	P	0.35*	NA	A	BioSampler, BC-251	

96. (Myers et al. 2022)	2020–2021	USA	Resi	P S	0.35*–15.4	NA	A	PTFE filter		†
97. (Azizi Jalilian et al. 2022)	2020–2021	Iran	Resi	P	NA	NA	NA	PTFE filter, impinger		
98. (Munoz-Price, Rivera, and Ledeboer 2022)	2020	USA	Resi	P S	0.35*	NA	A	MD8		
99. (Ben-Shmuel et al. 2020)	2020	Israel	Resi	P S	NA	NA	NA	MD8		
100. (Moharir et al. 2022)	2020–2021	India	Resi	P S	NA	NA	NA	MD8		
101. (Linde et al. 2023)	2020–2021	Netherlands	Resi	P S	NA	NA	A	Conical Inhalable Sampler, BC-251, BioSampler, Electrostatic Dust Collector	V	
102. (Correia et al. 2022)	2020–2021	Portugal	Resi	P S	NA	NA	A	Gelatin filter, Sioutas impactor, petri dish		

Hosp: Hospital; Resi: Residential; P: primary; S: secondary; W: without known emission sources.
A: available, NA: not available; AGP: aerosol-generation procedure; V: viable virus detected.
*0.35 and 6 were assumed values for US homes and hospital wards, respectively, based on ASHRAE (2020); 0.6 was assumed for Germany homes based on (Brelih and Seppänen 2011); 6 for Chinese hospital wards was based on (沈晋明 and 刘燕敏 2015).
†A home with and without air purifiers was treated as two separate homes in the analysis due to the great differences in ACH.
Patient info includes days post symptom onset, symptoms, clinical results, disease severity, and so on.

positive result, a total of six air samples were combined into a single pooled sample, which was then treated as a singular entity for analysis purposes. Out of the 27 papers that documented non-zero airborne virus concentrations, 5 of them did not provide concentrations for individual samples. Instead, they reported the median (Styczynski et al. 2022), mean (Grimalt et al. 2022; Guo et al. 2020), or minimum and maximum (Hu et al. 2020; Moore et al. 2021) concentrations, which were assigned to positive air samples as an imputation method (Gareth et al. 2013). Since virus concentrations in air from those studies spanned from 0 to 10^9 GE/L, the concentration was transformed by a base-10 logarithmic transformation as $\log_{10}$(concentration (GE/L) + 1) to account for a skewed distribution (Cortez and Morais 2007; Menard 2002) (Figures 2–5).

Positivity rate was determined by taking the ratio of positive air sample counts to total air sample counts at a given location. A sample was considered positive if the virus was detectable in at least one replicate with at least one gene primer. A suspected-positive (Winslow et al. 2022) or an inconclusive sample (Linde et al. 2023) was treated as a positive sample since false negatives were more concern than false positives. For size-segregated samplers, the sample was considered positive if the virus was detected in at least one stage. The positivity rate was calculated for primary rooms and secondary rooms in each hospital or residence and for locations without known sources in each hospital. If multiple hospitals or homes were sampled without reporting the corresponding positivity rate, use of an imputation technique (Gareth et al. 2013) entailed assigning an average positivity value to each hospital (Ben-Shmuel et al. 2020; Kotwa et al. 2022; Liu et al. 2021; Moore et al. 2021; Styczynski et al. 2022; Winslow et al. 2022) or home (de Man et al. 2022), as indicated in the online supplementary information.

2.4. Extraction of ACH information

The ACH values of the primary rooms were extracted from the 93 studies and compiled in Table 1. References 1–80 were for hospital settings while references 81–102 were for residential settings. Nine studies covered both settings (8/90; 18/97; 28/91; 36/89; 50/98; 59/92; 68/99; 70/100; and 72/82). Most studies reported ACH information received from facilities rather than measurement by the researchers themselves. This review assumed that the reported ACH values were actual. If ACH information was

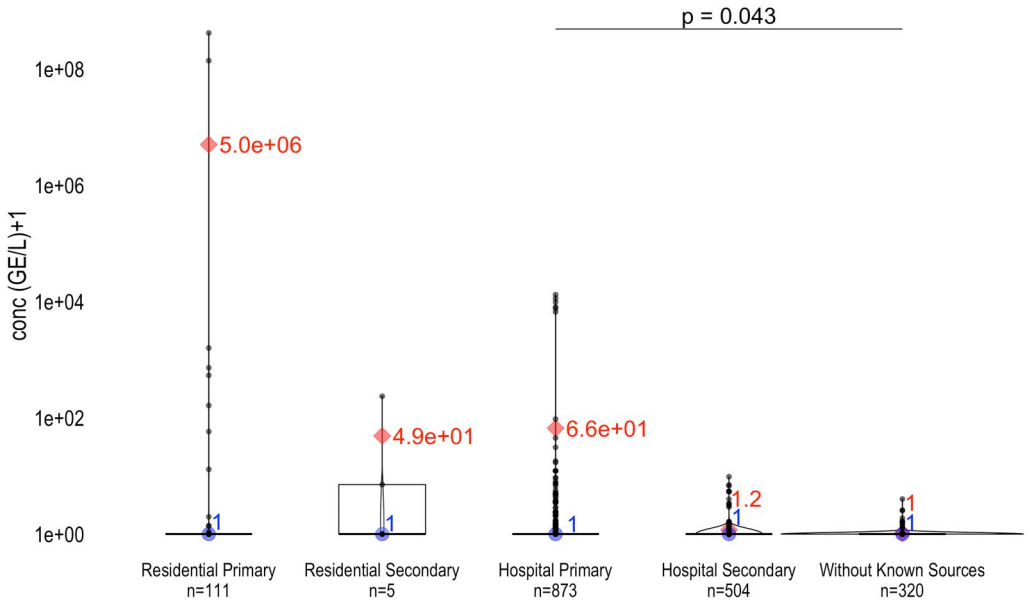

Figure 2. SARS-CoV-2 concentration across different location types.
The Y axis is in logarithmic scale. Each black dot corresponds to an observation of (concentration + 1). The median is represented by the blue circle, whereas the mean is denoted by the red diamond. The numerical value under each location type reflects the number of observations within each respective group. A p value is marked in the figure when it is less than 0.05 to suggest significant difference between two groups. The room wherein the COVID-19 patient spent the most time is defined as the "primary" room, and adjacent rooms or rooms less-frequented by the patient are considered "secondary" rooms. Rooms without known SARS-CoV-2 emission sources in hospital settings (rooms without known sources) include outpatient wards, radiological imaging rooms, emergency departments, fever wards, etc.

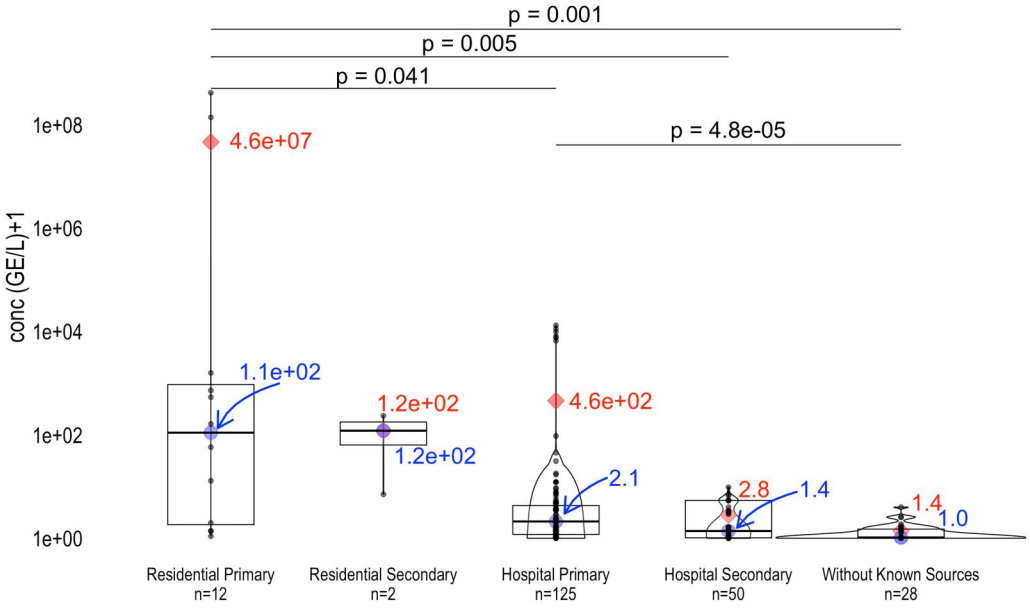

Figure 3. SARS-CoV-2 concentration across different location types excluding zero values.
Each black dot corresponds to an observation of (non-zero concentration + 1) in logarithmic-transformed scale. The median is represented by the blue circle, whereas the mean is denoted by the red diamond. The numerical value under each location type reflects the number of observations within each respective group. A p value is marked in the figure when it is less than 0.05 to suggest significant difference between two groups. The room wherein the COVID-19 patient spent the most time is defined as the "primary" room, and adjacent rooms or rooms less-frequented by the patient are considered "secondary" rooms. Rooms without known SARS-CoV-2 emission sources in hospital settings (rooms without known sources) include outpatient wards, radiological imaging rooms, emergency departments, fever wards, etc.

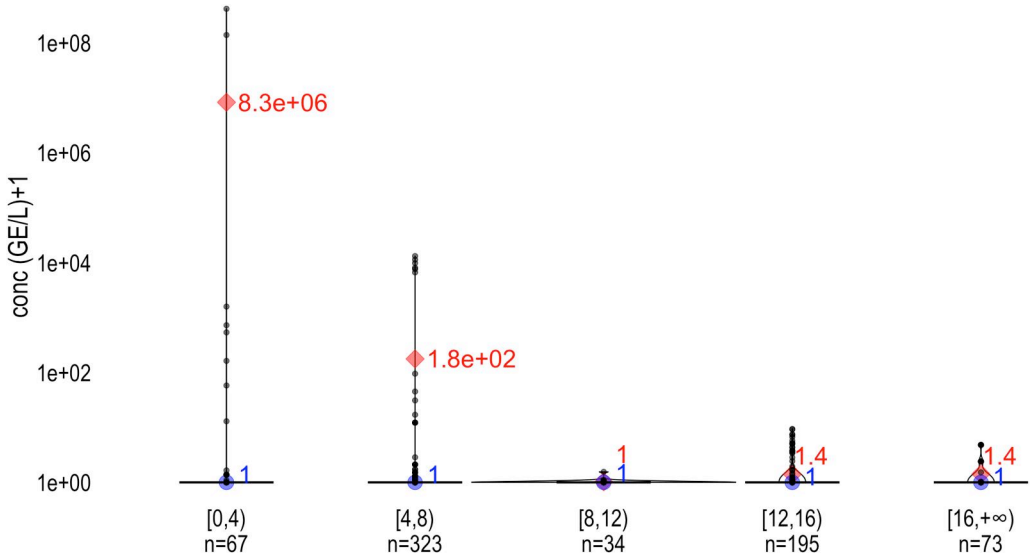

Figure 4. SARS-CoV-2 concentration across different ACH ranges among primary rooms.
Y axis is logarithmically transformed. One was added to the concentrations to account for zero values. Each black dot corresponds to an observation (concentration + 1). The median is represented by the blue circle, whereas the mean is denoted by the red diamond. The numerical value of each ACH group reflects the number of observations within each respective group. A p value is marked in the figure when it is less than 0.05 to suggest significant difference between two groups.

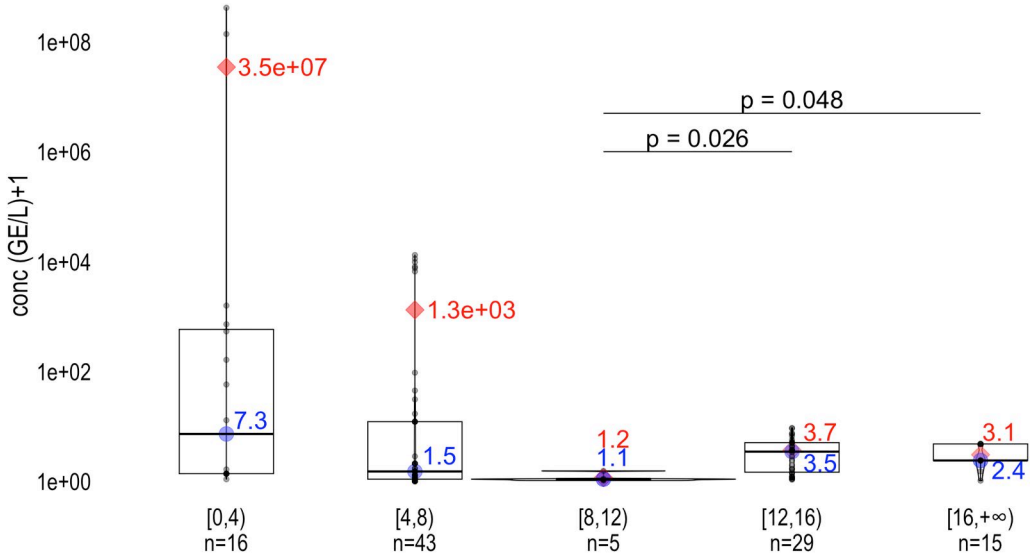

Figure 5. SARS-CoV-2 concentration across different ACH ranges among primary rooms when zero values are excluded.
The Y axis is in logarithmic scale. Each dot corresponds to an observation of (1+ non-zero concentration). The median is represented by the blue circle, whereas the mean is denoted by the red diamond. The numerical value under each ACH group reflects the number of observations within each respective group. A p value is marked in the figure when it is less than 0.05 to suggest significant difference between two groups.

not provided in a study, an ACH value of 0.35 was assigned to residences in US according to American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) 62.2-2016. Depending on the room type in the hospital, an ACH value based on ASHRAE (2020) was assigned if the location was in the US or Guobiao (a Chinese standard) (吕品 2021; 沈晋明 and 刘燕敏 2015) if the location was in China. It is important to acknowledge that ASHRAE standards may not be mandatory for some states, and a significant number of non-hospital buildings do not adhere to these guidelines for ventilation. For example, environments like educational institutions, commercial structures, and residential dwellings may not comply with the standards. Consequently, assuming that these buildings are constantly operating at the recommended level may not be accurate. Hospitals, on the other hand, generally

adhere to the ASHRAE standards. ACH values of 0.6 were assigned to homes in Germany based on the average ACH value found for German homes (Brelih and Seppänen 2011). For ACH in hospitals in other countries where there was no recommendation or regulation, no assumption on ACH was made, and those papers were excluded from the analysis examining how ACH values affect positivity rates and virus concentrations. To assess the effect of ACH on virus concentration, it is preferable to use the ACH value that corresponds to the specific room being sampled. In cases where the ACH for the sampled room were not provided, the average ACH value for the corresponding room type in that hospital was utilized as a substitute. Upon examining the impact of ACH on positivity rates, the average ACH value for each residential or hospital facility was computed across all primary-occupancy locations. The positivity rate associated with locations of primary- and secondary-occupancy was grouped based on primary room ACH. For studies that only mentioned the minimum ACH, the minimum ACH value was used. In cases where portable air purifiers were utilized (Myers et al. 2022; Rodríguez et al. 2021), the sampling site with and without purifier operation was treated as two distinct sites due to considerable differences in ACH between the two scenarios. The ACH for sites with air purifiers was calculated based on the air purifier volumetric flowrate and the volume of the room.

2.5. Assessment of virus concentration based on location type and ACH range

Since not all studies have quantified the virus concentration, only papers that provided concentration information (Table 1, references 1–49 and 81–91) were included in the location type-concentration analysis ($n = 55$). Twenty-eight ($n = 28$) of them, comprising 25 in hospital settings and 6 in residential settings (three studies assessed both settings), yielded no detectable virus, suggesting airborne virus concentrations below detectable limits. Twenty-seven ($n = 27$) studies, comprising 24 (references 26–49) sampling campaigns in hospital settings and 5 (references 87–91) in residential settings (two studies assessed both settings), successfully detected the virus and were able to quantify its concentration. A violin plot with all data points was created (Figure 2) to compare how different locations affect SARS-CoV-2 concentrations in air (using measures of viral RNA as a surrogate for direct measures of virus concentrations, such as plaque-forming units of virus per liter of air.

Virus aerosol concentrations in primary rooms were compared against ACH values. To lessen the influence of noise associated with the uncertainties in ACH values, we categorized ACH values into discrete ranges, rather than treating them as continuous-valued data points, and that allowed for a more robust analysis framework. Rooms were grouped into 5 categories based on ACH (Figure 4): [0,4), [4,8), [8,12), [12,16) and [16,+∞). To assess to what extent the uncertainties associated with the assumptions on ACH assignation may impact the analysis, we carried out a sensitivity analysis. Using the average of geometric means (0.67) and geometric standard deviations (1.98) of US homes calculated from (Nazaroff 2021), more than 80% of the time, the ACH fall into the range of [0,4) based on Monte Carlo simulation (Cullen and Frey 1999), a method widely applied to handle uncertainties in data. Additionally, the ACH was observed to be less than 1.2 in 90% of the households (Nazaroff 2021). Even when an ACH value of 0.35 or 0.6 was assigned based on ASHRAE (2022) or Brelih and Seppänen (2011), the ACH consistently fell under the same group. Hence, assigning single values for residences in US and German enhanced simplicity without hampering the robustness of the method. Regarding ACH in hospital settings, field measurements were limited, thus preventing us from doing sensitivity analysis in a similar manner. Generally, hospitals just comply with the minimum requirement to minimize operational costs. Thus, studies included in the ACH-concentration analysis were those that quantified the virus concentration and either reported the facility's ACH value or used a regulated ACH value as a surrogate. A total of 37 studies met the requirement (Table 1, references 1–17, 26–42, 81, 87–89), among which 19 studies (Table 1, references 26–42, 87–89) documented virus detection.

Most air samples did not contain detectable quantities of virus, which can be attributed to a few factors. For instance, while the symptoms may persist and oronasopharyngeal samples may continue to yield positive test results in the later stages of the infection, virus was only actively being shed during the early stage (Malik et al. 2021). However, air sampling studies rarely report the infection stage of patients. It is possible that by the time the sampling took place, the patient was at the late phase of the infection and not emitting virus anymore. Additionally, due to insufficient sampling duration, or inability of the sampler to

collect virus-laden particles from air, the testing procedure may lack sensitivity to identify the presence of a virus in air samples when the air actually contains the virus, yielding false negatives. To account for the possibility of obtaining negative air samples due to conducting samplings at the late phase of the illness and false negatives, additional plots of virus concentration in air without zero values were created for different location types (Figure 3) and ACH ranges (Figure 5). This allowed us to gain a more accurate understanding of the presence of viruses within our sampled environments. Only 12% (217 out of 1813) of data points were non-zero when assessing location type vs. virus concentration. Only 16% (108 out of 692) of data points were non-zero when assessing ACH vs. virus concentration. Exclusion of zero data points could introduce bias *via* selection bias and loss of information. Cases of true negative of air samples during early stage of infection may exist and zero concentration could be representative of a subset of the total environment, such as when the individuals do not shed virus despite being infected. The zero values, while possibly due to poor sampling or other factors, still provide information about the presence or absence of the virus in the air (Cai, Parast, and Ryan 2010). Excluding all zero values in analysis could also lead to an overestimation of the virus concentration, skewing results in the direction of higher concentrations. However, it is environments with higher virus concentrations that are most worrisome in terms of exposure risk. As a disparity in ACH was proposed as a possible reason for dissimilar virus concentrations between hospital and residential settings, the distribution of primary room ACH for hospitals and residences was compared using a histogram (Figure 6) for sampling sites with primary-location virus concentrations and known ACH values.

2.6. Assessment of positivity rate based on location type and ACH range

The analysis of location type vs. positivity rates involved a total of 93 studies, with 80 studies (Table 1, references 1–80) focusing on hospital settings and 22 papers (Table 1, references 81–102) focusing on residential settings (nine studies assessed both settings). All studies that provided ACH values or allowed assignation of ACH values based on assumptions were included in the analysis of ACH-positivity rate, which included 60 papers (Table 1, references 1–17, 26–42, 50–65, 81, 87–89, 92–96, and 98). Three references were counted twice as they sampled in both settings (36/89; 50/98; 59/92). A violin plot was generated (Figure 7) to assess the impact of location type on positivity rate. To investigate the impact of ACH on positivity rate in locations of primary- and secondary-occupancy, a two-sided violin plot was generated, wherein rooms were categorized according to primary room ACH (Figure 8).

2.7. Statistical analysis

Non-parametric Kruskal-Wallis tests (McKight and Najab 2010) were used to examine whether statistically significant differences exist in positivity rates and SARS-CoV-2 concentrations among different groups for both location type and ACH. The application of this method has merit due to its ability to examine hypotheses among three or more groups. Non-parametric Wilcoxon rank sum tests (Wilcoxon, Katti, and Wilcox 1970) with Bonferroni corrections (Weisstein 2004) were used to assess pairwise differences between groups. Bonferroni corrections were applied to minimize the chance of mistakenly concluding statistically significant differences arose when conducting multiple hypothesis tests.

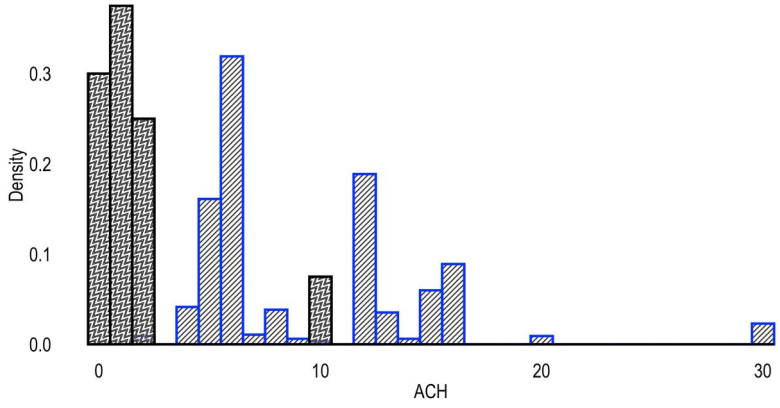

Figure 6. ACH distribution among hospitals and residences.
The wavy bin in black and stripe bin in blue represent residences and hospitals, respectively.

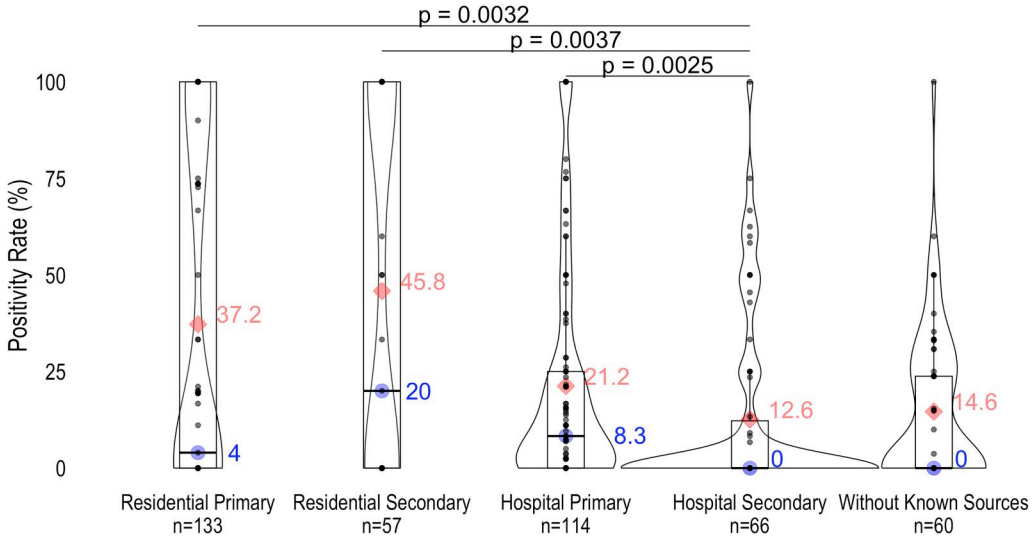

Figure 7. Positivity rate of air samples among different location types.
The median is represented by the blue dot, whereas the mean is denoted by the red diamond. Gray dots represent observations, and ones with darker color means dots overlap. The numerical value under the location type reflects the number of observations within each respective group. A p value is marked in the figure when it is less than 0.05 to suggest significant difference between two groups. Mean and median values are indicated in red and blue, respectively. The room wherein the COVID-19 patient spent the most time is defined as the "primary" room, and adjacent rooms or rooms less-frequented by the patient are considered "secondary" rooms. Rooms without known SARS-CoV-2 emission sources in hospital settings (rooms without known sources) include outpatient wards, radiological imaging rooms, emergency departments, fever wards, etc.

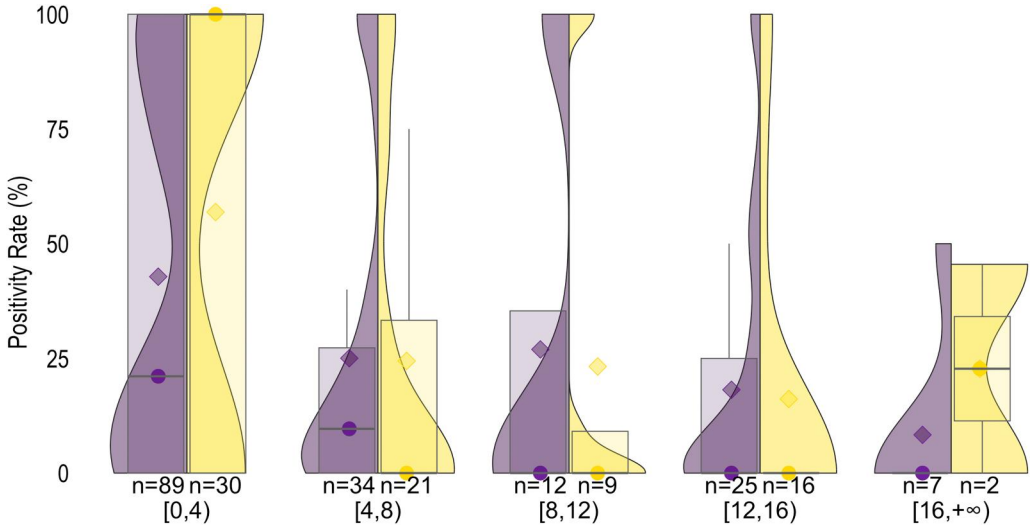

Figure 8. Positivity rate of air samples in primary and secondary locations grouped by ACH.
The purple violins on the left represent the positivity rate distribution in primary locations while the yellow violins on the right represent that in secondary locations. The median is represented by the purple and yellow circle for primary and secondary locations, respectively, whereas the mean is denoted by the purple and yellow diamond for primary and secondary locations, respectively. The numerical value under each group reflects the number of observations within each respective group. Regardless of primary or secondary rooms, no significant difference was found between different ACH ranges. No significant difference was found between primary and secondary locations under the same ACH group.

ACH groups were categorized by location (primary or secondary), and Wilcoxon rank sum tests were used to examine the differences in positivity rates within subgroups. A two-sided p-value <0.05 was considered statistically significant for all tests. While medians are typically employed as a measure of centrality for non-normally distributed data, we have also reported means to provide a comprehensive view of central tendency. This approach is particularly relevant in the context of our dataset, which includes extremely high values such as those reported in Nannu Shankar et al. (2022). They warrant particular attention due to their association with superspreading events (Prentiss, Chu, and Berggren 2020), during

which individuals become highly contagious and capable of transmitting the disease to a much larger number of people than usual. The inclusion of both means and medians in our analysis is therefore justified by the need to accurately capture the typical values in the dataset (medians) while also recognizing the impact of extreme cases (means), especially given the heightened exposure risk associated with superspreading events.

Data analysis and plotting was performed in R script (R Core Team 2018) version 4.3.2, and details on air sample concentrations and positivity rates can be found in the Supplementary Materials section.

3. Results

SARS-CoV-2 was not detected for the vast majority of the air samples for all location types (Table 2, Figure 2). 86% (748 of 873) of observations in hospital primary locations showed undetectable virus concentrations (Figure 2, Figure 3). The same was true for 90% (454 of 504) of observations in hospital secondary locations. In residential primary locations, 89% (99 of 111) of observations showed no detectable virus. 60% (3 of 5) of observations in residential secondary locations likewise held no detectable virus. Observations from 91% (292 of 320) of samples from without a known source room in hospitals had no detectable virus. The extensive proportion of negative air samples can be attributed to the inefficiency of the sample collection method, suboptimal timing of sampling during the later stages of infection, inadequate sampling duration and limitations in the sensitivity of the detection technique. Given the high number of samples with undetectable virus concentrations, the only significant difference in virus concentrations was found between hospital primary rooms (mean $= 6.5 \times 10^{1}$ GE/L, median $= 0$ GE/L) and rooms without known sources (mean $= 3.3 \times 10^{-2}$ GE/L, median $= 0$ GE/L) ($p = 0.043$, Figure 2). The maximum concentration reported for hospital primary rooms (1.3×10^{4} GE/L) was lower than residential primary rooms (4.2×10^{8} GE/L). Similarly, the maximum concentration reported in hospital secondary rooms (8.7 GE/L) was lower than that found in residence secondary rooms (2.3×10^{2} GE/L). The maximum concentrations recorded in secondary rooms in hospitals (8.7 GE/L) and residences (2.3×10^{2} GE/L) were both lower than primary rooms (1.3×10^{4} GE/L for hospital and 4.2×10^{8} GE/L for residential). Locations in rooms without a known source in hospitals had the lowest maximum concentration (3.0 GE/L). After the removal of samples with undetectable virus concentrations, significant differences existed between rooms without known sources (mean $= 3.8 \times 10^{-1}$ GE/L, median $= 3.6 \times 10^{-2}$ GE/L) and both hospital primary rooms (mean $= 4.6 \times 10^{2}$ GE/L, median $= 1.1$ GE/L, $p = 4.8 \times 10^{-5}$) and residential primary rooms (mean $= 4.6 \times 10^{7}$ GE/L, median $= 1.1 \times 10^{2}$ GE/L, $p = 0.001$). These findings showed the impact of the presence of emission sources and underscored the role of isolation measures in curtailing the spread of the virus. A significant difference also existed between hospital secondary rooms (mean $= 1.8$ GE/L, median $= 3.8 \times 10^{-1}$ GE/L) and residential primary rooms (mean $= 4.6 \times 10^{7}$ GE/L, median $= 1.1 \times 10^{2}$ GE/L, $p = 0.005$). Hospital primary rooms (mean $= 4.6 \times 10^{2}$ GE/L, median $= 1.1$ GE/L) likewise differed from residential primary rooms (mean $= 4.6 \times 10^{7}$ GE/L, median $= 1.1 \times 10^{2}$ GE/L, $p = 0.041$, Figure 3).

Table 2. Number of SARS-CoV-2 detected and undetected air samples by location and ACH range.

	$Hosp_{Prim}$	$Hosp_{Seco}$	$Resi_{Prim}$	$Resi_{Seco}$	Without
Total	873	504	111	5	320
Detected	125	50	12	2	28
Undetected	748	454	99	3	292

$Hosp_{Prim}$: Hospital Primary rooms; $Hosp_{Seco}$: Hospital Secondary rooms; $Resi_{Prim}$: Residential Primary rooms; $Resi_{Seco}$: Residential Secondary rooms; Without: rooms without known sources.

	[0,4)	[4,8)	[8,12)	[12,16)	[16,+∞)
Total	67	323	34	195	73
Detected	16	43	5	29	15
Undetected	51	280	29	166	58

Table 3. Mean and medians of SARS-CoV-2 concentration in GE/L and positivity rates by location and ACH range.

	$Hosp_{Prim}$	$Hosp_{Seco}$	$Resi_{Prim}$	$Resi_{Seco}$	Without
Concentrations (GE/L)					
All samples					
Mean	6.5×10^{1}	1.8×10^{-1}	5.0×10^{6}	4.8×10^{1}	3.3×10^{-2}
Median	0	0	0	0	0
Positive samples					
Mean	4.6×10^{2}	1.8	4.6×10^{7}	1.2×10^{2}	3.8×10^{-1}
Median	1.1	3.8×10^{-1}	1.1×10^{2}	1.2×10^{2}	3.6×10^{-2}
Positivity rate (%)					
Mean	21.2	12.6	37.2	45.8	14.6
Median	8.3	0.0	4.0	20.0	0.0

$Hosp_{Prim}$: Hospital Primary rooms; $Hosp_{Seco}$: Hospital Secondary rooms; $Resi_{Prim}$: Residential Primary rooms; $Resi_{Seco}$: Residential Secondary rooms; Without: rooms without known sources.

	[0,4)	[4,8)	[8,12)	[12,16)	[16,+∞)
Concentrations (GE/L)					
All samples					
Mean	8.3×10^{6}	1.8×10^{2}	2.5×10^{-2}	4.1×10^{-1}	4.2×10^{-1}
Median	0	0	0	0	0
Positive samples					
Mean	3.5×10^{7}	1.3×10^{3}	1.7×10^{-1}	2.7	2.1
Median	6.3	5.1×10^{-1}	9.9×10^{-2}	2.5	1.4
Positivity rate (%)					
Primary rooms					
Mean	42.8	25.0	27.0	18.2	7.5
Median	21.1	9.7	0.0	0.0	0.0
Secondary rooms					
Mean	56.9	24.4	23.2	16.1	22.8
Median	100.0	0.0	0.0	0.0	22.8

Conversely, virus concentrations in primary and secondary locations in the same setting were similar. The comprehensive mean and median for each group can be found in Table 3.

For all ACH ranges, around 80% of the air samples failed to detect the virus, as shown in Table 2. In groups defined by ACH levels [0,4), [4,8), [8,12), [12,16), and [16,+∞), zero-values constituted 76% (51/67), 87% (280/323), 85% (29/34), 85% (166/195), and 79% (58/73) of respective sample results. Concentration distributions within all groups were statistically similar, but maximum concentrations noticeably decreased between 0 and 12 (Figure 4). Upon removal of zero values, the mean virus concentrations decreased as ACH increased, with the exception at [8,12) (Figure 5). A significant difference between [8,12) (mean = 1.7×10^{-1} GE/L, median = 9.9×10^{-2} GE/L) and [12,16) (mean = 2.7 GE/L, median = 2.5 GE/L, $p = 0.026$), and between [8,12) (mean = 1.7×10^{-1} GE/L, median = 9.9×10^{-2} GE/L) and [16,+∞) (mean = 2.1 GE/L, median = 1.4 GE/L, $p = 0.048$) should be interpreted with caution due to the small sample size ($n = 5$) in the [8,12) group.

Hospitals had lower positivity rates than residences, possibly due to higher ACH rates in hospital settings (Figure 6). Positivity rates in hospital primary (mean = 21.2%, median = 8.3%) and secondary rooms (mean = 12.6%, median = 0%) differed significantly ($p = 0.0026$). Rates also differed between secondary rooms in hospitals (mean = 12.6%, median = 0%) and residences (mean = 45.8%, median = 20%, $p = 0.0037$). The violin shapes of primary and secondary rooms in residences are similar (Figure 7), suggesting comparable positivity rates.

A reduction in positivity rate was observed as ACH increased from [0,4) to [4,8), albeit without significant difference (Figure 8). Positivity rates appeared similar as ACH increased beyond 8, and no significant differences in positivity rates were found between primary rooms and secondary rooms across all ACH groups.

Table 1 summarizes the year and country in which the air sampling took place as well as the various air sampling methods employed across the literatures. Sampling methods ranged from filtration techniques (such as polytetrafluoroethylene polymer (PTFE), gelatin, polycarbonate, and mixed cellulose ester (MCE) filters) and cyclones (such as Coriolis μ, Coriolis Compact, WA 400 and BC-251) to impingers (such as BioSampler, standard midget and all-glass impinger) and water-based condensational particle growth devices (such as BioSpot and VIVAS). A few studies also employed passive air samplers.

4. Discussions

A database of 93 studies was created that met a prespecified set of criteria, and a meta-analysis of these studies was performed. One strength of our data synthesis and meta-analysis was reliance on the methodology described in the Cochrane Collaboration, an international network of researchers and health-care scientists/professionals who produce and disseminate high-quality systematic reviews. The methods, developed over decades, include an objective approach to selecting studies for systematic review to eliminate bias in study selection. Using the methods of Cochrane prevents the possibility that only studies are selected that satisfy the preconceived opinions of the scientist performing the data synthesis and meta-analysis. Bias during the study selection process has been objectively minimized. A possible drawback of data synthesis and a meta-analysis is that the studies may differ in a number of important ways such as endpoint measurement procedures, devices used to collect critical data, and variability in study conduct such as extent of missing data. This heterogeneity may lead to excess variability, and differences in effects between groups may go unnoticed compared to a well-done single study with less variability. On the other hand, the data synthesis and meta-analysis provides a broad, unbiased landscape of the issues being examined.

This meta-analysis was used to examine the SARS-CoV-2 concentration and positivity rate among residences and hospitals. Our results show that the virus was recovered at greater concentrations and with greater consistency in residences than in hospitals, suggesting that residential environments have a greater risk of exposure to airborne pathogens when pathogen-emitting hosts are present. Evidence published by studies comparing hospitals and residences (Mathur 2022), proportionally larger COVID-19 case counts from residential outbreak events (Qian et al. 2021), and higher positivity rates in residential environmental samples compared to hospital environments (de Man et al. 2022; Munoz-Price, Rivera, and Ledeboer 2022) suggest similar circumstances. Our holistic assessment demonstrates a broader trend of higher exposure risk to airborne SARS-CoV-2 in residential areas with known pathogen-emitting sources compared to hospital counterparts. A higher risk of exposure may translate to a higher risk of disease transmission as susceptible hosts are exposed more frequently to a higher concentration of the virus. The disparity in exposure risk between hospitals and residences is likely contributed by the differences in ACH rates.

Our findings agree with the result of computational fluid dynamics modeling, which argues that higher ACH rates lead to lower exposure risk (Rivas et al. 2022). Air purifiers have also been suggested as beneficial devices for SARS-CoV-2 exposure risk reduction due to their improvement of effective supply of filtered air. According to Myers et al. (2022) and Rodríguez et al. (2021), the use of air purifiers facilitated reduction of airborne SARS-CoV-2 from 44% to 25%, and from 100% to 20%, respectively. The observed discrepancy can plausibly be attributed to the selection of air purification devices and the adherence to predetermined behavioral patterns, or lack thereof. Parhizkar et al. (2022) collected air samples in a controlled chamber with COVID-19 patients and showed that viral load decreased when ACH $>$ 9 compared to when ACH $<$ 4.5. Horve et al. (2022) reported that SARS-CoV-2 concentrations and likelihoods of recovering virus increased with decreasing ACH in college dormitories. Together, these studies show that in both controlled and uncontrolled environments, ACH rate affects the collection of airborne viruses from indoor air. It is therefore sensible that the compilation of data achieved by this meta-analysis shows that grouping locations into high- and low-ACH groups defined as hospitals and residences, respectively, yields a result that shows greater exposure risk in low-ACH environments with pathogen-emitting sources present. This greater exposure risk supports a growing consensus that indoor settings with low air change rates contribute to the propagation of infectious illnesses spreading through the air.

Our analyses did not reveal significant differences in positivity rates between primary and secondary locations in all ACH ranges. This implies that the risk of exposure is comparable whether an individual shares a room with the patient or occupies a separate room. We acknowledge that the diverse protocols employed in each study introduced potential noise into our analysis, which can impact the overall robustness of our results. The comparable positivity rate observed in both primary and secondary rooms could be potentially explained by the movement of air resulting from the opening and closing of doors by healthcare providers during entry and exit of the ward in hospital settings. This allows the virus-laden particles to escape to secondary locations. In contrast, individuals who are self-isolating in their residences typically exhibit milder symptoms and may visit secondary locations on an intermittent basis or leave the primary room door open. Hence, virus can be shed in secondary locations during the visit or transported to secondary locations *via* the open door. On the other hand, for hospital settings, which were characterized by high ACH, a significantly lower level of positivity rate was found in secondary locations than primary locations. It is likely due to negative pressure in certain wards which restricts the movement of airborne virus from movement into outside spaces. The significant difference in positivity rates between hospital primary and secondary locations, in contrast to the lack of significance between primary and secondary locations within high ACH settings, may appear contradictory at first glance. The disparity is attributable to the abundance of observations available in the location type analysis, whereas the paucity of data points in the ACH analysis impeded our ability to obtain a statistically significant difference in that specific context.

Minimum ACH targets recommended by ASHRAE are as follows: homes (0.35), retail spaces (2.0), classrooms (2.3), gyms (5.3), intensive care units (6), and operating rooms (20) (ASHRAE 2020, 2022). While studies included in this meta-analysis were limited by the scope of design to a small subset of the ACH rates and could not alone represent the totality of the built environment, this meta-analysis encompassed a broad spectrum of values from 0 to above 16. As a result, it provides a more extensive overview of the detection of viruses from indoor air in relation to ACH. The present study offers evidence from real-world situations indicating that increased ACH can decrease the likelihood of elevated viral concentrations in the air. It suggests that an increased ACH may mitigate the exposure risk to other respiratory pathogens, including airborne viruses, bacteria, and fungi. It was also found that SARS-CoV-2 concentration and the positivity rate reduction were small when ACH value was above eight, indicating high ACH may potentially disperse the virus and transport it throughout the room (Kalivelampatti Arumugam et al. 2022). It should also be noted that even when ACH value was higher than 16, the positivity rate was not zero. Hence, to further reduce the risk, other measures are needed, such as wearing N95 respirators (Mizukoshi et al. 2021).

Virus emission rates might confound our analyses, depending on activity types, activity intensity, and infection stage. Coleman et al. (2021) found that virus emission rate varied from 63 to 5,821 gene copies per participant's expiratory activity. Such substantial heterogeneity between individuals was also observed in Edwards et al. (2021). A source study (Gregson et al. 2021) showed that, whether for singing or speaking, there were sharp rises in particle mass concentration as the sound level went up. As indicated by a

simulation study, under the same environmental conditions, coughing can result in higher virus concentration in room air, compared to normal breathing (Riediker and Tsai 2020). Compared to non-aerosolization processes, hospital-related aerosol-generating procedures, such as bronchoscopy, cardiopulmonary resuscitation, and extubation, may have higher emission rates than coughing or breathing (Kohanski, Lo, and Waring 2020). Infection stage determines whether the patient is actively shedding virus or not. Studies show that early-stage patients had a higher likelihood of emitting detectable RNA from exhaled breath (Coleman et al. 2021), and as the illness stage progressed, the viral load would reduce as measured in nasal and mouth swabs (Horve et al. 2022). COVID-19 patients exhale infectious virus typically for only a week (Wölfel et al. 2020) or two (Sohn et al. 2020). Some can shed virus for up to 20 days (van Kampen et al. 2021) following the onset of symptoms. Although viral RNA could be continuously identified in biological samples by RT-PCR analysis, this might be linked to the formation of neutralizing antibodies in COVID-19 patients 5–10 days post infection (Sohn et al. 2020; van Kampen et al. 2021). Many papers included in this study lacked critical patient information, such as the infection stage and symptoms. Of the 38 papers that provided patient information, they primarily reported results from clinical samples (e.g., saliva or nasal swabs) or documented patient symptoms. Specific infection stages of patients were often absent. Among papers that mentioned infection stages, reporting conventions varied, with some using days post-symptom onset and others relying on days after the first positive clinical test result.

The placement of the sampler is a pivotal determinant in field sampling, which could influence the resultant virus concentrations. Unfortunately, comprehensive information regarding the precise sampler placement, including whether it was positioned downwind or upwind, the height at which it was put and the distance between the sampler and the patient, was not consistently provided in the field sampling studies included in our analysis. Moreover, in cases where this information was reported, the patient-sampler distance exhibited variability across different studies and, at times, within the same study. If the virus aerosols are well mixed in space, which is usually assumed in the mass balance model, then virus concentrations would be similar across the whole space. In the case of an isolation home study from the Netherlands, researchers found the difference in RNA concentration between near the mouth and far away from the mouth was minimal, which can be explained by the accumulation of RNA under poor ventilation over time (de Man et al. 2022). However, in most cases, it is unlikely that the virus concentration is homogeneous, and it is more likely to get a higher virus concentration near the source than far-field (Parhizkar et al. 2022), due to the dilution and dispersion of the exhaled plume over time. In addition, a substantial reduction in risk was also seen when the emission source was in the upwind direction compared to the downwind direction, as suggested by a CFD simulation (Ho 2021a).

Variation in sampling techniques and the broad spectrum of air samplers used potentially introduced disparities in particle collection efficiency. Lab-based comparison by nebulizing SARS-CoV-2 in simulated saliva reported lower physical collection efficiency when using liquid impingers than when using impaction-based samplers, such as NIOSH BC-251, filters or Sioutas cascade impactor (Ratnesar-Shumate et al. 2021). When using filter-based samplers and cyclone samplers, particle extraction from filter or solid surface into liquid media is usually needed for RNA quantification through PCR. For gelatin filters, since it is soluble in water, the extraction process is easier and more efficient compared to other types of filters. On the other hand, such extraction is not needed for liquid-based samplers such as BioSampler and BioSpot. While BioSampler is very effective in collecting larger bioaerosols such as bacteria or fungi, it is not as effective in capturing submicron hydrophobic virus, where collected viruses are subject to re-aerosolization (Riemenschneider et al. 2010). A water condensational growth tube BioSpot-VIVAS can collect fine particles efficiently by amplifying them and gently impacting onto the liquid media in petri dish (Lednicky et al. 2016). Hence, future experiments should be designed to allow the quantification of air sampler collection efficiencies.

Experimental design parameters, especially the volume of air collected, and the sensitivity of the PCR methods selected, introduce variability among the studies considered in this meta-analysis. The volume of air sampled and the sensitivity of PCR may have an impact on whether virus RNA can be detected in the air sample, which influences the positivity rate in our analysis. In the early phase of the pandemic, Faridi et al. (2020) utilized a standard midget impinger to sample 90 liters of air in an Iranian hospital, but failed to detect any SARS-CoV-2 in the air samples. While the result initially suggested the virus might not be airborne, it's important to consider that

factors such as the limited volume of air sampled, the collection efficiency of the impinger, or the sensitivity of the detection method used could have influenced these results. Additionally, sampling start time (e.g., 9 AM vs 1 PM) can also affect the RNA concentration retrieved. For example, SARS-CoV-2 RNA was only found in the sample collected by Coriolis® μ (100 L/min) during the first 10 min of a 60-minute time frame (Silva et al. 2022). The two other consecutive Coriolis® μ samplings performed within the same time frame were negative for SARS-CoV-2 RNA despite a higher airflow rate (200 L/min and 300 L/min, respectively). This was because the intubation took place in the initial 10 min of the sampling, and led to point of air contamination, while the negative findings in the second and third samples can be explained by the fast RNA clearance by the room's ventilation system. A study from an isolation home also indicated that even on the same day, using the same BioSpot sampling at the same location, the concentration calculated from the first sample was twice that from the second sample (Vass et al. 2022), which might be due to the difference in air flow patterns of the time frames and the frequency of coughing during the two periods. A simulation involving mass balance modeling revealed that for the same patient, the time to reach a concentration plateau varied under different ventilation rates (Riediker and Tsai 2020). Hence, under the same ACH rate, the retrieved concentration can vary depending on whether the sample is taken under the concentration plateau or before the concentration reaches the steady state.

Temporal and spatial variation in sampling events potentially involved SARS-CoV-2 variants. Numerous studies failed to specify the SARS-CoV-2 variant detected, making it challenging to determine the exact variant infecting the patients. Different variants may result in varying emission rates from infected hosts. A study showcased significant differences in viral loads among delta, gamma, alpha and G20 variants using saliva samples (King et al. 2022), although another study demonstrated that the breath emission rates of omicron variant (4.56×10^3 to 3.59×10^7 copies/hour) and delta variant (2.01×10^3 to 1.47×10^6 copies/hour) were comparable with no statistically significant difference (Li et al. 2022); the same work revealed that there was no significant difference in viral load in throat swabs between alpha, delta and omicron variants at the time when the patients were admitted to the hospital. Apart from the abovementioned factors, relative humidity (Parhizkar et al. 2022) and airflow patterns in space can influence the exposure risk, adding uncertainties to the analysis, though their information is typically not available in sampling studies.

Dual analyses were performed on virus concentration data grouped by ACH and location due to the zero-inflated values. It is possible that some of those zero values were false negatives for reasons discussed above. Additionally, negative results could also arise if samples were collected during the later stages of infection. For example, a study in Germany households failed to detect any virus in air samples despite the absence of ventilation (Döhla et al. 2022). The negative result may be attributed to the late stage of infection, but time post-diagnosis or symptom onset was not reported in the study. Moreover, the accuracy of virus detection hinges on proper sampling methods and reliable RT-PCR analysis. Inaccuracies in these procedures or study designs could lead to false negatives, potentially masking variations between different groups. This uncertainty introduced by false negatives highlights for researchers the importance of a thoroughly planning of data collection processes based on the current body of knowledge to help minimize the risk of mistaken conclusions.

One of the limitations of our study is that we compared virus' genome copy number (genome equivalent; GE) in a sample through RT-qPCR. This method does not provide a measure of the quantity of infectious virions therein, which are responsible for causing the illness. RT-qPCR detects all viral genetic material, but not all of it comes from viable viruses. For example, virus particles released from cells typically consist of a mixture of fully formed viable virus particles (infectious virions), defective virus particles that may or may not be complete virions (including defective or biologically active but not infectious particles), and virus nucleic acid covered with protective protein (nucleoprotein) but lacking external virus coat proteins (Marcus, Ngunjiri, and Sekellick 2009). Hence, detection of a virus GE doesn't necessarily equate to the presence of infectious virus, and the equivalence in GE concentration may not imply an equivalent level of health risk across different environments. It is crucial to determine the viable virus count associated with a given GE, which is usually done through plaque assays or by obtaining the Median Tissue Culture Infectious Dose ($TCID_{50}$). The viable virus count will always be lower than the GE value. Proof of infectivity and determination of infectious virus counts require cell culture methods. However, such work for SARS-CoV-2 requires highly trained scientists to perform within BSL3 or BSL4 laboratories. Such facilities and personnel are limited. In cell culture systems, the GE to infectious SARS-CoV-2

particle ratio ranges from 10–100 virus genomes for each infectious virion (Mautner et al. 2022). The infectious dose of SARS-CoV-2 was estimated to be 10 inhaled infectious virions per susceptible (immunologically naive) human volunteer (Killingley et al. 2022). Furthermore, determination of SARS-CoV-2 viability in samples obtained using air samplers is not always straightforward using cell culture systems, as other respiratory viruses present in the air may also replicate in the cells chosen for the viability assays (Lednicky et al. 2021; Lednicky et al. 2020b; Nannu Shankar et al. 2022). Last but not the least, traditional air sampling methods and long sampling durations can lead to inactivation of virions through impaction, desiccation, or other means (Pan, Lednicky, and Wu 2019; Rahmani et al. 2020; Tang et al. 2015; Verreault, Moineau, and Duchaine 2008). Presently, there is insufficient data related to viable SARS-CoV-2 collected from ambient air in variable types of built environments to perform useful metadata analyses. Therefore, our analysis has relied on the imperfect surrogate of virus detectable by PCR to assess exposure risk. We recommend that researchers quantify viable virus through cell culture methods whenever possible.

Our study did not consider how different airflow patterns affect exposure risk. Assessment using CFD models was beyond the scope of our study. Further, rather than being measured by researchers, the ACH values were either based on the HVAC system reported by the facility or assigned according to ASHRAE/Guobiao standards. Due to system aging or inaccurate assumptions for missing data, the ACH values might not be accurate. Our study does not consider how HVAC design or maintenance influences virus concentrations. In mechanically ventilated places, the outside air ratio differs. Filters are mounted in the ventilation system to avoid recirculating contaminated air or carrying the pathogen from one room to another. Different grades of filters vary in particulate removal efficiencies and therefore will have variable effectiveness at removing virus-laden particles (Azimi and Stephens 2013). Mounting ultraviolet germicidal irradiation (UVGI) in HVAC systems can further reduce the exposure risk by deactivating the virus (Li et al. 2021). Particle removal efficiency plays a crucial role in infection control in practical settings. This paper exclusively focuses on the ACH parameter, which is calculated by dividing the volume flowrate by the volume of the room. There was a deficiency in the available information pertaining to the specific filter type utilized in each individual study. For the 2 studies included in this meta-analysis that involved air purifiers in households, High Efficiency Particulate Air (HEPA) filters were used in purifiers (Myers et al. 2022; Rodríguez et al. 2021). In the United States, it is recommended that hospitals utilize HEPA filters. Nevertheless, the verification of this claim remains uncertain due to the limited reporting of the filter utilized in the HVAC system within field sampling studies. Regarding hospitals located outside of the United States, our knowledge of their regulatory frameworks is constrained.

Another limitation is that the result lacks statistical power because the exposure risk cannot be determined by ACH rate alone. Unlike well-designed experiments with defined conditions, there are no standard protocols for SARS-CoV-2 air sampling: samplers were placed at different distances from the patient and at different heights above ground; the distances between primary and secondary rooms varied between studies and within the same study; different samplers that work on different mechanisms were employed; rooms housing distinct human subjects with varied symptoms and at various infection stages were sampled; and different primers were used to quantify SARS-CoV-2 RNA. For instance, different research groups targeted different SARS-CoV-2 genes (ORF1ab, RdRp, E, S or N) in quantitative molecular tests. This variation in primer selection could have affected the effectiveness of molecular tests as SARS-CoV-2 mutated from one variant to another. The statistical power was hindered by the lack of data. Not all papers included in this analysis reported the concentration of each air sample or provided sufficient information for us to compute the positivity rate for each site. Instead of excluding these papers from the analysis, the imputation method was applied to potentially alleviate the bias. The risk of acquiring COVID-19 is also dependent on human factors, such as the presence of co-morbidities and age. Importantly, the risk also depends on the virus strain and genetic lineage. For example, contemporary SARS-CoV-2 strains are better able to cause human infections than the virus that caused the start of the COVID-19 pandemic. Our recommendation for future field sampling studies is to ensure the inclusion of critical information such as patient illness details, virus strain, precise air sampler placement, PCR-based concentration determinations, environmental conditions (e.g., RH and temperature) and ACH and HVAC information. This comprehensive approach will greatly enhance the quality and depth of future research in this field.

5. Conclusions

This data synthesis and analysis compiled data from 93 publications involving air sampling for SARS-CoV-2. This meta-analysis represents to our knowledge the first use of published field sampling data concerning

SARS-CoV-2 concentrations and air sample positivity rates from hospitals and residences. This work complements many computational fluid dynamics models, mass balance models, and behavior-scripted chamber sampling by providing a comparison of SARS-CoV-2 presence according to the type of indoor setting and associated air change rates. Findings reported here show a negative correlation between ACH (ranging from 0 to >16) and airborne SARS-CoV-2 concentration, suggesting that ACH can affect exposure risk. Residences, characterized by lower air change rates, generally had higher virus concentrations and an increased likelihood of detecting positive air samples as compared to hospitals. That reality underscores the heightened risk of exposure to SARS-CoV-2 in environments with low air change rates. Exposure risk remained similar between residential primary and secondary rooms and decreased in hospitals in areas away from primary patient rooms. That circumstance demonstrates that the adjacent areas to where patients are isolating themselves can pose a high exposure risk if the primary rooms have low air change rates. We therefore suggest that ACH be increased in indoor settings where persons with COVID-19 are present to reduce the risk of potential virus transmission.

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