EVIDENCE SUMMARY

Should carbon dioxide (CO2) monitors be used to reduce transmission of COVID-19?

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RECOMMENDATION

We recommend the use of carbon dioxide (CO2) monitors in enclosed spaces to guide actions to improve ventilation and reduce transmission of SARS-CoV-2.
(Moderate certainty of evidence; Strong recommendation)

Consensus Issues
The panel made a strong recommendation for the use of carbon dioxide (CO2) monitors because of the moderate certainty of evidence based on an indirect study that showed much higher risk of contracting tuberculosis when exposed to a room whose air reached 1000 parts per million (ppm) of carbon dioxide. The panel believed CO2 monitors could serve as a real-time guide to initiate activities that improve air ventilation (such as promoting distancing, opening windows, or turning on electric fans). However, two panelists still voted for a weak recommendation due to (1) unknown accuracy of various commercial monitors in detecting CO2 levels and (2) concerns with regard to the actual use of industrial-grade monitors (training of personnel, number of monitors needed, calibration, preventive maintenance) in different institutions. Even with the use of CO2 monitors, the public must continue to observe the precautionary measures of handwashing, wearing face masks, and observing physical distancing to avoid infection with COVID-19.

Key Findings

We found no studies that directly answered the question on whether carbon dioxide level determination can be used to prevent SARS-CoV-2 infection. There were observational studies that reported no infection when there was increased air ventilation and the CO2 levels were low. In these studies, many factors affecting CO2 levels were considered simultaneously real-time, such as use of personal protective equipment (PPEs), activity of persons in the room, duration of stay in the room, and size of the room, among others. The CO2 levels, as detected by carbon dioxide sensors, were correlated with air ventilation and in most studies, the CO2 level was designated to be a surrogate or proxy to COVID-19 risk of transmission. Indirect evidence showed that people exposed to a room with more than or equal to 1000 parts per million (ppm) of carbon dioxide in the air, as measured by a CO2 monitor, had as high as 16x higher risk of contracting tuberculosis, compared to those in a room with lower CO2 levels.

The other studies investigated the presence of the virus in air (aerosol and droplets), and as fomites. Although there was a disagreement existed among the studies, as two studies were able to isolate the virus in the air, while the other was able to isolate the virus only as fomites, it may be possible that the negative growth of the virus may not mean that it is absent.

Introduction

The transmission of SARS-CoV-2 via aerosols has been reported to be one of the mechanisms of the spread of the virus.[1] Several studies have shown that indoor air quality is associated with carbon dioxide levels, and CO_2 levels have been considered to be a surrogate measure of transmission risk of respiratory infections that are spread through droplet and aerosol mechanisms.[2-5] SARS-CoV-2 virus has been detected in particles with diameters of <100um that can float in the air for hours, and in exhaled air of COVID-19 patients as well as in hospital air [6,7]. Carbon dioxide is postulated to contain infected viral pathogens as it is exhaled from COVID-19 patients.[6] In addition, CO_2 levels may indicate an increase in the number of occupants in an enclosed area and their activity level.[8] Through mathematical modelling and indoor scenarios, the CO_2 levels can proxy the COVID-19 infection risk by applying the Wells-Riley model and its modifications.[4] Following this logic, increasing levels of CO_2 may indicate poor indoor air quality and thus increased infection risk.[9-13] This was the focus of a recent review on indoor CO_2 sensors for COVID-19 risk mitigation, which concluded that although CO_2 monitoring can help address ventilation inadequacy, indoor CO_2 levels should not be interpreted as a proxy for COVID-19 risk since SARS-CoV-2 transmission depends on many factors, of which ventilation is only one [13]. There was one simulation study that measured the relationship of aerosol concentration and CO_2 concentration in a simulated enclosed area such as a concert hall. The study showed a linear positive correlation between aerosol concentration (p/cm3) and CO_2 level (ppm).[14]

Viral Presence

We found three studies that directly measured the virus in exhaled breaths or air samples within the vicinity of the COVID-19 patient. In the study by Ma et al. (2020) [6], they measured the presence of the virus in the exhaled breath, air and surface of patients with COVID-19. Their results showed that the highest virus content was in EBC (exhaled breath condensate) 14/52 (26.9%), then in surface swabs (13/242; 5.4%) and lastly, in air 1/26 (3.8%).

In a case-control study by Lednicky et al. (2020) [7] with six cases (five positive controls, including one as case and control), air samples were collected in the rooms of two COVID-19 patients, one with active RT-PCR and virus culture. Viable virus was isolated from air samples collected 2 to 4.8 m away from the patients. The genome sequence of the SARS-CoV-2 strain isolated from the material collected by the air samplers was identical to that isolated from the NP swab from the patient with an active infection.

In the last paper, Cheng et al. (2020) [15], did a diagnostic study with six COVID-19 patients (symptomatic and asymptomatic). They collected air samples in single rooms of patients with airborne infected isolation rooms (AIIR) with 12 air changes per hour (ACH). All air samples were negative for SARS-CoV-2 RNA in the six patients singly isolated inside the AIIR. A second group of samples yielded 19/377 (5%) of environmental samples (bedrails, lockers, bed tables – area of 9 cm^2) near 21 patients. The cell phone had the highest concentration of the virus: 7.8% (7/77) followed by bed rail 4/74 (5.4%). There was significant correlation between viral loads in clinical samples and positivity of environmental samples ($p<0.001$).
In a closed space with an infected individual, it is possible that viral presence through exhaled particles may be present both in air samples and as fomites that can settle in environmental areas near the infected individual such as bed rails, chairs and tables within the closed room.

Review Methods

We searched Pubmed, TRIP database, clinicaltrials.gov, Epistemonikos, medrxiv, Google Scholar, and Google to identify articles related to indoor CO_2 monitoring and COVID-19 risk of infection. Public health guidance documents that used CO2 monitoring as a surrogate for infection risk were also sourced. Our search included the following PICO elements: P – individuals without COVID-19, at risk for COVID-19, healthcare workers, essential frontliners, household and occupational contacts, vaccinated individuals, general public; I – use of CO2 monitors/levels; C – non-use of CO2 monitors/levels; O – risk of COVID-19 infection, risk for respiratory diseases, indoor air quality. Our search also utilized Boolean operator combinations and synonyms like "rooms," "enclosed spaces," "indoor," "CO2," "carbon dioxide," "air quality," "COVID-19," and "SARS CoV-2."

We included cross sectional studies, retrospective cohort and experimental studies (before and after an intervention) to determine CO2 levels in real-time with the different types of ventilation. We included preprints and examined study protocols as well.

Results

We found no studies that directly answered the research question, and the studies subsequently presented constitute indirect evidence

The studies included in this review evaluated (1) effects of CO2 level in risk of tuberculosis or nosocomial infection, (2) relationship of air ventilation on CO2 concentration, (3) CO2 and aerosol concentration, (4) effects of CO2 level in sick building syndrome (SBS), and (5) possible harm/misinterpretation in the use of CO2 monitors.

Effect of Ventilation and CO2 concentration on TB transmission:
The similarity in the mode of transmission for SARS-CoV-2 and Tuberculosis may show an indirect evidence in the SARS-CoV-2 transmission in a group wehre there the CO2 levels is more than 1000ppm in a closed area. In a retrospective cohort study on the effect of ventilation and level of CO2 concentration on TB infection, Du et al. [16] evaluated 1665 contacts and investigated how ventilation rate was improved with CO2 monitoring and, as a corollary to this, how improvement of ventilation rate decreased the number of tuberculosis cases.

The study noted the differences between those who acquired and did not acquire TB in terms of the CO2 levels, with a threshold set at 1000 parts per million in the room where their exposure or contact occurred. Comparing the exposed group (room with CO2 levels ≥1000ppm) and the non-exposed group (room with CO2 levels < 1000ppm) in accordance with the number of TB cases, the exposed group was 16 times more likely to have TB infection (RR 16.1, 95% CI 2.17-119.5).

The results of the study are summarized in the table below.

Table 1. Acquired TB infection and Room CO2 level (ppm)

Contact under CO2 level ≥1000ppm	Acquired TB (n=22)	Did not acquire TB (n=1643)	*P* value
NO	1 (4.5%)	722 (43.9%)	< 0.0001
YES	21 (95.5%)	921 (6.1%)	

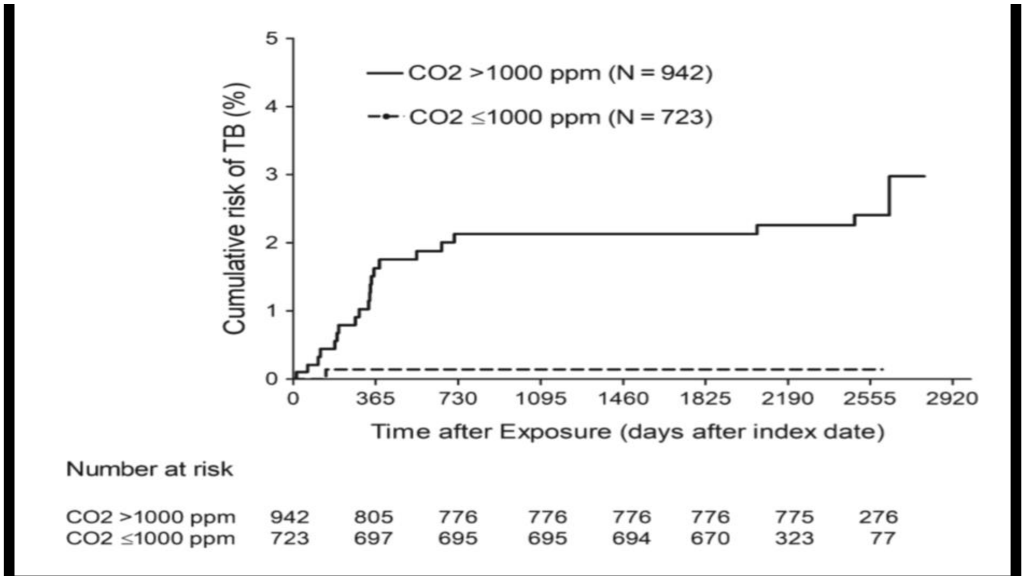

Figure 1. Kaplan-Meier estimates for the risk of contacts by ventilation status

Air Ventilation Protocol on CO2 Concentration
The studies by Di Gilio et al. [2], Vassella et al. [12], and Lu et al. [17] showed the relationship of CO2 concentration and ventilation rate: the higher the ventilation rate, the lower the CO2 levels. The study by Lu et al. [17] investigated, over a one-month period (February 2020), places where COVID-19 patients were present. They placed CO2 monitors in two major areas of the hospital and monitored the CO2 levels, air ventilation rates and the occurrence of nosocomial COVID-19 infections during this period. According to their data, approximately 90 patients were registered at the hospital each day so for the whole month of February in 2020, approximately 2520 patients were included. During the study period, five COVID-19 patients were present. However, no one contracted the COVID-19 infection during the study period.

CO2 level and Aerosol Concentration
In a simulated study [14] using a concert hall as a setting of an enclosed area, aerosol generation was made with a dummy infector with and without mask. Their study showed a direct linear positive correlation between aerosol concentration and CO2 concentration with an r = 0.77 (Figure 2).

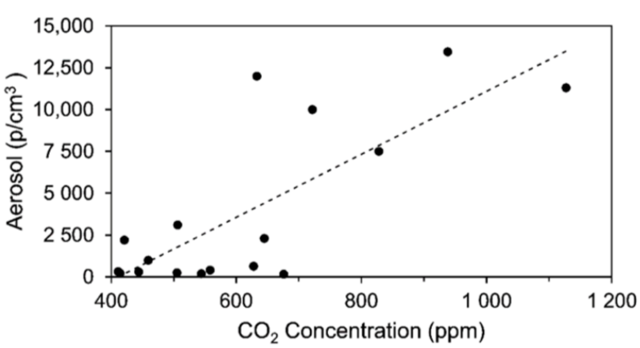

Figure 2. Relationship between aerosol and CO2 concentration

CO2 level and Sick Building Syndrome
Studies by Tsai et al. [18] and Hou et al. [19] found a correlation between CO2 levels and sick building syndrome (SBS), which was defined as having symptoms that cannot be associated with a well-defined cause but that appear to be linked with time spent in a building. Symptoms of SBS include eye irritation, headache, feeling of stuffiness, URTI, or GI complaints. The study by Tsai et al. [19] was a cross sectional study with 111 office workers in an office floor. The OR was measured for each symptom and correlated with CO2 concentration of <500ppm vs. >800 ppm. Results showed that eye irritation had an OR = 1.7 (95% CI 1.1-2.7; p = 0.01) and URTI had an OR = 1.7 (95% CI 1.0-2.7; p=0.03).

The second study by Hou et al. [19] was conducted over an 11-month period (March 2018-February 2019). A questionnaire was given every month to the sample population (n=1285). The AOR (adjusted odds ratio) of relative humidity for general (fatigue, heavy head, headache, dizziness, difficulty concentrating) and skin SBS (dry facial skin, dry ears, dry hands) was higher in areas with high CO2 concentrations than in those with low CO2 concentrations (OR= 1.02, 95% CI 0.97-1.08 for general SBS; OR = 1.03, 95% CI 0.99-1.08 for skin SBS).

Possible Harm on the Use of CO2 monitors
The review by Eykelbosh [13] on the use of indoor CO2 sensors for COVID-19 risk mitigation identified two risks of using CO2 sensors: technological dependency and misinterpretation. The article argued that although CO2 has been proposed as a proxy for COVID-19 risk, many factors may come into play such as the size of the room, occupants' activity, use of masks, etc.

They explained that the use of CO2 monitors may be 1) threshold-based, where one sets an appropriate action limit, or 2) trend-based, where a data logging feature is used to display the CO2 curve and an action is taken when the curve is going upward. For both approaches, the actions to reduce CO2 levels may include the following: open windows and doors, take periodic breaks where occupants can leave the room, reduce occupancy and avoidance of high intensity activities, increase fresh air supply, keep ventilation fans running during occupied periods, and install local exhaust systems. Placement of CO2 monitors should be 0.5-2.0 meters above floor and should be avoided in the following: near windows, near 2m of any human contact and within 2m of open flame.

In theory, technological dependence and misinterpretation may occur. Technological dependence occurs when the focus becomes the readout on the sensor rather than on promoting awareness: eg. masks, distancing, etc. Misinterpretation may include a sense of complacency when CO2 level is low or below threshold.

Evidence to Decision
The price of a CO2 sensor/monitor ranges in online shops from Php865 – Php4,501.[20] While these are readily accessible and available to individual users in metropolitan areas with internet connection, the same cannot be said for all rural or geographically isolated and disadvantaged areas (GIDAs) unless funded and sourced by third parties.

Appraisal of Included Studies
We appraised the study by Du et al [17] using the Newcastle Ottawa Scale (NOS) for cohort studies. The over-all certainty of evidence was moderate using GRADEPRO, since we downgraded for indirectness but increased by 2 steps because of large magnitude of association.

Recommendations from Other Groups in Pandemic Era

From Eykelbosh [13]

Source	Document Type	Description	CO_2 Action Limit
German Umweltbundesamt[21]	Guidance document	Recommends fixed or portable CO_2 “traffic lights” in schools to remind teachers and students to periodically open windows to facilitate classroom ventilation.	Lower green-yellow threshold set at 1000 ppm; yellow- red threshold set at 2000 ppm.
Minnesota Department of Health[22]	Guidance document	Recommends CO_2 monitoring to assess ventilation adequacy in classrooms with high occupancy.	Keep rooms below 800 ppm.
UK Scientific Advisory Group for Emergency[23]	Public health guidance document	Supports the notion of using CO_2 monitors to identify poorly ventilated spaces and prioritize them for remediation. Notes that low CO_2 levels do not necessarily indicate sufficient ventilation in low-occupancy or high-volume spaces. Rejects the notion that CO_2 can be used as a direct proxy of COVID-19 risk.	Spaces with CO_2 levels >1500 ppm should be prioritized for remediation. Spaces with aerosol-generating activities should aim for 800 ppm CO_2.

US Centers for Disease Control and Prevention[24]	Public health guidance document	Supports using portable CO2 sensors with a logging function to monitor indoor spaces.	A portable air cleaner should be considered for spaces that cannot be maintained below 800 ppm.
Washington State[25]	Public health guidance document	CO2 monitoring required to ensure that “open air” eating places (i.e., patios or restaurants with large open windows) are truly open to the outdoors.	If seated occupants are exposed to >450 ppm for 15 min, they must be moved to a better ventilated table.
Department of Labor and Employment (Philippines) [26]	Public Guidelines for workplaces and public transport to prevent and control the spread of Covid-19	CO2 monitoring (Section 6.B.2. Quantitative Assessment). CO2 level inside an enclosed space may be determined by using a calibrated CO2 monitoring device	CO2 shall not exceed 1,000ppm.

Research Gaps

Although CO2 monitoring may indicate indoor air quality, there is still paucity of evidence regarding the relationship of CO2 levels and COVID-19 transmission risk. There are no studies that compare CO2 levels with a control group. Direct studies looking into the role or benefit of using CO2 monitors to decrease COVID-19 cases are needed.

There is one ongoing study [27] that aims to determine the efficacy and feasibility of CO2 monitors to maintain indoor CO2 concentrations below 800-1000 ppm.

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Appendix 1. Evidence to Decision

Summary of initial judgements prior to the actual panel meeting (N = 6)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Problem	No (2)	Yes (4)				• CO2 levels have been considered to be a surrogate measure of transmission risk of respiratory infections that are spread through droplet and aerosol mechanisms • CO2 levels may indicate an increase in the number of occupants in an enclosed area and their activity level [8]. • Through mathematical modelling and indoor scenarios, the CO2 levels can proxy the COVID-19 infection risk by applying the Wells-Riley model and its modifications [4]. • Increasing levels of CO2 may indicate poor indoor air quality and thus increased infection risk. [9-12]
Benefits	Large (2)	Moderate (1)	Small (2)	Uncertain (1)		• Detects CO2 levels: Indirect evidence showed increased likelihood of TB infection in individuals who had been in the room with CO2 levels ≥1000ppm when compared to those in room with CO2 level < 1000 ppm (RR = 16.1, 95% CI: 2.17-119.5) • In most studies that investigated CO2 levels and air ventilation, increased air ventilation has been associated with a decrease in CO2 levels. Some studies found also found a correlation between CO2 levels and sick building syndrome (SBS). • Beneficial in construction planning to know no. of occupants in enclosed spaces (even in not COVID)

Harm	Large	Small (3)	Uncertain (3)	Varies			None reported aside from technological dependency and misinterpretation
Certainty of Evidence	High	Moderate (4)	Low (1)	Very low (1)			The overall certainty of evidence is moderate.
Balance of effects	Favors intervention (2)	Does not favor intervention (1)	Uncertain (3)	Varies			• Indirect evidence showed increased likelihood of TB infection in individuals who had been in the room with CO2 levels ≥1000ppm when compared to those in room with CO2 level < 1000 ppm (RR = 16.1, 95% CI: 2.17-119.5) • In most studies that investigated CO2 levels and air ventilation, increased air ventilation has been associated with a decrease in CO2 levels. Some studies found also found a correlation between CO2 levels and sick building syndrome (SBS). • None reported aside from technological dependency and misinterpretation
Values	Important uncertainty or variability	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability (2)			• No research evidence found
Resources Required	Uncertain	Large cost (6)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• No research evidence found
Certainty of evidence of required resources	No included studies (3)	Very low (2)	Low	Moderate	High (1)		• No research evidence found

Cost effectiveness	No included studies (4)	Favors the comparison	Does not favor either the intervention or the comparison (2)	Favors the intervention		• No cost-effectiveness studies available.
Equity	Uncertain (5)	Reduced (1)	Probably no impact	Increased		• No published studies available on use of CO2 monitors in the Philippines.
Acceptability	Uncertain (6)	No	Yes	Varies		• No published studies available on use of CO2 monitors in the Philippines. DOLE has recommended air change per minute within occupied workspaces maintains CO2 levels below 1000 ppm at all times.
Feasibility	Uncertain (4)	No	Yes (2)	Varies		• No published studies available on use of CO2 monitors in the Philippines. DOLE has recommended air change per minute within occupied workspaces maintains CO2 levels below 1000 ppm at all times.

Appendix 2. Search Yield and Results

PubMedSearchHistory-7

Search number	Query	Sort By	Filters	Search Details	Results	Time
18	Exhaled CO2 as COVID-19 infection risk proxy for different indoor environments and activities			("exhalate"[All Fields] OR "exhalation"[MeSH Terms] OR "exhalation"[All Fields] OR "exhalations"[All Fields] OR "exhaled"[All Fields] OR "exhaling"[All Fields] OR "exhale"[All Fields] OR "exhales"[All Fields]) AND "CO2"[All Fiel	0	12:09:13
17	Exhaled CO2 as COVID-19 infection risk proxy for different indoor environments and activities - Schema: all			"Exhaled"[All Fields] AND "CO2"[All Fields] AND "COVID-19"[All Fields] AND "infection"[All Fields] AND "risk"[All Fields] AND "proxy"[All Fields] AND "different"[All Fields] AND "indoor"[All Fields] AND "environments"[All Field:	0	12:09:13
16	(#1) AND (#12)			("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields]) AND ("crowd s"[All Fields] OR "crowding"[MeSH Terms] OR "crowding"[All Fields] OR "crowd"[All Fields] OR "crowded"[All Fields] OR "crowd	1	11:56:42
15	crowding			"crowd s"[All Fields] OR "crowding"[MeSH Terms] OR "crowding"[All Fields] OR "crowd"[All Fields] OR "crowded"[All Fields] OR "crowds"[All Fields]	21,874	11:56:11
12	((#6) AND (#9)) AND (#11)			("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "cov	13	11:55:17
14	(#9) AND (#6)			(("C02"[All Fields] AND ("level"[All Fields] OR "levels"[All Fields])) OR (("carbon dioxide"[MeSH Terms] OR ("carbon"[All Fields] AND "dioxide"[All Fields]) OR "carbon dioxide"[All Fields]) AND ("level"[All Fields] OR "levels"[All Fi	262	11:37:38
13	Similar articles for PMID: 32837691			32837691,34177075,33085569,33615383,34051507,33797051,32834937,34456454,33778137,33967376,21431823,34181766,32288019,16297217,23074468,19812072,32874703,34414068,27611368,33746487,31172603,3	62	11:01:48
11	((indoor space) OR (closed space)) OR (closed ventilation)			(("indoor"[All Fields] OR "indoors"[All Fields]) AND ("space"[All Fields] OR "space s"[All Fields] OR "spaces"[All Fields])) OR (("close"[All Fields] OR "closed"[All Fields] OR "closely"[All Fields] OR "closeness"[All Fields] OR "clo	34,158	10:49:09
10	Indoor space			("indoor"[All Fields] OR "indoors"[All Fields]) AND ("space"[All Fields] OR "space s"[All Fields] OR "spaces"[All Fields])	1,879	10:48:37
9	(#8) OR (#7)			("C02"[All Fields] AND ("level"[All Fields] OR "levels"[All Fields])) OR (("carbon dioxide"[MeSH Terms] OR ("carbon"[All Fields] AND "dioxide"[All Fields]) OR "carbon dioxide"[All Fields]) AND ("level"[All Fields] OR "levels"[All Fie	129,905	10:47:48
8	(C02 level) OR (Carbon Dioxide Level)			("C02"[All Fields] AND ("level"[All Fields] OR "levels"[All Fields])) OR (("carbon dioxide"[MeSH Terms] OR ("carbon"[All Fields] AND "dioxide"[All Fields]) OR "carbon dioxide"[All Fields]) AND ("level"[All Fields] OR "levels"[All Fie	21,754	10:47:21
7	(C02) OR (Carbon Dioxide)			"C02"[All Fields] OR ("carbon dioxide"[MeSH Terms] OR ("carbon"[All Fields] AND "dioxide"[All Fields]) OR "carbon dioxide"[All Fields])	129,905	10:46:38
6	(((COVID-19) OR (SARS-CoV-2)) OR (COVID infection)) OR (COVID)			"covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covi	177,529	10:45:03
5	(#3) AND (#2)			("indoor air"[Journal] OR "indoor air int conf indoor air qual clim"[Journal] OR ("indoor"[All Fields] AND "air"[All Fields]) OR "indoor air"[All Fields]) AND ("carbon dioxide"[MeSH Terms] OR ("carbon"[All Fields] AND "dioxide"[Al	874	10:43:49
4	(#2) OR (#3)			"carbon dioxide"[MeSH Terms] OR ("carbon"[All Fields] AND "dioxide"[All Fields]) OR "carbon dioxide"[All Fields] OR ("indoor air"[Journal] OR "indoor air int conf indoor air qual clim"[Journal] OR ("indoor"[All Fields] AND "air"	149,474	10:02:43
3	indoor air			"indoor air"[Journal] OR "indoor air int conf indoor air qual clim"[Journal] OR ("indoor"[All Fields] AND "air"[All Fields]) OR "indoor air"[All Fields]	21,309	10:02:17
2	Carbon dioxide			"carbon dioxide"[MeSH Terms] OR ("carbon"[All Fields] AND "dioxide"[All Fields]) OR "carbon dioxide"[All Fields]	129,039	10:01:47
1	(SARS-CoV-2) AND (crowding)			("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields]) AND ("crowd s"[All Fields] OR "crowding"[MeSH Terms] OR "crowding"[All Fields] OR "crowd"[All Fields] OR "crowded"[All Fields] OR "crowd	344	09:56:31

Appendix 3. Table of Included Studies

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Effect of Ventilation and CO2 concentration on TB transmission							
Du CR, Wang SC, YU MC, Chiu TF Wang JY, Chuang PC, Jou R, Chan PC, Fang CT. Effect of ventilation improvement during a tuberculosis outbreak in under ventilated university buildings. Indoor Air.2020; 30:422-432.	Retrospective Cohort study design (for all contacts in outbreak)			Evaluated 1665 contacts Acquired TB = 22 Did not have TB = 1643 Contact under CO2 >1000ppm +TB. -TB NO. 1 (4.6%). 722 (44%) YES. 21 (95.5%). 921 (56%) P<0.0001	Room <1000ppm CO2 Improving ventilation rate to 23.6-25.1 L/s/p (14-15 ACH) helped end the TB outbreak. Ventilation improvement to lessen CO2 to <1000ppm was associated	Room >1000ppm CO2	1/21 had TB infection in the INTERVENTION Group While 21/22 had TB infection in the CONTROL Group 97% decrease in infectious TB cases among contacts (95% CI: 50-99.9%) for those CO2 <1000ppm

Air Ventilation Protocol on CO_2 concentration							
Di Gilio A, Palmisani J, Pulimeno M, Cerino F, Cacace M, Miani A, de Gennaro G. CO2 concentration monitoring inside educational buildings as a strategic tool to reduce the risk of Sars-CoV-2 airborne transmission. Environmental Research 2021. 202.111560. https://doi.org/10.1016/j.emvers.2021.111560.	Experimental, pilot study. *The premise is that indoor CO2 monitoring was suggested as a practical proxy of transmission risk of respiratory infectious disease. In indoor environments an excess of CO2 levels over outdoor levels could be related to the increased probability to inhaled breath exhaled by other people – thus to infection risk.	Italy	9 classrooms, 147-152 students	Students Pre-school	1st stage. Realtime CO2 monitoring 2nd stage. If CO2 levels approach 700 ppm, the following were done: Leave door open, open windows for 10min during breaks, open windows if the above don't work to lower CO2 levels.	No Protocols	Lowering of CO2 levels after instituting the protocol.
Vassella CC, Koch J, Henzi A, Jordan A, Waeber R, Iannccone R, Charriere R. From spontaneous to strategic natural window ventilation: Improving indoor air quality in Swiss Schools. Int J Hyg Environ Health. 2021. 113736.	Cross sectional	100 classrooms Range/classroom 3-26		CO2 levels decrease with increased ventilation and reminders for people to be aware of the benefits of ventilation compared to standard [no reminders/flyers on ventilations during breaks].	CO2 level Median: 1600pmm	CO2 level.Median: 1097 ppm Natural ventilation + mechanical + flyers, lessons on ventilation, + ventilation during breaks or open	

Lu Y, Li Y, Zhou H, Lin J, Zheng Z, Xu H, Lin B, Lin M, Liy L. Affordable measures to monitor and alarm nosocomial SARS-CoV-2 infection due to poor ventilation. Indoor Air. 2021; 00:1-10. Doi:10.1111/ina.12899.	Experimental Used CO2 levels as surrogate assessment method of noscomial infection risk. Prospective cohort: Case Study	Infrared CO2 sensors: Moderate [characterize exhaled breath]. +/- 50ppm. Measurement interval of 5 minutes [0.8-1.2m above ground]. Placed in the fever clinic [natural ventilation]; emergency department [mechanical ventilation] **CO2 level was used to estimate ventilation rates and can be diluted when ventilation rates are increased.	No infections were observed. No comparator. Infection among HCWs were just monitored and the airflow rate was noted at the time of the encounters with patients in different areas of the hospital based on number of infectors [Covid-19 patients]. Under the protection of level 2 PPE, an outdoor airflow rate of 21 L/(s·person) was sufficient to prevent SARS-CoV-2 hospital-acquired infection in Changgung Hospital. *Indoor CO2 concentration represents the comprehensive effects of occupancy and the outdoor airflow rate. The ventilation can be sufficient to maintain a relatively low CO2 concentration in an overrowded room, which is dangerous for diseases that can be transmit-ted through close contact, such as COVID-19.	In this study, aided with personal protection and disinfection measures, outdoor airflow rate per person of 15–18 L/(s·person) was sufficient to prevent nosocomial infection when there was only one COVID-19 patient, and 21 L/(s·person) was sufficient during throat swab sampling.	Theoretical determination of upper limit of CO2	Practical implications: The study showed that with personal protection and disinfection, the outdoor airflow rate per person of 15–18 L/(s·person) was sufficient to prevent nosocomial infection when there was only one COVID-19 patient, and 21 L/(s·person) was sufficient during throat swab sampling.

CO2 level and Sick Building Syndrome

Dai-Hua Tsai, Jia-Shiang Lin & Chang-Chuan Chan (2012) Office Workers' Sick Building Syndrome and Indoor Carbon Dioxide Concentrations, Journal of Occupational and Environmental Hygiene, 9:5, 345-351, DOI: 10.1080/15459624.2012.675291	Cross-sectional study that used an SBS questionnaire and compared it to CO_2 levels.	Correlate SBS [sick building syndrome] and CO_2 concentrations -SBS, symptoms that cannot be associated with a well-defined cost but appear to be linked with time spent in a building.		CO_2 concentrations are used as surrogate for indoor ventilation. SBS included eye irritation, headache, tiredness, fatique, tension, URTI, or GI complaints, skin irritations.	Used two time periods for questionnaire. Participants should be able to answer both.	CONCLUSION Indoor CO_2 ≥800ppm were associated with an increase in workers' SBS, especially eye irritation and URTI.	+association between SBS and indoor CO_2 levels: specifically [tired/strained eyes, dry/irriitated eyes, difficulty in remembering
Hou J et al. Associations of indoor CO_2 concentrations, air temperature, and humidity with perceived air quality and sick building syndrome symptoms in Chinese homes. Indoor Air. 2021; 00:1-11.	Cross-sectional study Correlate CO_2 levels with perception of dry air and skin SBS symptoms.			*CO_2 was positively associated with the percentage of perceived stuffy odor. Low CO_2 levels were less likely to have skin SBS symptom (dry facial skin, dry ears, dry hands)			

Appendix 4. Detailed Study Appraisal

Author(s): Emmanuel P. Estrella, MD, MSc, Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS Myzelle Anne Infantado, PTRP, MSc (cand.)
Question: CO_2 levels below 1000ppm versus =/> 1000ppm
Setting: Community or healthcare setting
Bibliography: Du CR, Wang SC, YU MC, Chiu TF Wang JY, Chuang PC, Jou R, Chan PC, Fang CT. Effect of ventilation improvement during a tuberculosis outbreak in under ventilated university buildings. Indoor Air.2020; 30:422-432.

Assessment of quality of a cohort study – Newcastle Ottawa Scale	
Selection (tick one box in each section):	
1. Representativeness of the intervention cohort	
a) truly representative ★	☐
b) somewhat representative ★	√☐
c) selected group of patients	☐
d) no description of the derivation of the cohort	☐
2. Selection of the non intervention cohort	
a) drawn from the same community as the intervention cohort ★	√☐
b) drawn from a different source	☐
c) no description of the derivation of the non intervention cohort	☐
3. Ascertainment of intervention	
a) secure record ★	√☐
b) structured interview ★	☐
c) written self report	☐
d) other / no description	☐

4. Demonstration that outcome of interest was not present at start of study a) yes ★ b) no	√ ☐ ☐
Comparability (tick one or both boxes, as appropriate): 2 vs 1	
1. Comparability of cohorts on the basis of the design or analysis a) study controls for age, sex, marital status ★ b) study controls for any additional factors (e.g. socio-economic status, education) ★	☐ √ ☐
Outcome (tick one box in each section): 3 vs 3	
1. Assessment of outcome a) independent blind assessment ★ b) record linkage ★ c) self report d) other / no description	☐ √ ☐ ☐ ☐
2. Was follow up long enough for outcomes to occur a) yes, if median duration of follow-up >= 6 month ★ b) no, if median duration of follow-up < 6 months	√ ☐ ☐
3. Adequacy of follow up of cohorts a) complete follow up: all subjects accounted for ★ b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, ★ or description of those lost suggesting no different from those followed c) follow up rate < 80% (select an adequate %) and no description of those lost d) no statement	√ ☐ ☐ ☐ ☐

The assessment for this study using the Newcastle Ottawa Scale is that the study had 4 STARS in the Selection Domain, 1 STAR in the Comparability Domain, 3 STARS in the OUTCOME Domain.

Converting NOS scales to AHRQ (Agency for Health Research and Quality) standards, 4 Stars in Selection domain, 1 Star in the Comparability Domain, and 3 Stars in the outcome Domain, the study is of GOOD QUALITY.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 5. GRADE Evidence Profile

A recent study on the effect of ventilation and CO2 levels on TB infection was published by Du et al. The following figures are grade evidence profile tables for the study. This was a cohort study on university students and employees and the effect of ventilation improvement on TB infection. The intervention here was increasing ventilation to have a CO2 level of < 1000pmm.

Author(s): Chun-Ru Du, Shun-Chic Wang, Ming-Chih Yu, Ting-Fang Chiu, Yann-Yuan Wang, Pei-Chun Chuang, Ruwen Jou, Pei-Chun Chan, Chi-Tai Fang
Question: CO2 ≥ 1000ppm compared to CO2 < 1000 in preventing TB Transmission
Setting: University Setting
Bibliography: Du CR, Wang SC, YU MC, Chiu TF Wang JY, Chuang PC, Jou R, Chan PC, Fang CT. Effect of ventilation improvement during a tuberculosis outbreak in under ventilated university buildings. Indoor Air.2020; 30:422-432.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CO2 ≥ 1000ppm	CO2 < 1000	Relative (95% CI)	Absolute (95% CI)		
TB Infection (assessed with: CXR, Sputum)												
1	observational studies	not serius[a]	not serious[a]	serious[b]	not serious[c]	very strong association	21/942 (2.2%)	1/723 (0.1%)	**RR 16.12** (2.17 to 119.54)	**21 more per 1,000** (from 2 more to 164 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide variation in the type of patients that were included in the study
b. Different type of infection, but related in the manner of transmission