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Graphical-mathematical model to estimate CO2 concentration level as an indicator of SARS-CoV-2 transmission.

Modelo gráfico-matemático para estimar el nivel de concentración de CO2 como indicador de la transmisión del SARS-CoV-2.

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ABSTRACT

The first documented cases of Coronavirus disease of 2019 (COVID-19) in Wuhan city (Hubei province, China) were caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), studies mention viral transmission is more common in indoor and poorly ventilated environments compared to outdoor environments or environments with abundant airflow. In this context, this research aimed to estimate, through a mathematical model by a Box-Behnken design, the time and occupancy required in a physical space to reach CO_2 levels that exceed the risk level established as a safer condition of 700 ppm for SARS-CoV-2 transmission. According to the proposed mathematical model, it is possible to predict safe conditions. With this, it was found that natural ventilation is the best option to reduce CO_2 concentration, considering the occupancy/m^3 and time, allowing a constant airflow; the use of air conditioners to control the temperature in rooms without natural ventilation is suggested; notwithstanding, these types of equipment are not designed to reduce CO_2 concentration. Thus, their use in rooms with open windows and doors leads to a shorter equipment lifetime, for this reason, its operation in special conditions, such as in rooms without natural ventilation should be considered.

KEY WORDS: SARS-CoV-2, carbon dioxide, mathematical model, air quality, ventilation, occupancy.

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R E S U M E N

Los primeros casos documentados de la enfermedad por Coronavirus de 2019 (COVID-19) en la ciudad de Wuhan (provincia de Hubei, China) fueron causados por el Síndrome Respiratorio Agudo Severo Coronavirus (SARS-CoV-2), los estudios mencionan que la transmisión viral es más común en interiores y en ambientes mal ventilados en comparación con espacios al aire libre o con abundante flujo de aire. En este contexto, esta investigación tuvo como objetivo estimar, a través de un modelo matemático (diseño de Box-Behnken), el tiempo y la ocupación requerida en un espacio físico para alcanzar niveles de CO_2 que superen el nivel de riesgo establecido como condición segura de 700 ppm para la transmisión de SARS-CoV-2. Con esto, se encontró que la ventilación natural es la mejor opción para reducir la concentración de CO_2, considerando la ocupación/m^3 y el tiempo, permitiendo un flujo de aire constante; se sugiere el uso de aire acondicionado para controlar la temperatura en habitaciones sin ventilación natural; no obstante, este tipo de equipos no están diseñados para reducir la concentración de CO_2. Por lo tanto, su uso en habitaciones con puertas y ventanas abiertas conduce a una vida útil más corta, por lo que se debe considerar su funcionamiento en condiciones especiales.

P A L A B R A S C L A V E : SARS-CoV-2, dióxido de carbono, modelo matemático, calidad del aire, ventilación, ocupación.

Introducción

Currently, more than three years after the first documented cases of Coronavirus Disease 2019 (COVID-19), in Wuhan city (Hubei, China), caused by Severe Acute Respiratory Syn-drome Coronavirus 2 (SARS-CoV-2), and declared a pandemic event in March 2020 by the World Health Organization (WHO, 2022), it reached a global public health threat due to the high transmission rate. Until January 30th, 2023 a number of 670.246.742 confirmed cases and 6.830.068 deaths have been reported worldwide (Johns Hopkins, 2022). Therefore, it is important to promote scientific research with multidisciplinary approaches to understand the underlying fac-tors of SARS-CoV-2 transmission routes to reduce the spread of this etiological agent.

Initially, different SARS-CoV-2 transmission routes were hypothesized; it is currently demonstrated that the transmission route is through exhaled air by infected persons (Chin *et al*., 2020; Buryukov *et al*., 2020; Belluco *et al.*, 2021; Chatterjee *et al.,* 2021), via virus-loaded microparticles (ø = 0.1 ー 100 μm), which can remain air suspended for minutes or even hours (Ranga, 2021; Coldrick *et al.,* 2022; Port *et al*., 2022). Additionally, Oba *et al*. (2021) described the relationship be-tween particle sizes and viral load. Where, infected subjects who presented Cycle thresh-old (Ct)

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values < 37 of specific genes such as the envelope (E) gene; therefore, the saliva droplets expelled will contain a greater number of virions with infection potential.

Thus, viral transmission is more probably in indoor and poorly ventilated environments compared to outdoor environments or environments with abundant airflow (Li *et al.,* 2021; Coyle *et al.,* 2021). Therefore, the risk of SARS-CoV-2 transmission can be increased in environments saturated by human exhalations, as occurs in indoor spaces. Given that a large population segment conducts its daily activities in enclosed spaces, it is crucial to control factors such as ventilation, human interaction, and behavior to prevent and control SARS-CoV-2 transmission (*Azuma et al.,* 2020).

Given this background, indoor carbon dioxide (CO_2) monitoring is suggested as a practical, low-cost approach for indirectly estimating the SARS-CoV-2 risk transmission (Peng & Jimenez, 2021). The increased concentration of this gas indoors is generally due to human exhalation and poor ventilation. In a study cited by Di Gilio *et al.* (2021), it is proposed that indoor CO_2 concentrations should not exceed 700 ppm in indoor spaces. Therefore, a limit of <700 ppm can be used as an indicator for the reference of areas with a lower risk for SARS-CoV-2 infection. Hence, this research aimed to estimate, through a mathematical model, the time and occupancy required in a physical space to reach CO_2 levels that exceed the risk level established for SARS-CoV-2 transmission.

Material and Methods

The model was built for an indoor classroom-type environment, with dimensions of 6.21 m in length, 7.93 m in width, and 2.9 m in height (142.8 m^3). Three physical spaces were used simultaneously, in which 15 people/space were seated for 50 min, simulating a regular school class. During this time, all persons wore facemasks.

Before the test, all participants n = 48 (23 men and 25 women) with an average age of 35 ± 7 years were measured anthropometrically (weight and height), to calculate the body mass index (BMI), through equation (1) and thus distribute the people homogeneously in each physical space.

$$\text{BMI} = \text{Weight (kg)} / (\text{Height})^2\ (\text{m}^2) \qquad (1)$$

In addition, to avoid including in this trial any asymptomatic SARS-CoV-2 carriers, a saliva sample (2 mL) was collected one day before the trial from all participants according to the protocol previously described by Girón-Pérez *et al.* (2021), the E gene was analyzed by qRT-PCR and the presence of the virus was analyzed through the adapted Berlin protocol (Corman *et al.,* 2020; Girón-Pérez *et al.,* 2021). All patients were duly informed, accepted the use of the information for scientific purposes, and signed an informed consent form before anthropometrics parameters measures and sample collection. This study was approved by the local bioethics panel under registration number CEBN/03/20.

Once the test began, the environment CO_2 concentration was permanently monitored during the session, using an indoor air quality equipment (LANGKOU, LKO2, China), with a CO_2 measurement range of 400 to 5000 ppm, resolution of 1 ppm, temperature range of -10 to 50 °C, particulate matter (PM) meter 0.5/1/10, the reading time of 1.5 s and PM changes of 5 s.

In each test, three factors were considered: 1) Time (min), 2) Percentage of people occupying the area (15 people/area, 1 people/9m^3), and 3) Type of ventilation (WV: without ventilation, NV: natural ventilation, NV+AC: natural ventilation plus air conditioning). Three levels were assigned to each of the three variables (Table 1) and a Box Behnken 3^3 statistical model was applied with a total of 15 experiments in triplicate.

Table 1. The experimental design used for CO_2 monitoring, a) factors and levels implemented in the study, b) combinations obtained by Box Behnken 3^3 design.

a)

No.	Factors	Levels		
1	Time (min)	15	30	50
2	Percentage of people occupying the area	0	25	50
3	Type of ventilation	WV	NV	NV+AC

b)

Treatment	Factors		
	Time	Occupancy (%)	Type of ventilation
1	15	0	NV
2	15	25	NV
3	15	25	WV
4	15	50	NV+AC
5	30	0	WV
6	30	0	NV
7	30	25	NV
8	30	25	NV
9	30	25	NV
10	30	50	WV
11	30	50	NV+AC
12	50	0	NV
13	50	25	WV
14	50	25	NV+AC
15	50	50	NV

WV: without ventilation, NV: natural ventilation, NV+AC natural ventilation plus air conditioning (Minisplit 110v Mirage 12000 British thermal units (BTU)).

Data were analyzed by a multi-factorial design of experiments, then a predictive equation for CO_2 estimation was obtained through response surface graphs with the combinations of time-ventilation (T/V) and ventilation-occupancy (V/O), considering a limit of $CO_2 < 700$ ppm, ideal ventilation, and occupancy (%) conditions were obtained through a Pareto diagram and mean comparison, α = 0.05 using Statistica® software version 12, California, USA.

Prediction equation evaluation

The predictive equation obtained was assessed in three indoor classroom type environments of the Autonomous University of Nayarit (108 m^3) considering 50 % occupancy (30 people), kept with the door and windows open for 120 min performing normal office activities. The CO_2 concentration was registered each 5 min. This study was carried out in triplicate.

Results and Discussion

More than a year after the onset of the COVID-19 pandemic, WHO accepted that short-range droplet inhalation predominates in SARS-CoV-2 transmission (WHO, 2022); however, indoor transmission is higher than in outdoor spaces. In line with this, Li *et al.* (2021) used a simple macroscopic continuum model to assess how the ventilation rate of a room significantly affects the short-term exposure to the risk of airborne infection transmission. Suggesting that, short- and long-range droplet airborne transport, considering ventilation, and occupancy, are crucial for air safety and quality. Therefore, mathematical modeling has been an important tool for estimating safe environmental air conditions.

Significance assessment of factors

The impact of factors (p = 0.05) is shown in Figure 1a, the Pareto diagram with standardized effects showed that ventilation, occupancy percentage, and time (min) independently can affect CO_2 concentration; therefore, if any of these factors are altered, the dependent variable will be affected (ventilation > occupancy > time). However, if CO_2 levels are exceeded (> 700 ppm), those factors did not show a response to CO_2 behavior. Hence, CO_2 levels will not decrease unless ventilation is increased or occupancy decreases. SARS-CoV-2 can be mainly transmitted by close contact or droplets deposited on surfaces. Although, the airborne transmission risk cannot be ignored, especially in indoor spaces where the risk of infection is high roughly 2 % in a space with a common ventilation rate (500-2500 m^3/h per infector for 0.25 h) (Dai & Zhao, 2020).

Ventilation types of evaluation

Means comparisons of the ventilation levels are shown in Figure 1b, in which two statistical groups with significant differences were observed: without ventilation (WV) and with natural ventilation (NV) / natural ventilation + artificial ventilation (air conditioning) (NV+AC). Thus, there are no significant differences (α = 0.05) when implementing the use of air conditioning in an indoor classroom-type environment. The dispersion angle of an exhaled microdroplet is influenced by the oral cavity structure, movement, and body heat, increasing accordingly to the exhaled flow rate; whereby, in a closed environment the surrounding room air contains exhaled droplets, whose concentration depends on the ventilation rate (Li *et al.,* 2021). This is supported

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by a validated computational fluid dynamics model of droplets and aerosol emission during exhalations, finding that microbial dispersion is driven by ventilation and distance between people (Coldrick *et al.,* 2022).

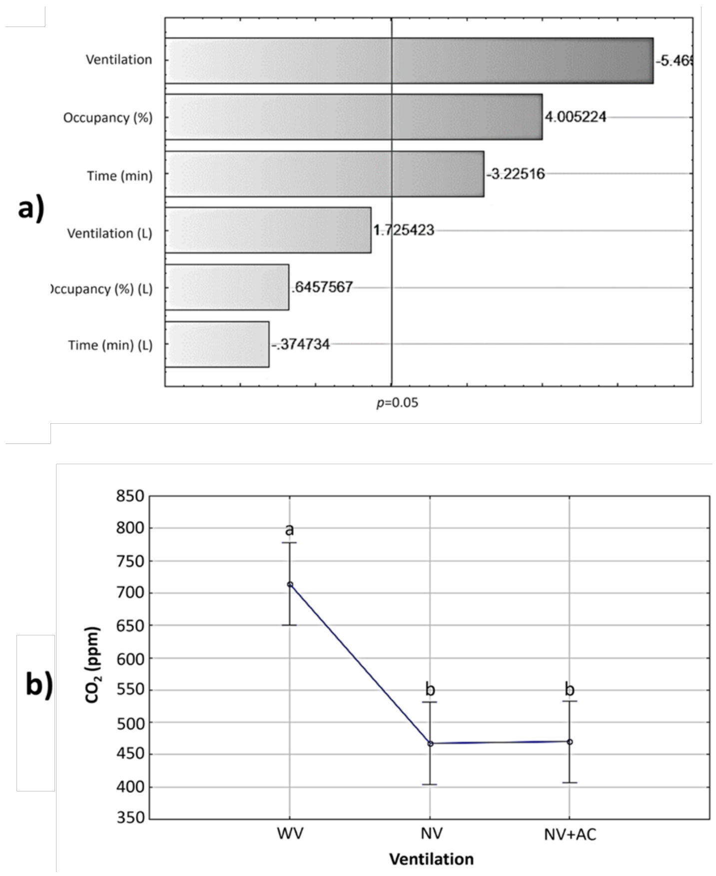

Figure 1. Statistical results.

a) Pareto diagram with standardized effects on the dependent variable CO_2 concentration (ppm) and the factors of the Box Behnken 3^3 designed model, b) mean com-parison analysis of ventilation types (levels) WV (without ventilation) a, NV (natural ventilation) b, VN+AC (natural ventilation + air conditioning) b. Vertical bars denote 95 % confidence intervals, calculated at $p < 0.00001$.

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Evaluation of factor interactions

The study of combinations between factors allows predicting behaviors and related impacts on evaluated variables. Figure 2 shows the response surface plots of the factors (T/V), where it was observed that the higher the ventilation, the longer the occupancy time in-creases. However, this may be linked to the third factor studied (occupancy %). Indoor spaces should be adequately ventilated according to occupancy, or maximum occupancy should be provided for spaces with a limited ventilation rate. Maximum occupancy should be determined by measuring the ventilation rate or by real-time monitoring of CO_2 concentration.

To confirm the impact of the T/V interaction, Figure 3 shows similar behavior for V/O, which evidences that the dominant factor is ventilation; therefore, it was considered as a fixed factor at its maximum level, since under this condition the mathematical model can estimate the greatest time or occupation percentage. Similar results were obtained considering three control variables to limit SARS-CoV-2 exposure within indoor environments: ventilation, physical distancing, and the use of masks (3-layer cotton masks) which con-tributed to aerosol exposure reduction (Coyle *et al.,* 2021).

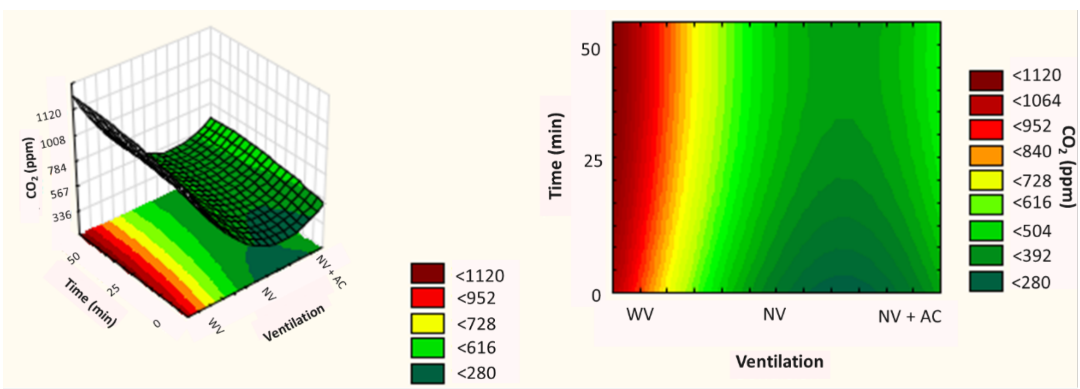

Figure 2. Response surface plot of the data analysis of the factors y-axis: CO2 concentration (ppm), x-axis: time (min), z-axis: ventilation.

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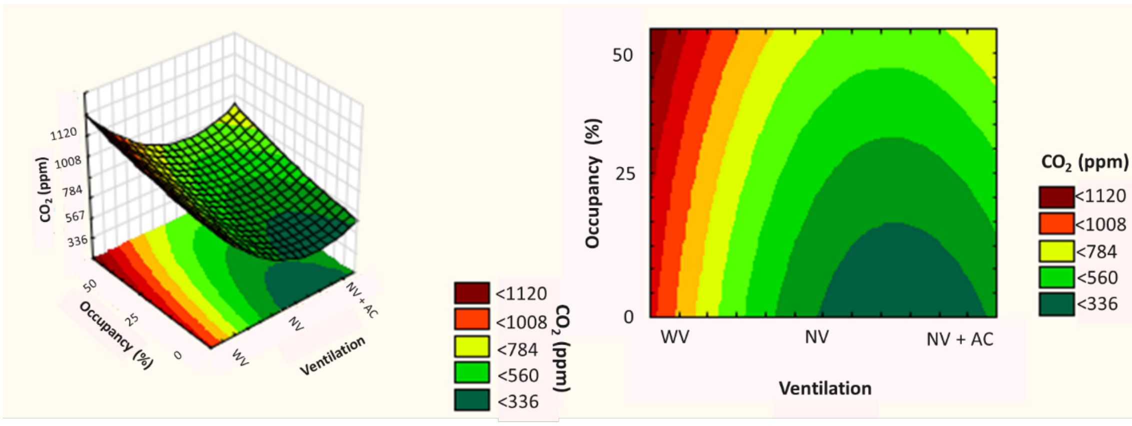

Figure 3. Response surface plot of the data analysis of the factors y-axis: CO_2 concentration (ppm), x-axis: occupancy (%), z-axis: ventilation.

Predictive equation

Once the dominant factor has been established, Figure 4 shows the behavior of the data associated with the CO_2 concentration, resulting in a predictive model as a function of time and area occupancy percentage, from these factors equation (2) is estimated, where z = CO_2, x = time, y = occupancy (%). The optimum result obtained was 50 % occupancy and a time limit of 1 h and 45 min.

$$z = x(-0.0001xy2+0.0054xy-0.0499x+0.0027y2+1.0942)$$
$$y(0.1525y+0.0572x+9.1821) + 500.0926 \qquad (2)$$

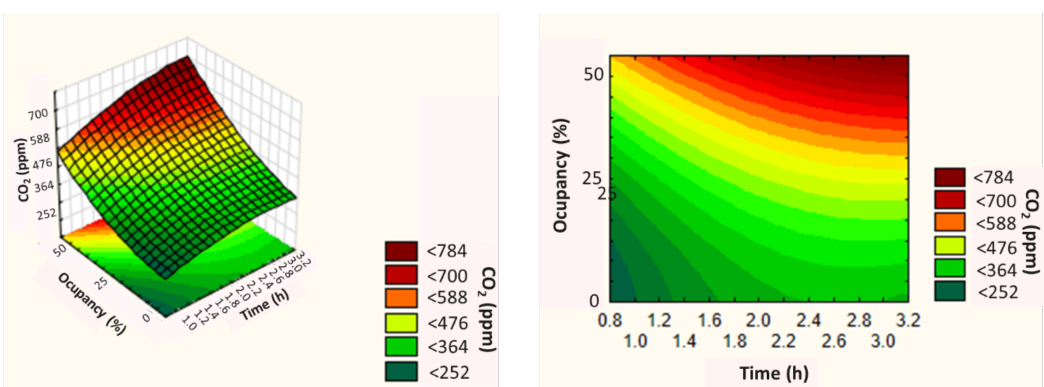

Figure 4. Response surface plot of the data analysis of the factors y-axis: CO_2 concentration (ppm), x-axis: occupancy (%), z-axis: time (h).

The CO_2 behavior evaluation, based on equation (2) is shown in Figure 5a, the maximum safe time in NV should not exceed 1 h and 45 min with a capacity of 50% occupancy considering 3.6 m^3 / person. These results are similar to reports on cognitive performance in students (16 - 23 years old) considering the combined effects of indoor temperature and CO_2 levels as markers of ventilation rates, suggesting an adequate space: environmental temperature 20 - 23°C, CO_2 concentration limit of 600 ppm in exposures no longer than 2 h (Ahmed *et al.,* 2022). Besides, decision-making performance is reduced by increasing CO_2 levels (1000 - 1500 ppm) in office-like spaces (Satish *et al.,* 2012). Thus, ventilation is a marker associated with productivity and cognitive activities such as vigilance, reasoning, and memory tasks (Kapalo *et al.,* 2018; Mundackal & Ngole-Jeme, 2020; Ahmed *et al.,* 2022).

Practical implications

The impact factors for a safe indoor classroom-type environment are ventilation > occupancy > time, considering a concentration of 700 ppm CO_2 indoors with natural ventilation. However, in rooms that do not have natural ventilation, it is necessary to use artificial ventilation which favors indoor airflow to reduce the spread of airborne respiratory diseases (Figure 5b). The use of air conditioners to control the temperature in rooms without natural ventilation is suggested; however, these types of equipment are not designed to reduce CO_2 concentration. Furthermore, operation in rooms with open windows and doors leads to a shorter equipment lifetime, and also an increased power demand, so its operation in special conditions, such as in rooms without natural ventilation, should be considered. Therefore, consideration of the type of ventilation (primarily natural ventilation), maximum occupancy, and time spent in office-like spaces are variables that should be considered as an effective and trustworthy strategy to ensure good air quality and, at the same time, mitigate the transmission risk infections in indoor environments.

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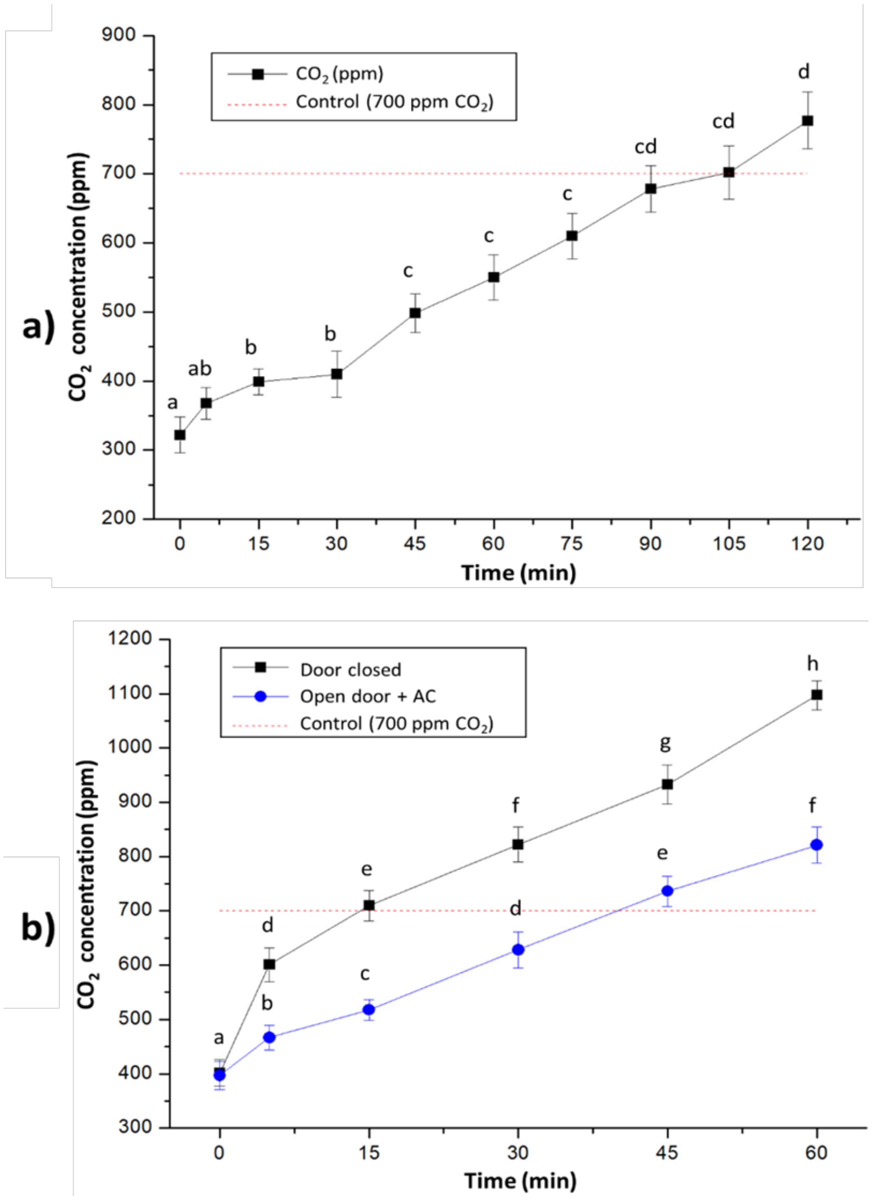

Figure 5. CO_2 **concentration monitoring for validation of the equation, a)** CO_2 **monitoring in spaces without natural ventilation access, b)** CO_2 **monitoring in spaces with access to natural ventilation. Data expressed as mean ± standard deviation (n=9).**

Conclusions

The impact factors for a safe indoor classroom-type environment are ventilation>occupancy>time, considering a concentration of 700 ppm CO2 indoors with natural ventilation. However, in rooms that do not have natural ventilation, it is necessary to use artificial ventilation which favors indoor airflow to reduce the spread of airborne respiratory diseases (Figure 5b). The use of air conditioners to control the temperature in rooms without natural ventilation is suggested; however, these types of equipment are not designed to reduce CO2 concentration. Furthermore, operation in rooms with open windows and doors leads to a shorter equipment lifetime, and also an increased power demand, so its operation in special conditions, such as in rooms without natural ventilation, should be considered. Therefore, consideration of the type of ventilation (primarily natural ventilation), maximum occupancy, and time spent in office-like spaces are variables that should be considered as an effective and trustworthy strategy to ensure good air quality and, at the same time, mitigate the transmission risk infections in indoor environments.

It is important to mention that this study seeks to establish with the minimum of controllable variables, (occupancy, time and types of ventilation) being other variables such as air turbulence disregarded since, the execution of this study sought to establish a safe measure in poorly ventilated spaces.

Contribución de los autores

Conceptualization, F.F.R.-C and M.S.N.-M; Methodology, F.F.R.-C., M.S.N.-M.; Formal Analysis, F.F.R.-C., M.S.N.-M., K.J.G.D.-R., G.A.T.-I. and G.H.V.-R.; Investigation, F.F.R.-C., M.S.N.-M., V.W.B.-C. and C.E.C.-R.; Data Curation, F.F.R.-C; Writing, F.F.R.-C., M.S.N.-M., V.W.B.-C. and M.I.G.-P.; Original draft preparation, F.F.R.-C., M.S.N.-M., V.W.B.-C., C.E.C.-R. and M.I.G.-P.; Writing—Review and Editing, F.F.R.-C., M.S.N.-M., V.W.B.-C. and C.E.C.-R.; Supervision and validation, project administration, funding acquisition: M.I.G.-P.

All authors have read and agreed to the published version of the manuscript.

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Declaraciones éticas

This study was approved by the local bioethics panel under registration number CEBN/03/20.

Declaración de consentimiento informado

Informed consent was obtained from all subjects involved in the study.

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Conflicto de interés

The authors declare that they haven´t conflicts of interest.

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